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Heparin induced thrombocytopenia: A case-based re-appraisal

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Abstract

Heparin-induced thrombocytopenia (HIT) is an immune mediated adverse drug reaction caused by the emergence of antibodies that activate platelets in the presence of heparin. Despite thrombocytopenia, bleeding is rare. HIT is strongly associated with thromboembolic complications involving both the arterial and venous systems. A number of laboratory tests are available to confirm the diagnosis; however, when HIT is clinically suspected, treatment should not be withheld pending the result. Fortunately, therapeutic strategies have been refined, and new and effective therapeutic agents are available. We present a case of HIT Type II. A review of HIT is presented, examining the important clinical symptoms and diagnostic indicators. The treatment of HIT is then discussed, with an emphasis on current therapies. An extensive literature review has been performed to present a comprehensive review of the causes, pathophysiology and treatment of HIT.

Introduction

There are two types of HIT described. Type I is a non-immune, mediated, asymptomatic, transient drop in platelet count that occurs in some heparin treated patients. It is typically characterized by a lesser fall in platelet count within the first two days after heparin initiation and often returns to normal with continued heparin administration [1,2].

Type II (HIT-II) is an immune-mediated disorder characterized by the formation of antibodies against heparin-platelet factor 4 complexes. Since The frequency of HIT varies from 0.5% to 5%, depending on the patient population studied [3]. A meta-analysis noted an incidence of 2.6 percent [4].

It has recently been proposed that the term "HIT type I" be changed to "non-immune heparin associated thrombocytopenia" and that the term "HIT type II" be changed to "HIT" to avoid confusion between the two syndromes

Case history

A 75 years old man was recently discharged following temporary pacemaker for complete heart block. The patient presented on discharge day 12 to our department of cardiology for permanent pacemaker with thrombocytopenia. The patient admitted to having shortness of breath, prior to admission in other hospital ,where he was diagnosed to have complete heart block with severe LV systolic dysfunction .He was put on TPI, and given low molecular weight heparin for DVT prophylaxis, as patient was not affordable for permanent pacemaker ,he remained on LMWH for around 10 days, after 10 days his platelet count was 60000, so he was referred to our department for further management. The patient denied having bloody or black stools. On admission we repeated his complete blood count, Hb-7, PC-7000, so we postponed the PPI, and sent immunoassays test for antibodies reactive against PF4/heparin or PF4/polyvinyl sulfonate, which came out to be positive.

Physical examination of the patient revealed man in mild distress. His blood pressure was 122/77 mmHg with a pulse of 60beats per minute (on TPI). he was breathing 16 times/minute with an oxygen saturation of 100%. He was afebrile. On head and neck examination, her pupils were equal, round, reactive to light and accommodation. His sclera was anicteric, revealing mild pallor. On cardiovascular exam, heart sounds were audible with regular rate and rhythm, normal S1 and S2, no murmurs. His lung fields are clear, with B/L vesicular breath sound. His extremities were symmetric without tenderness, cyanosis or pedal edema. His pulses were present and palpable bilaterally.

Her blood chemistry panel revealed a serum sodium of 132 mmol/L, potassium of 3.6 mmol/L, chloride of 102 mmol/L, bicarbonate of 22 mmol/L, BUN of 15 mg/dL, creatinine of 1.0 mg/dL and glucose of 92 mg/dL. Her Leukocyte count was 16.0 $x10^3$ per µL, with 83% neutrophils. Her hemoglobin was 7.1 g/dL, hematocrit 29.5% and platelet count was $5x10^3$ per µL. Arterial blood gas sampling showed a pH of 7.48, PaCO2 of 33 mmHg, PaO2 of 77 mmHg, and 97% and FiO2 of 21%. Chest x-ray normal.

On hospital day 2, the patient reported improvement of symptoms. Vital signs were within normal limits. Leukocyte count was 8.0 $x10^3$ per µL. Hemoglobin was 8.6 g/dL, hematocrit was 26% but platelet count was $3x10^3$ per µL. On hospital day 5. Leukocyte count was 9.9 $x10^3$ per µL, hemoglobin was 8.5 g/dL. Hematocrit 24.7%, platelet count was 20 $x10^3$ per µL. Platelets on admission were 60 $x10^3$ per µL. The patient was diagnosed with HIT. LMWH stopped, permanent pacemaker implantation was done in order to avoid any further need of DVT prophylaxis.

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Discussion

Clinical presentation

The initial sign of HIT usually is the development of thrombocytopenia. The major manifestations of venous thrombosis are deep vein thrombosis (DVT) and pulmonary embolism (PE). Other manifestations include venous limb gangrene and cerebral sinus thrombosis [5]. Upper extremity DVT has also been described in HIT, but it is less common than lower extremity DVT [6]. Most upper extremity DVT occurred in patients with central venous catheters (CVC) and at the CVC site. Arterial thrombosis is less common in HIT but can lead to significant clinical complications including stroke, myocardial infarction, acute limb ischemia from peripheral arterial occlusion, or kidney infarction. White clot syndrome refers to platelet-rich aggregations leading to arterial thrombosis [7]. Finally, skin necrosis on fat-rich areas such as the abdomen are commonly seen in HIT. Similar to warfarin-induced skin necrosis, erythema is followed by purpura and hemorrhage leading to necrosis, however there are no deficiencies in anticoagulants [8].

Onset

There are three patterns for the onset of thrombocytopenia related to heparin exposure described [1,9]. The most common pattern, typical-onset of HIT, occurs in 4 - 10 days after initial exposure to heparin with a fall in platelet count of > 50 percent. The second pattern, delayed onset HIT, occurs a mean of 9 days after heparin stopped, but can be as long as 40 days [10-12]. Delayed HIT may account for 13 - 15% of all cases of HIT [13]. Early onset of HIT may be seen in about 30% of patients with persistent antibodies due to heparin therapy within the previous one to three months. The median time of platelet fall was 10.5 hours after the start of heparin administration [14].

Risk factors

The risk of developing HIT is related to many factors, including the type of heparin product administered, route of administration, duration of therapy, patient population and previous exposure to heparin [15]. The use of unfractionated heparin (UFH) rather than low molecular weight heparin (LMWH), surgical rather than medical patients and female sex, have been associated with greater risk of developing HIT. Some surgical populations, such as cardiac transplant or neurosurgery patients have somewhat higher risk [16,17]. Antibodies are more likely to form in patients undergoing cardiac surgery with an incidence as high as 15 to 20% than in orthopedic patients. Interestingly, orthopedic surgery patients compared with cardiac surgery patients, who are receiving unfractionated heparin post-operatively are less likely to develop heparin PF4-antibodies (14% versus 50% by antigen assay), yet more likely to develop HIT (4.9% versus 1.0%) [18,19]. HIT was rarely found among patients less than 40 years of age as well as in women following delivery [20].

Pathophysiology

Following administration of heparin, a heparin neutralizing protein present within platelets (PF4) binds to heparin. This complex provokes the formation of antibodies, IgG and IgM, which bind to the heparin-PF4 complex. This leads to platelet activation. Platelet activation leads to release of more PF4 with subsequent positive feedback. Also, platelet activation leads to platelet aggregation and premature removal which results in thrombocytopenia, release of micro-particles with pro-thrombic activity. Microvascular endothelial cells are activated, resulting in the release of interleukin 6, von Willebrand factor, and other adhesion molecules.

Diagnosis

Since time of onset can range between hours to several weeks, clinical suspicion for HIT is important in recognizing and starting therapy. The diagnosis of HIT is made on clinical grounds since assays generally take a long time, whereas immediate therapy is critical to avoid often fatal complications of HIT. The following clinical scenarios should raise clinical suspicion in any patient received LMWH: onset of otherwise unexplained thrombocytopenia, venous or arterial thrombosis associated with thrombocytopenia, a platelet count that has fallen 50 percent or more from a precious value, necrotic skin lesions at heparin injection sites or acute systemic reactions subsequent to IV heparin bolus administration [21].

The criteria used in the diagnosis of HIT include [22]: (1) Normal platelet count before commencement of heparin. (2) Thrombocytopenia defined as a drop-in platelet by 30% or a drop of 50% from patient baseline. (3) Onset of thrombocytopenia typically 5 - 10 days after initiation of heparin treatment. (4) Acute thrombotic event. (5) Exclusion of thrombocytopenia after cessation of heparin. (6) HIT antibody seroconversion.

Diagnosis can be made utilizing a clinical scoring system based on the pretest probability of HIT known as the 4Ts: Thrombocytopenia, Thrombosis, Timing, and other causes [23]. A score is determined based on the scoring system summarized in Table 1. A score from 0 - 3 denotes low probability, 4 - 5 denotes an intermediate probability and 6 - 8 denotes a high probability of HIT.

Diagnostic tests

Two general types of assays can be used to detect antibodies [24,25]. Most widely commercial enzyme immunoassays test for antibodies reactive against PF4/heparin or PF4/polyvinyl sulfonate. ELISA test is very sensitive (91% to > 97%), whereas a negative test strongly suggests the absence of HIT. In contrast, platelet activation assays detect HIT antibodies upon their platelet-activating properties. The gold standard for diagnostic tests for HIT is the 14 C-serotonin release assays. A

Table 1. Pretest probability of HIT

Pretest probability of HIT	Score
Thrombocytopenia	
Platelet count fall > 50% and nadir > 20,000	2 points
Platelet count fall 30 - 50 % or nadir 10 to 19,000	1 point
Platelet count fall < 30% or nadir < 10,000	0 points
Timing of platelet count fall	
Clear onset between days 5 and 10 or platelet count fall at ≤ 1 day if prior heparin exposure within the last 30 days	2 points
Consistent with fall at 5 to 10 days but unclear (eg, missing platelet counts), onset after day 10, or fall ≤ 1 day with prior heparin exposure within 30 to 100 days	1 point
Platelet count fall at < 4 days without recent exposure	0 points
Thrombosis	
Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus	2 points
Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis which has not been proven	1 point
None	0 points
Other causes	
Nonapparent	2 points
Possible	1 point
Definite	0 points

positive test is the release of 14 C-seroton when therapeutic (0.1 U/ML) concentrations are used, rather than high (100 U/mL) concentrations. A positive test was strongly associated with thrombocytopenia starting 5 or more days after heparin exposure [26]. Heparin-induced platelet aggregation assay is a specific test for diagnosing HIT, but lacks sensitivity [25]. A positive test shows low background aggregation with no added heparin, aggregation with the addition of a low concentration of heparin, and absent aggregation with high heparin concentration.

Current therapies

When the diagnosis of HIT is confirmed, therapeutic doses of alternative non-heparin anticoagulants are usually required. Heparin treatments must be stopped immediately including heparin-bonded catheters and heparin flushes. Patients remain at risk for thrombosis from heparin cessation alone. Patients should be given a non-heparin anticoagulant. Coumadin should not be given. Prophylactic platelet transfusions should not be given [11].

Direct thrombin inhibitors

Direct thrombin inhibitors which include Bivalirudin, Argatroban and Lepiridin, directly inhibit procoagulant and prothrombotic actions of thrombin. They do not require a cofactor to inhibit thrombin. They are active against both free and clot-bound thrombin. They do not interact with or produce heparin dependent antibodies.

Conflicts of interest

The authors declare there is no conflicts of interest, and no funding has been received from any source for publication of this manuscript. The article has not been submitted anywhere else.

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