CASE REPORT

# Heparin-induced thrombocytopenia after MitraClip: A case report

## MitraClip sonrası heparinin tetiklediği trombositopeni: Olgu sunumu

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***Summary–*** Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis are potentially fatal adverse reactions to heparin therapy caused by the formation of polyclonal antibodies against the platelet factor 4-heparin complex. Fatal limb and organ damage or death may occur as a result of this immunological drug reaction. Described in this case report is the management of a patient who developed HIT after undergoing a MitraClip transcatheter mitral valve repair. The aim was to encourage clinicians to pay special attention to a frail patient who receives heparin therapy and to advise clinicians that clinical scores and laboratory tests should be used as a complement for certain diagnosis. The decision about continuation or cessation of heparin therapy is an important cornerstone for hospitalized patients with HIT.

***Özet–*** Heparinin tetiklediği trombositopeni (HTT) ve tromboz (HTTT), platelet faktör 4 (PF4)-heparin komplekslerine karşı oluşan antikorların oluşumu ile tetiklenen ölümcül bir heparin yan etkisidir. Bu immünolojik ilaç reaksiyonu hayatı tehdit eden ekstremite ve organ hasarları ile ölüme neden olabilir. Bu olgu sunumu ile MitraClip transkateter mitral kapak tamiri sonrası heparinin tetiklediği trombositopeni gelişen bir hastanın yönetimini sunmaktayız. Olgu sunumumuz ile klinikçilere, düşkün hastalarda heparin tedavisi kullanırken dikkatli olmalarını ve hastanede yatan hastaların tedavisinde önemli bir köşe taşı olan heparinin kesilmesi ya da devam edilmesi kararı verilirken klinik skorlama sistemleri ve laboratuvar testlerini tamamlayıcı olarak kullanmalarını hatırlatmayı amaçladık.

Heparin-induced thrombocytopenia (HIT) is potentially fatal adverse reaction to heparin therapy that is caused by the formation of polyclonal antibodies against the platelet factor 4 (PF4)-heparin complex. This immune reaction leads to a hypercoagulable state that increases the risk of a possibly life-threatening arterial or venous thrombosis. Clinically, HIT may manifest as skin lesions at the heparin injection site or with acute systemic reactions like chills, fever, dyspnea, or chest pain. When arterial or venous thrombosis occurs, the disorder is known as heparin-induced thrombocytopenia and thrombosis (HITT).

Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) can cause HIT; however HIT is more common with UFH. Martel et al.[1] found an incidence of HIT of 2.6% with UFH and 0.2% with LMWH in their meta-analysis.

Presently described is the case of a patient with HIT syndrome due to LMWH use after a MitraClip (Abbott Vascular, Inc., Santa Clara, CA, USA) transcatheter mitral valve repair for severe mitral regurgitation.

**Abbreviations:**

| | |
|---|---|
| *DOAC* | *Direct oral anticoagulant* |
| *HIT* | *Heparin-induced thrombocytopenia* |
| *HITT* | *Heparin-induced thrombocytopenia and thrombosis* |
| *LMWH* | *Low-molecular-weight heparin* |
| *PF4* | *Platelet factor 4* |
| *UFH* | *Unfractionated heparin* |
| *VKA* | *Vitamin K antagonist* |

## CASE REPORT

A 61-year-old man was hospitalized with acute decompensated chronic heart failure. His medical history included coronary artery bypass grafting 5 years prior, diabetes mellitus, chronic kidney disease, chronic heart failure, and interstitial lung disease. His

*Received:* August 08, 2017 *Accepted:* September 15, 2017

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current medications were acetylsalicylic acid 100 mg/day, furosemide 120 mg/day, metoprolol 100 mg/day, ramipril 10 mg/day, spironolactone 50 mg/day. The electrocardiogram results indicated a sinus rhythm with right bundle branch block (QRS duration: 120 milliseconds). A transthoracic echocardiogram and a transesophageal echocardiogram revealed left atrial and ventricular enlargement and pulmonary hypertension (systolic pulmonary artery pressure: 50 mm Hg). The ejection fraction was 30%. In addition, he had severe secondary mitral regurgitation and moderate tricuspid regurgitation. Since the patient was symptomatic despite guideline-recommended optimal heart failure therapy, and had a high surgery risk, the heart valve team decided to perform a MitraClip transcatheter mitral valve repair.

After a successful mitral valve repair procedure, the mitral regurgitation was mild to moderate. His symptomatic status improved. A weight- and age-adjusted dose of LMWH was initiated for deep vein thrombosis prophylaxis during coronary care unit follow-up. Laboratory results indicated that his platelet count declined from 229,000 $mm^3$ to 57,000 $mm^3$ on the fourth day of LMWH therapy. Thrombocytopenia was confirmed with a peripheral blood smear. Blood disorders that affect the bone marrow were not considered because the red blood cell and white blood cell counts were normal. The patient didn't have any known autoimmune disease or cancer. There were no signs of viral infection or history of drug use that could cause thrombocytopenia. Therefore, HIT syndrome was suspected. A blood sample was collected to check for antibodies of heparin complexes in an enzyme-linked immunosorbent assay (ELISA) test. The 4Ts score indicated an intermediate probability for HIT syndrome. LMWH treatment was terminated without waiting for the ELISA test results and fondaparinux was administered. Once the platelet count reached 150,000 $mm^3$, warfarin was initiated and maintained for 4 weeks as recommended in the American College of Chest Physicians (CHEST) guideline for patients with acute HIT or HITT. On the 10$^{th}$ day after heparin cessation, the platelet count had normalized and the ELISA test results corroborated the diagnosis (PF-4 antibody level ≥1.00 OD units).

The patient was discharged with no symptoms and a normal platelet count on the 12$^{th}$ day of hospitalization.

**Table 1. 4T score**

| | | | |
|---|---|---|---|
| Thrombocytopenia | Platelet count fall >50% and nadir ≥20%x$10^9$/L | | 2 |
| | Platelet count fall between 30–50% OR nadir 10–19 x$10^9$/L | | 1 |
| | Platelet count fall <30% OR platelet nadir <10x$10^9$/L | | 0 |
| Timing of platelet count fall | Clear onset between day 5–10 following commencement of heparin OR ≤1 day (if previous heparin exposure within 30 days) | | 2 |
| | Consistent with onset at 5–10 days after commencement of heparin OR onset after day 10 OR fall less than 1 day (if heparin exposure within 30–100 days) | | 1 |
| | Platelet count fall <4 days without recent exposure to heparin | | 0 |
| Thrombosis or other sequelae | New thrombosis(confirmed) OR skin necrosis OR acute systemic reaction post iv unfractionated heparin bolus | | 2 |
| | Progressive OR recurrent thrombosis OR non-necrotizing (erythematous skin lesions) OR suspected thrombosis. | | 1 |
| | None present | | 0 |
| Other causes for thrombocytopenia present | None apparent | | 2 |
| | Possible | | 1 |
| | Definite | | 0 |
| Total score | | | 0–8 |
| Pre-test probability | Low: 0–3 | Intermediate: 4–5 | High: 6–8 |

## DISCUSSION

HIT is a rare complication of heparin therapy with high morbidity and mortality. It is not just limited to thrombocytopenia; the activation of platelets also increases thrombin generation. As a result of this immunological drug reaction, fatal limb and organ damage or death may occur. HIT occurs among 1% of hospitalized patients receiving heparin and 4.8% and 0.6% orthopedic surgery patients receiving postoperative UFH and LMWH, respectively.[2] Girolami et al.[3] reported that HIT-related antibodies occurred much often more in patients who underwent cardiovascular surgery than in patients who underwent orthopedic surgery.

The point of interest for clinicians about HIT is the decision to continue using heparin as a critical anticoagulant agent or cease the heparin therapy and chose an alternative non-heparin anticoagulant. The current treatment options for HIT are argatroban, fondaparinux, and bivalirudin. In the present case, fondaparinux was used.

Since an urgent decision about the treatment strategy is required and waiting for laboratory results takes time, a clinical assessment of the probability of HIT is required. The most common pre-test probability assessment is the 4T score: thrombocytopenia, the timing of the platelet decline, the presence of thrombosis, and other potential causes of thrombocytopenia (Table 1).[4]

After a clinical assessment, other biochemical coagulation tests (activated partial thromboplastin time, anti-factor Xa) to check for heparin overdose and additional laboratory tests to confirm the HIT diagnosis using either immunological (ELISA) or functional assays (serotonin release assay) are required. Functional assays have greater specificity than immunoassays; however, many institutions offer only immunoassays, as functional assays are time-consuming and not widely available.

When the HIT/HITT diagnosis is definitive, it is important to forward manage anticoagulation in acute cases. The evidence-based CHEST guidelines recommend oral vitamin K antagonist (VKA) therapy for 4 weeks, at least in isolated HIT. If there is thrombosis as well, oral VKA therapy is continued for least 3 months.[5] VKA therapy can be initiated when the platelet level reaches $150x10^9$/L.

Recently, Tran et al.[6] published a study about the use of direct oral anticoagulants (DOACs) in the management of HIT. Their study provided a promising alternative for the management of HIT/HITT. The research indicated that use of DOACs allowed for cost savings in the areas of a reduced length of hospital stay compared with argatroban, bivalirudin, and fondaparinux. Furthermore, DOACs represent an additional non-parenteral option with similar potential benefits. Off-label use of fondaparinux for HIT has increased with experience. There is a need for further investigations about the effects of DOACs in the management of HIT. Therefore, we did not elect to use DOACs in our case.

Misdiagnosis of HIT can have adverse outcomes. McMahon et al.[7] established that misdiagnosed HIT was often inappropriately documented as a heparin allergy. Their results revealed that 68% of 239 patients with new HIT were misdiagnosed and were unnecessarily treated with an alternative parenteral anticoagulant. When the suspicion of HIT emerges, the clinician should use clinical probability scores and confirm the diagnosis with a peripheral blood smear and laboratory tests.

This case report describes the management of a patient who developed HIT after a MitraClip transcatheter mitral valve repair. We advise clinicians to pay special attention to a frail patient who receives heparin therapy, even if the therapy is limited to a flush dosage. Making the decision to continue or to cease heparin therapy is an important cornerstone for hospitalized subjects with HIT. Therefore, clinical scores and laboratory tests should be used to determine a certain diagnosis.

**Informed consent:** Written informed consent was obtained from the patient for the publication of case report and accompanying images.

**Peer-review:** Externally peer-reviewed.

**Conflict-of-interest:** None declared.

**Authorship contributions:** Concept: E.B.Ö.; Design: C.Ç.; Supervision: N.N.G.; Materials: Ö.Ç.; Data collection /or processing: Ö.Ç.; Analysis and or interpretation: Ü.Y.S.; Literature serach: Ü.Y.S.; Writing: Ö.Ç.

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*Keywords:* 4T score; heparin-induced thrombocytopenia; heparin-induced thrombocytopenia and thrombosis; platelet factor 4.

*Anahtar sözcükler:* 4T skoru; heparinin tetiklediği trombositopeni; heparinin indüklediği trombosis; platelet faktör 4 (PF4).