Massive Pulmonary Embolism in a Patient with Heparin Induced Thrombocytopenia: Successful Treatment with Dabigatran

Heparin İlişkili Trombositopenili Bir Hastada Masif Pulmoner Emboli: Başarılı Dabigatran Uygulaması

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Abstract
Heparin induced thrombocytopenia (HIT) is a rare, potentially fatal, immune-mediated complication of heparin therapy, associated with thrombosis and thrombocytopenia. In this study, a successful dabigatran administration in a case with massive pulmonary thromboembolism (mPTE) and HIT is presented. 57 years-old female, who was receiving low molecular weight heparin (LMWH) (0.4 mL once a daily, S.C. for 11 days) due to total knee replacement, was referred to our clinic with the hypotension and syncope attacks. Her echocardiography and pulmonary CT angiography findings were consistent with mPTE. We detected a serious decrease in her platelet count highly suggestive for HIT (plt: 54x10³/µL). LMWH was discontinued and dabigatran was started (150 mg twice daily). After platelet count increased over 150x10³/µL, dabigatran was switched to warfarin. Since heparin is widely used in medicine, all physicians need to be aware of this life threatening complication of heparin. Replacing heparin with an alternative anticoagulant such as dabigatran may become a life-saving strategy especially in case of HIT complicated with mPTE.

Keywords: Dabigatran, heparin, low molecular weight heparin, new oral anticoagulants, pulmonary embolism.

Öz
Heparin ilişkili trombositopeni (HIT), heparin tedavisinin nadir ancak ölümcül olabilen immun aracılı komplikasyonu olup, tromboz ve trombositopeni ile seyreden. Burada HIT ve masif pulmoner tromboemboli (mPTE) olgusunda başarılı Dabigatran (oral trombin inhibitörü) uygulaması sunulmaktadır. Total diz replasmani nedeniyle profilaktik düşük moleküler ağırlıklı heparin (DMAH, 0,4 mL 1x1, S.C., 11 gün) tedavisi altında olan 57 yaşındaki kadın hasta hipo-tansiyon ve senkop yakınmalarnıyla klinijimize sevk edildi. Ekokardiyografi ve pulmoner BT anjiyografi bulguları mPTE bulguları ile uyumlu idi. HIT tanısını düşündüren tromboz sayılardan belirgin düşme tespit edildi (plt: 54x10³/µL). Aldığı DMAH ve warfarin tedarisi hemen kesilerek Dabigatran başlandı (2x150 mg). Trombosit sayısı 150x10³/µL üzerine çıktıktan sonra dabigatran warfarin ile değiştirildi. Tüm hekimler tıpta yaygın olarak kullanılan heparinin hayatı tehdit eden bu komplikasyonunu akılda tutmalıdır. Heparinin dabigatran gibi alternatif bir antikoagulan ile değiştirilmesi mPTE ile komplike olmuş HIT oğullarında hayat kurtaran bir strateji olabilir.

Anahtar Kelimeler: Dabigatran, heparin, düşük moleküler ağırlıklı heparin, yeni oral antikoagülanlar, pulmoner emboli.

Introduction

Heparin induced thrombocytopenia (HIT) is a rare but potentially fatal, antibody-mediated adverse drug reaction of heparin therapy. It is caused by IgG antibodies that recognize the complex of heparin-platelet factor 4 (PF4) and associated with devastating thromboembolic complications, including pulmonary embolism (PE), ischemic limb necrosis necessitating limb amputation, acute myocardial infarction, and stroke [1]. HIT frequency differs depending on the type and duration of usage of heparin. It occurs among 1% of hospitalized patients receiving heparin, and 4.8% and 0.6% of orthopaedic surgery patients receiving postoperative unfractionated heparin (UFH) and low molecular weight heparin (LMWH), respectively [2]. Mortality rate is as high as 20%, and earlier diagnosis and treatment have resulted in a better prognosis, with mortality and major morbidity of 6% to 10% [1]. Here we want to present a case of dabigatran administration in a patient with massive pulmonary thromboembolism (mPTE) and HIT, which occurs under the prophylaxis of unilateral knee replacement with LMWH.
Case Report

A 57 years-old female patient was referred to our clinic with the diagnosis of mPTE. She had shortness of breath and chest tightness and suffered from syncope attacks. She was obese, hypertensive for 14 years and received LMWH (enoxaparin 0.4, 1x1 subcutaneously) due to prophylaxis of unilateral total knee replacement for 11 days. All of her laboratory test results and platelet counts were found to be within normal limits before (313x10^3/µL) and after (181x10^3/µL - 203x10^3/µL) surgery. At the 11th day of prophylaxis, postoperative 5th day, platelet level decreased more than 50% and liver function tests increased (AST: 1570 IU, ALT: 770 IU), and echocardiographic examination revealed enlarged right side of the heart, SPAP: 70 mmHg and a freely moving 50x10 mm echogenic image (thrombus?) in the right atrium. Next day, she was referred to our clinic after changing her treatment to warfarin plus LMWH (enoxaparin 0.8 mL, S.C., twice in daily). On the admission day to our clinic, her physical examination showed that TA: 90/60 mmHg, pulse: 102/min., fever: 36.4°C, respiratory rate: 44/min., O₂ Sat: 88% and, a systolic murmur at tricuspid valve. All other physical system examinations were within normal limits. Routine hemogram revealed that WBC: 13.2x10^3/µL, Hb: 11.9 g/dL, Htc: 35.5%, Plt: 66x10^3/µL-54x10^3/µL, and D-Dimer: 4490 ng/mL. Serum electrolytes and renal function tests were within normal limits, but liver function tests suggested for a toxic or ischemic liver abnormality (AST: 1834 U/L, ALT: 912 U/L, LDH: 2621 mg/dL, total bilirubin: 2.21 mg/dl, direct bilirubin: 0.7 mg/dL, GGT: 640 U/L, prothrombin time: 25.9 sec., INR: 2.29). Chest x-ray revealed increased cardiothoracic index and bilateral pulmonary artery enlargement. Arterial blood gas analyses showed mild hypoxia and respiratory and metabolic alkalosis (pH: 7.47, PaCO₂: 36.2 mmHg, PaO₂: 48.8 mmHg, HCO₃: 27.3 mmol, O₂ Sat: 86.3%). In order to evaluate the extension of PTE, pulmonary CT angiography was performed and it showed bilateral widespread thrombi located all lobar and segmental pulmonary artery branches (pulmonary vascular obstruction index: 20) (Figure 1). Doppler ultrasonography of lower limbs also showed an acute thrombus at right popliteal vein. These clinical and laboratory findings were highly suggestive for the diagnosis of HIT according to 4T scale (8 points). Unfortunately, we could not determine the presence of HIT antibody (heparin-PF4 complex) with functional or immunological assays because of unavailability of our laboratory conditions. LMWH and coumadin were discontinued immediately and dabigatran (an oral thrombin inhibitor) was started (150 mg twice daily). A few days later, her platelet count (Figure 2) increased and liver function tests decreased to the normal ranges. Her vital signs, oxygenation status and symptoms were also improved gradually. We switched to warfarin therapy after platelet value increased over 150x10^3/
μL. After two days at the therapeutic INR level, dabigatran was stopped and the patient was discharged from hospital. We recommended her lifelong folic acid replacement and anticoagulant therapy due to her genetic mutational test results showing both prothrombin 20210A and methylene-tetrahydrofolate reductase (MTHFR) C677T heterozygous mutations.

Discussion

There are two different types of heparin-induced thrombocytopenia. The first one, HIT type I (non-immune HIT), has no increased risk of thrombosis and effects up to 10% of patients. Although the mechanism of HIT type I is still unknown, it usually occurs within the first two days of heparin treatment and leads to a mild, transient and asymptomatic thrombocytopenia (rarely <100,000/mm³). The second one, HIT type II, is rare but potentially fatal, immune-mediated complication of heparin therapy. It is caused by IgG antibodies that recognize the complex of heparin–platelet factor 4 (PF4) and associated with thrombosis and thrombocytopenia. It typically develops 5 days after starting heparin therapy, but can occur sooner with recent heparin exposure (within 24 hours) or rarely have a delayed onset (3 weeks after cessation) [1, 2].

Heparin induced thrombocytopenia antibodies may develop up to 8% of heparinized patients, and approximately 1-5% of them have thrombocytopenia [3]. Although thrombocytopenia is the most common presenting feature of HIT, in up to 25% of patients with HIT, the development of thrombosis precedes the development of thrombocytopenia [4]. The most common complication of HIT is venous thrombosis and represents itself as a DVT and/or PTE, the most common life-threatening thrombotic event, in 17% to 55% of untreated patients with a mortality rate from 18.8 to 50% [1, 3, 5, 6]. Although it may not be possible to differentiate between the development of HIT in a patient with PTE and development of thromboembolism due to HIT, we thought that our patient experienced a mPTE attack as a complication of HIT. Our hypothesis is supported by the fact that she had thrombocytopenia and she was also receiving DMAH for prophylactic purpose before the mPTE symptoms began. However, unfortunately the presence of HIT was undiagnosed until the patient had thrice hypotension and syncope attacks. In patients with HIT arterial thrombotic events such as myocardial infarction, thrombotic stroke or major limb ischemia may also occur, but less often (from 3%-10%) [1]. No arterial thrombotic event was detected in our case. Our patient had severe ischemic hepatic failure, which might occur from multiple causes such as systemic hypotension, hepatic artery thrombosis or HIT associated hepatic necrosis-DIC syndrome [7].

Heparin induced thrombocytopenia frequency differs depending on the type and duration of usage of heparin, gender, history of recent heparin exposure and patient setting (medical vs surgical patients). It is generally associated with unfractionated heparin therapy and occurs among 1% of hospitalized patients receiving heparin, but infrequently with LMWH treatment [6]. In our case, although a LMWH has been used at prophylactic dose, its long-term use may cause an increased risk. In orthopaedic surgery, patients receiving postoperative prophylactic heparin may experience HIT approximately 10 times more with UFH compared to LMWH.

Any decrease more than 50% in thrombocyte count in a patient treated with any kind of heparin could be HIT. Cessation of heparin and starting an alternative effective anticoagulant treatment is essentially required. The diagnosis of this clinicopathologic syndrome is based on compatible clinical picture and confirmed by in vitro demonstration of PF4/heparin antibodies using functional and immunological methods [1, 2, 8]. Although functional assays represent the gold standard in the definitive serological diagnosis of HIT, we could not perform since these assays are not readily available in our country. Instead, we used clinical 4T scoring system and found high pre-test probability of HIT [8]. In most cases, although platelet count is low, this fall cannot be tied for any other reason. As expected, we could not find any relevant clinical findings, which might be associated with thrombocytopenia such as history of transfusion or use of another drug, clinical findings of sepsis or thrombotic thrombocytopenic purpura.

In case of HIT and mPTE, managing anticoagulation can be extremely difficult and challenging due to limited therapeutic options currently available. Bivalirudin, argatroban, danaparoid and lepirudin are alternative agents for heparin, but unfortunately they are not available in our country [1, 9]. If we would not face supply problems or it can be retrieved from the market in our country, we would use fondaparinux sodium, a parenteral factor Xa inhibitor, which could be used successfully in patients with HIT [1, 10]. Apixaban and Rivaroxaban are new oral factor Xa inhibitors, but only rivaroxaban is recently approved for the treatment of acute PTE in our country [1]. Since patient’s liver function test result was consistent with toxic hepatitis, we also could not use it. Dabigatran, an oral thrombin inhibitor, is a new agent for the prevention and treatment of acute VTE and may be a viable treatment option of HIT [1, 9, 11]. Since it does not require laboratory monitoring, long-term experience of this drug is still under investigation [9]. Since dabigatran is not approved yet for the treatment of acute VTE in our country, we use it only in acute hyperthrombotic phase of VTE to bridge to warfarin after platelet value increased over 150x10⁹/µL. Insertion of a vena cava inferior (VCI) filter for the prevention...
of embolic events is controversial. Although DVT had been detected in our case, we did not consider the insertion of a VCI filter since the platelet count was very low and these devices might cause massive thrombotic event itself in the setting of acute HIT.

In conclusion, since both heparin and LMWH are widely used in medicine, all physicians need to be aware of this life threatening complication of heparin treatment. Platelets count should be monitored specially 3-5 days in those treated with any kind of heparin. In case of HIT, immediate withdrawal of heparin therapy and replacing it with an alternative anticoagulant such as dabigatran should be remembered.

**Informed Consent:** There was no need for written informed consent from the patient who participated in this study.

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