Heparin-induced Thrombocytopenia As A Cause of Deep Venous Thrombosis: Effectiveness of Fondaparinux in Dialysis Patients

Derin Ven Trombozu Sebebi Olarak Heparine Bağlı Trombositopeni: Diyaliz Hastalarında Fondaparinux Etkinliği

Hülya TAŞKAPAN[1]
Doğu KARAHAN[2]
İrfan KUKU[3]
Sait KOÇ[2]

1 İnönü University, Turgut Özal Medical Center Nephrology Department, Malatya, Turkey
2 İnönü University, Turgut Özal Medical Center Internal Diseases Department, Malatya, Turkey
3 İnönü University, Turgut Özal Medical Center Hematology Department, Malatya, Turkey

ABSTRACT

A 63-year-old woman with Stage 5 chronic kidney disease presented with severe weakness, nausea, and vomiting. A catheter was inserted to the right femoral vein for hemodialysis. She received low molecular weight heparin (LMWH) (enoxaparine sodyum) during two consecutive hemodialysis sessions. The patient developed swelling of the right leg four days after catheter insertion. Heparinisation with unfractionated heparin was initiated because it was thought the patient had a femoral venous catheter-induced acute deep venous thrombosis. The platelet count decreased to 23 $x10^3/mm^3$ on the first day of heparin infusion. Re-evaluation of the platelet count records showed that the number of platelets had dropped from 119 $x10^3/mm^3$ to 80 $x10^3/mm^3$ after LMWH, but this had gone unnoticed. Heparin was stopped and the patient was given Fondaparinux, a synthetic selective inhibitor of activated factor X, for alternative anticoagulation at a dose of 2.5 mg every other day subcutaenously and later started on peritoneal dialysis. The patient was discharged on warfarin after 20 days. Venous doppler revealed no thrombosis at the right main deep and surface femoral vein on the 32nd day. It seems that the deep venous thrombosis was related to Type II heparin-induced thrombocytopenia with localized vascular injury due to the hemodialysis catheter predisposing to the thrombotic event. In conclusion, heparin-induced thrombocytopenia (HIT) can cause deep venous thrombosis, and should not be overlooked in patients with a reduced platelet count on dialysis. Use of Fondaparinux was effective in clearing the thrombosis.

KEY WORDS: Heparin, Thrombocytopenia, Thrombosis, Dialysis

ÖZ

Altmış üç yaşındaki, evre 5 kronik böbrek hastası bir kadın hasta ciddi halsizlik, bulantı, kusma yakınması ile başvurdu. Hemodiyaliz için sağ femoral vene kateter yerleştirildi. Takip eden 2 hemodiyaliz seansında düşük molekül ağırlıklı heparin uygulandı. Kateter yerleştirilmesinin 4. gününde sağ bacakta şişme oldu. Katetere bağlı akut derin ven trombozu düşünüldüğü için standart heparin başlanıldı. Heparin infüzyonunun ilk gününde, trombosit sayısı 23 $x10^3/mm^3$ e düştü. Hastanın kayıtları yeniden gözden geçirildiğinde düşük molekül ağırlıklı heparin kullanımından sonra trombosit sayısının 119 $x10^3/mm^3$'ten 80 $x10^3/mm^3$'e düşmüş olduğu; ancak fark edilmediği anlaşıldı. Heparin kesildi ve alternatif olarak Heparin Fondaparinux, aktive faktör X ün bir sentetik selektif inhibitörü, 2,5 mg günaşırı subkutan olarak verildi ve periton diyalizine başlanıldı. Hasta 20 gün sonra varfarin ile taburcu edildi. Otuz ikinci günde yapılan venöz doppler sağ ana derin ve yüzeyel femoral vende tromboz saptamadı. Derin ven trombozu heparin ile ilişkili tip II trombositopeni ile birlikte trombotik olaylara yatkınlık sağlayan hemodiyaliz kateterlerinde dolayı oluşan lokalize vasküler hasarı ile ilişkili görünüyor. Sonuç olarak heparin ile ilişkili trombositopeni derin ven trombozuna neden olabilir ve trombosit sayısı azalan diyaliz hastalarında göz ardı edilmemelidir. Fondaparinux trombozu temizlemede etkindir.

ANAHTAR SÖZCÜKLER: Heparin, Trombositopeni, Trombozis, Diyaliz

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Correspondence Address:
Hülya TAŞKAPAN
İnönü Üniversitesi Turgut Özal Tıp Merkezi, İç Hastalıkları AD, Nefroloji BD, Malatya, Turkey
Phone : +90 422 341 06 60
GSM : +90 530 356 18 94
E-mail : hulyataskapan@yahoo.com

INTRODUCTION

Hemodialysis patients are repeatedly exposed to heparin and are at risk for developing heparin-induced thrombocytopenia (HIT), which is the most important drug-induced immune-mediated type of thrombocytopenia (1). HIT is associated with high morbidity and mortality if not recognized (2-4). Treatment of HIT in these patients requires substitution of heparin with an alternate anticoagulant for dialysis. Alternate agents such as the heparinoids and the direct thrombin inhibitors (lepirudine, hirudine and argatroban) have been used, but careful dosing and monitoring of the anticoagulant effect is required. Despite careful dosing, hemorrhagic complications can occur with these drugs and their use is therefore limited and there are no specific antidotes available for treatment of hemorrhagic complications (5).

Fondaparinux is a synthetic pentasaccharide that catalyzes the inhibition of factor Xa by antithrombin, resulting in the inhibition of thrombin generation. It does not interact with heparin-PF4 complexes, and the formation of a sensitizing complex resulting in an HIT is not possible. Many case reports and retrospective reviews have shown that Fondaparinux can be used in the treatment of thrombosis due to HIT (7,8). Recombinant factor VIIa can be used to reverse the anticoagulant effect of fondaparinux in case of severe bleeding with fondaparinux anticoagulation (7,8). Fondaparinux, like lepirudine, is eliminated primarily through the kidneys (and is contraindicated in patients with creatinine clearance <30 ml/min), thus making the issue of appropriate dosing in dialysis patients uncertain (6-8). There is only one previous case report about its usage in dialysis patients with thrombosis (9).

We report the successful use of fondaparinux in a dialysis patient with heparin-induced trombocytopenia and deep vein thrombosis.

CASE

A 63-year-old woman was admitted to the hospital with complaints of severe weakness, nausea, vomiting, headache and dizziness. On admission her blood pressure was 150/90 mm/Hg and her blood tests showed hemoglobin 7.6 g/dl, leukocyte count 9900/mm^3, platelets 119 x10^3/mm^3, BUN 162 mg/dl, and serum creatinine 8.74 mg/dl. A Tenchkoff peritoneal catheter was inserted percutaneously for continuous dialysis treatment. However she had severe uremic symptoms during the recovery period following the peritoneal catheter insertion. A femoral hemodialysis catheter (Sentia, Ankara, Turkey) was inserted to the right femoral vein and she was started on hemodialysis. She received low molecular weight heparin (CLEXANE, enoxaparine sodium) during two consecutive hemodialysis sessions. On the fourth day after insertion of the hemodialysis catheter, she developed swelling of the right leg where the femoral hemodialysis catheter was inserted and was unable to walk. A venous doppler revealed acute thrombosis at the right main deep and surface femoral vein and the femoral hemodialysis catheter was removed. Her prothrombin time (PT), activated partial thromboplastin time (aPTT), and liver function tests were all within normal limits. In the hypercoaguation workup, the Factor V Leiden mutation was negative and Protein C and S activities were normal. Heparinization with unfractionated heparin at 500 IU/h was initiated because it was thought that the patient had venous catheter induced, acute deep femoral vein trombosis. Pulmonary tromboembolism was excluded. The platelets had decreased to 23x10^3/mm^3 on the first day of heparin infusion. When the records of platelet counts were re-eavaluted, we noticed that the platelet count had dropped from 119 x10^3/mm^3 to 80 x10^3/mm^3 after LMWH usage for two consecutive hemodialysis sessions and the deep venous thrombosis was detected on the fourth day. Table I shows the changes in platelet counts and treatment method. The diagnosis of heparin-induced thrombocytopenia was based on the clinical criteria as we could not check antibodies to HPF4, and heparin was stopped. We initiated fondaparinux, a synthetic selective inhibitor of activated factor X, for alternative anticoagulation because we had no other available specific treatment such as danaparoid, r-hirudin, argatroban at that time. Fondaparinux (ARIXTRA®, Sanofi-Syntelabo) was started at 2,5 mg every other day subcutaneously. Peritoneal dialysis was initiated with 1500 ml volume at the 15th day after the insertion of peritoneal dialysis catheter because of the preference of the patient. Platelet counts started to increase two days after the administration of fondaparinux. No bleeding or new thrombosis was observed. She was started on warfarin after her platelet count reached 100 x10^3/mm^3. Fondaparinux and oral anticoagulants overlapped for 5 days, with an international normalized ratio (INR) of over 2 for at least 2 days before fondaparinux was stopped. The patient was discharged on warfarin after 20 days. Venous doppler at the 32nd day revealed no thrombosis at the right main deep and surface femoral veins. No adverse effects were noted at day 60 of follow-up.

DISCUSSION

We first suspected deep vein thrombosis related with the femoral hemodialysis catheterization in our patient as central venous catheters placed in the femoral vein are known to cause lower extremity deep venous thrombosis in 25% of the patients (10). Allen et al. (11) found an even higher rate of overall thrombosis at 38% among patients with peripherally inserted central catheters. We initiated high dose unfractionated heparin, but observed a dramatic decrease in her platelets within a day of initiating heparin and HIT was suspected and diagnosed clinically; we could not perform the heparin-induced platelet activation test (HIPA) or check serum IgG, IgA, and IgM to heparin-platelet factor 4 complexes (HPF4) because these methods were not available in our hospital.

We do not have any information on whether the patient had previous exposure to heparin before this admission. However, when we rechecked the records of the platelet counts, we realized that the platelet count had dropped from 119 x10^3/mm^3 to 80 x10^3/mm^3 after LMWH use for two consecutive hemodialysis sessions

Table I: The changes in platelet numbers and treatment method.

Date	Hemodialysis	The number of platelets	Treatment	
27.11.2008		119 $x10^3/mm^3$		
28.11.2008				Peritoneal catheter was inserted
30.11.2008		138 $x10^3/mm^3$		
01.12.2008	1. session	136 $x10^3/mm^3$	Enoxaparine sodyum	
03.12.2008	2. session	80 $x10^3/mm^3$	Enoxaparine sodyum	
04.12.2008		80 $x10^3/mm^3$	Heparin was initiated	
05.12.2008		23 $x10^3/mm^3$ -16 $x10^3/mm^3$	Heparin was stopped	
06.12.2008	3. session	26 $x10^3/mm^3$	(2,5mg) Fondaparinux	Jugular hemodialysis catheter was inserted
07.12.2008			(2,5 mg) Fondaparinux	
08.12.2008		34 $x10^3/mm^3$		
09.12.2008		54 $x10^3/mm^3$	(2,5 mg) Fondaparinux	
10.12.2008		79 $x10^3/mm^3$		
11.12.2008		117 $x10^3/mm^3$	(2,5 mg) Fondaparinux	Warfarin was initiated

and the deep venous thrombosis was detected on the fourth day. Thereafter, we observed a further decrease in her platelet count (to 23 $x10^3/mm^3$) within a day of initiating unfractionated heparin. Two clinical entities of HIT can be distinguished. HIT type I (non immune) is characterized by a mild and transient asymptomatic thrombocytopenia that develops early (usually within the first two days) and disappears equally quickly once the heparin is withdrawn and is not associated with an increased risk of thrombosis. The second form of HIT, HIT type II, is immune-mediated and associated with a risk of thrombosis despite low platelet counts. Immune complexes composed of heparin, PF4, and IgG bind to platelet or endothelial cells and result in strong platelet activation, platelet aggregation and thrombosis (1). The platelet count in patients with pre-existing heparin-PF4 antibodies from a previous exposure and sensitization to heparin may decrease within the first 3 days or even hours after re-exposure to heparin (rapid-onset HIT). However, the onset of thrombocytopenia usually occurs 4 to 14 days after the administration of the heparin in patients receiving heparin for the first time. In delayed-onset HIT, the thrombocytopenia occurs 5 or more days after heparin withdrawal (1,5).

The guideline for "Heparin-induced thrombocytopenia: recognition, treatment, and prevention" (5) for patients receiving heparin, or who have received heparin within the previous 2 weeks, recommends excluding the diagnosis of HIT II if the platelet count falls by ≥50%, in the presence of a thrombotic event between days 4 to 14 following initiation of heparin, even if the patient is no longer receiving heparin therapy when the thrombosis or thrombocytopenia has occurred. The guideline recommends use of an alternative, nonheparin anticoagulant, such as lepirudine, argatroban, bivalirudine, or danaparoid over further UFH or LMWH therapy, and no further anticoagulation (5).

Heparin-induced antibodies have been reported to occur in 0-12% of hemodialysis (HD) patients. It is reported that HIT II typically appears 5-8 days after initiation of heparin therapy in patients on hemodialysis (3). The following criteria for HIT with thrombosis in hemodialysis patients were also used by some authors: (a) clotted fibers in the dialyzer, with clot formation in drip chambers, (b) increased extracorporeal circuit pressure or occluded extracorporeal circuit observed under the prolongation of activated partial thromboplastin time of 1.5 to 2 times the baseline by continuous heparinization, (c) repeated and progressive increase of the severity of clot formation, and (d) acute thrombocytopenia with more than 20% reduction of platelet count. The detection of antibodies to heparin-platelet factor 4 complex (HPF4) is yet another diagnostic feature of HIT but is not mandatory for the diagnosis (2-4).

It seems that our patient had type II HIT; deep vein thrombosis could be related to HIT and localized vascular

injury may have predisposed to the thrombotic events in HIT II. We initiated fondaparinux because we had no other available specific treatment such as danaparoid, r-hirudin, argatroban for HIT at that time. We gave half of the normal dose of 2.5 mg every second day because 50–75% overall of fondaparinux is eliminated by the kidneys. We did not see any bleeding problem or any complication during fondaparinux use. We switched the patient from hemodialysis to peritoneal dialysis because of the patient preference.

In conclusion, one important cause of deep venous thrombosis is heparin-induced thrombocytopenia (HIT), and should be considered in patients with an even slightly reduced platelet count on dialysis. Heparin should be withdrawn if HIT is suspected. Fondaparinux can be a useful agent to treat HIT in dialysis patients. Peritoneal dialysis may serve as an alternative treatment for ESRD patients suffering from HIT.

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