Türk Göğüs Kalp Damar Cerrahisi Dergisi 2012;20(3):600-603
doi: 10.5606/tgkdc.dergisi.2012.114

Aortic valve replacement in a patient with factor VII deficiency

Faktör VII eksikliği olan bir hastada aort kapak replasmanı

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A 69-year-old man who had never experienced episodes of bleeding was admitted to our hospital with the complaints of dyspnea, palpitation and orthopnea. Electrocardiography, echocardiography and laboratory tests revealed atrial fibrillation, severe aortic stenosis and elevated INR level (2.18). Coagulation tests due to isolated INR elevation showed that the activity of factor VII (FVII) decreased to 9% and the patient was diagnosed with isolated FVII deficiency. As FVII activity<10% is associated with high risk of bleeding during surgical procedures, recombinant FVII (rFVIIa) 40 mcg/kg was administered intravenous bolus infusion two hours before surgery. Aortic valve replacement was performed using a-23 mm bioprosthesis. The activity level of FVII during anesthesia induction and aortic cross declamping were 29% and 22%, respectively. Hemostasis was easy to secure and no extra dose of rFVIIa was given. The patient did not experience any postoperative problem or severe bleeding. Warfarin sodium was not administered to the patient, as he had atrial fibrillation, as well as bioprosthesis implantation and an INR level of 2.5. At the end of a-two-year follow-up period, the patient had a good exercise tolerance without any bleeding or thromboembolic complication. Factor VII deficiency is an extremely rare inherited bleeding disorder. Replacement therapy with rFVIIa with close monitoring of FVII activity is a reliable way to manage patients with FVII deficiency who are scheduled to undergo valvular cardiac surgery.

Key words: Factor VII deficiency; recombinant FVIIa; valve replacement.

Daha önce hiçbir kanama deneyimi olmayan 69 yaşındaki erkek hasta nefes darlığı, taşikardi ve ortopne yakınmasıyla hastanemize başvurdu. Yapılan elektrokardiyografi, ekokardiyografi ve laboratuvar test incelemeleri sonucunda atriyal fibrilasyon, ciddi aort darlığı ve izole yüksek INR seviyesi (2.18) saptandı. İzole INR yüksekliği nedeniyle yapılan koagülasyon testleri sonucunda, faktör VII (FVII) aktivitesinin %9'a düştüğü saptandı ve izole FVII eksikliği tanısı konuldu. FVII aktivitesi %10'un altında olan hastalarda cerrahi işlemler esnasında yüksek kanama riski olduğu için, ameliyattan iki saat önce 40 mcg/kg dozunda rekombinan FVIIa (rFVIIa) intravenöz bolus infüzyon uygulandı. Aort kapak replasmanı 23 mm'lik biyoprotez kapak ile yapıldı. Anestezi indüksiyonunda ve aortik kros klemp kaldırıldığında, FVII aktivite düzeyi sırasıyla %29 ve %22 idi. Hemostaz kolaylıkla sağlandığı için ek doz rFVIIa verilmedi. Ameliyat sonrası hastada herhangi bir sorun ve ciddi bir kanama olmadı. Hastaya atriyal fibrilasyonda olduğu, yanı sıra protez implantasyonu ve INR değeri 2.5 civarında izlendiği için warfarin sodyum tedavisi başlanmadı. İki yıllık takip sonunda, hasta iyi egzersiz toleransı ile kanama ya da tromboemboli komplikasyonu olmadan izlendi. Faktör VII eksikliği, oldukça nadir rastlanan kalıtsal bir kanama bozukluğudur. Faktör VII eksikliği olan ve valvüler kalp kapak cerrahisi planlanan hastalarda, rFVIIa yakın FVII aktivitesi takibi yapılarak güvenle kullanılabilir.

Anahtar sözcükler: Faktör VII eksikliği; rekombinan FVIIa; kapak replasmanı.

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2012.114
QR (Quick Response) Code

Received: November 29, 2009 *Accepted:* February 24, 2010

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Factor VII (FVII) deficiency (or hypoproconvertinemia) is an extremely rare, inherited bleeding disorder.[1] Major surgery in patients with this deficiency has been reported to be endangered by intra- or postoperative bleeding unless a replacement therapy is used.[2] Herein we describe the case of a patient with low FVII activity who underwent open heart surgery with cardiopulmonary bypass (CPB). We focus on the peri- and postoperative management of this rare coagulation disorder with a replacement therapy which included a recombinant activated coagulation factor VII (rFVIIa) concentrate.

CASE REPORT

A 69-year-old man was referred to our cardiology clinic with dyspnea, tachycardia, and orthopnea. At admission, his hemoglobin level was normal. The prothrombin time (PT) was 22.8 seconds (s) (normal 11-13.5 s), the international normalized ratio (INR) was 2.18, and the activated partial thromboplastin time (APTT) was 28.4 s (normal 23-33 s). Coagulation tests, including an FVII assay, led to a diagnosis of isolated FVII deficiency with a 9% decrease in the level of FVII activity. He had never experienced episodes of even minor bleeding, for example epistaxis, gum bleeding, or easy bruising. He had no hepatic dysfunction and he had never undergone surgical intervention before. The patient was not on any anticoagulant or antiaggregant therapy.

In the general physical examination, auscultation revealed a mid-systolic ejection murmur over the aortic area and arrhythmia. The first electrocardiogram (ECG) revealed atrial fibrillation with a heart rate of 78 bpm. Echocardiography showed a stenotic aortic valve with a maximum gradient of 69.7 mmHg and a 0.9 cm^2 valvular area. Degrees of both aortic and mitral valvular insufficiencies were 2/4.

An initial dose of 20 mcg/kg of rFVIIa was given (weight of the patient: 60 kgs) two hours before cardiac catheterization, and since there was no refractory bleeding, the dose was not repeated after the procedure. Cardiac catheterization revealed 2/4 aortic insufficiency (AI), and there was no significant coronary lesion. Following echocardiography and cardiac catheterization, the patient proceeded to aortic valve replacement. Since he had atrial fibrillation, low-molecular-weight heparin (enoxaparin) was administered 1 mg/kg twice daily for a week in the preoperative period. Before the operation, a blood examination revealed PT 23.4 s, INR 2.12, and a markedly decreased level of FVII activity (8%) (Table 1). Other factor levels and activities were within the normal range.

We administered 40 mcg/kg of rFVIIa as an intravenous bolus infusion two hours before the operation. The chest was entered through a median sternotomy. The initial finding was a heart of good contractility. Standard CPB was established after heparinization (3 mg/kg) and cannulation of the aorta and right atrium, and the left ventricle (LV) was vented. The operation was performed under hypothermia at 28 °C. Cold crystalloid cardioplegia was directly infused into the coronary ostia for myocardial protection. The prosthesis of choice for aortic valve replacement was a 23 mm Hancock II® bioprosthesis (Medtronic Inc, Minneapolis, MN). The CPB lasted 88 minutes, and the aortic cross-clamping time was 69 minutes. The total operation time was 158 minutes. The patient was weaned from CPB uneventfully. The levels of FVII activities at the times of the induction of anesthesia and aortic declamping were 29% and 22%, respectively. After the reversal of heparin, the activated clotting time returned to 127 s. Hemostasis was easy to secure, and no extra dose of rFVIIa was given. The patient's postoperative course was uncomplicated, and there was no significant postoperative bleeding. The total drainage from the mediastinal chest tubes was 500 ml (250 ml, 150 ml and 100 ml for postoperative day 0, day 1 and day 2, respectively). During the two-day intensive care unit stay, bags of fresh frozen plasma and a bag of packed red cells were given. The total PT was kept at approximately 30-35%, with the INR at approximately 2.5 and the PT around 25 s. Since he had atrial

Table 1. Preoperative blood examination data

				Coagulation factor activities	
					%
White blood cell	6300/mm^3	APTT	28.7 s		
Erythrocyte	377x104/mm^3	PT%	37%	Factor II	88
Hemoglobin	12.3 g/dL	PT INR	2.12	Factor V	81
Hematocrit	36.3%	PT	23.4	Factor VII	8
Platelet	26.8x104/mm^3	Fibrinogen	329 mg/dL	Factor VIII	>100
Thrombin time	17.1 s	AT III	117%	Factor X	>100

APTT: Activated partial thromboplastin time; PT: Prothrombin time; AT III: Antithrombin III; INR: International normalized ratio.

fibrillation and an aortic bioprosthesis implanted, we did not prefer a more coagulable state. He was discharged on the seventh postoperative day, and no bleeding or thrombotic complications occurred after surgery. At the last follow-up, he remained asymptomatic with good exercise tolerance.

DISCUSSION

Factor VII is synthesized in the liver and has the shortest half-life (three-six hours) of all the coagulation factors. Severe FVII deficiency usually presents with various bleeding symptoms. It is characterized by prolonged PT and normal APTT as FVII affects only the extrinsic pathway of the coagulation cascade. Transmission is autosomal recessive.[1] The prevalence of FVII deficiency has been estimated at 1/500.000. The clinical spectrum is vast, but bleeding especially occurs in the homozygotes or composite heterozygotes with a factor activity of less than 20%. The necessity for routine preoperative replacement therapy for this disorder has been questioned. The reason why some patients bleed and others do not is unclear. Nevertheless, most reported operations have been performed under the protection of replacement therapy since hemorrhaging has occurred in surgical procedures when there was no replacement therapy. The precise levels of FVII needed for sufficient hemostasis in surgical procedures are not known. Our patient had never experienced bleeding problems even though he had residual FVII activity of 8%. When FVII levels are lower than 10%, there is a correlation with severe bleeding,[3] although that was not the case with this patient. In the past, substitution therapies used to prevent or treat bleeding in FVII deficient patients were fresh frozen plasma (FFP), pooled factor complex concentrate, or prothrombin complex concentrates (PCCs). However, the efficacy of such agents is now considered to be suboptimal as their use might cause an unwanted increase in the plasma levels of other coagulation factors and might also be associated with thrombotic complications and an increased risk of infection.[2,3]

Recombinant activated coagulation factor VII (rFVIIA) (eptacog alpha) is the generic name for NovoSeven®. It is a highly concentrated preparation and a second generation recombinant product. Thus, it is devoid of other human proteins or human viruses, and this nullifies the possibility of transmission of HIV or hepatitis.[4] It initiates the coagulation cascade by binding with the tissue factor at the site of injury and causes the formation of sufficient amounts of thrombin to trigger coagulation.[4] The rationale behind the use of rFVIIA in FVII deficiency is self evident since it provides only the missing factor.

Most reports have recommended replacement therapy for patients with FVII deficiency who will undergo major surgery, especially open heart surgery with CPB.[5] However, a review of the literature revealed only four reported cases of open heart surgery in patients with FVII deficiency.[5] In all of these cases, the FVII deficiency was less than 10%, and the replacement therapy was carried out to maintain the plasma FVII concentration at approximately 15% to 25%. The administration varied from a single dose to multiple doses or continuous infusion from as low as 11-25 mcg/kg to as high as a cumulative dose of >400 mcg/kg. The suggested dose is 40-90 mcg/kg. The dose may have to be repeated in two to four hours intervals during surgery and up to 48 hours postoperatively if bleeding persists.

It was shown in a recent report that rFVIIa treatment might also be used successfully in children with severe FXI deficiency in open heart surgery with CPB.[6]

It is possible that a bleeding tendency with a mild FVII deficiency might be aggravated by the blood artificial surface interaction initiated by CPB and hemodilution. Tissue factor (TF) is the main activator of the coagulation system during CPB. Factor VII, as well as other extrinsic factors, could be greatly consumed by blood activation via TF, especially when highly activated aspirated blood from non-vascular structures is reinfused during CPB.

Therefore, in cardiac surgery under CPB, FVII replacement therapy should be readily available if there is a severe deficiency.

A concern in cardiac patients receiving rFVIIa is the risk of a thromboembolic event,[7] especially because CPB may up-regulate local and systemic blood-borne TF. We administered a low dose of 40 mcg/kg rFVIIa as a bolus infusion two hours preoperatively. Since complete hemostasis was secured easily and no bleeding or thrombotic complications occurred after surgery, we did not repeat the dose.

It has been recently reported that pooled human plasma-derived FVII concentrate might be a safe, effective, and predictable replacement therapy for FVII deficiency in cardiac surgery patients and could be an alternative for rFVIIa.[8] The authors used a regimen with an initial bolus of 20 U/kg, followed by a fixed dose of 600 U FVII (7 U/kg) with increasing dosage intervals in our patient who had coronary artery bypass grafting with CPB.

Before the operation, we had a detailed discussion with our patient regarding his hemotological condition and outcome following various kinds of valve replacement strategies, and we especially emphasized the data which had been previously published in the literature, After this discussion, bioprosthesis was chosen. Hence, the patient had aortic valve replacement with a bioprosthesis, and he had atrial fibrillation. We monitored the PT and INR and preferred to keep it at approximately 2.5. We did not intervene with FFP or rFVIIa. We are convinced that our regimen was adequate since no bleeding or thrombotic complications occurred. At the last follow-up, he remained asymptomatic without any thromboembolic or bleeding complications.

The use of NovoSeven® is a reliable way to manage coagulation disorders due to FVII deficiency in cardiac valvular surgery under CPB with close monitoring of FVII activity so as not to cause any thrombotic complications.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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