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Heparin-induced Thrombocytopenia: A Narrative Review of Clinical Implications

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Abstract

Heparin-induced thrombocytopenia is a rare immune-mediated complication of heparin therapy, characterized by a decrease in platelet count by more than 50% of the baseline. Typically occurs between 5 to 10 days after the initiation of heparin. Incidence in the United States ranges from 0.2% to 3.0%, depending on the population studied and the diagnostic criteria used. HIT has been categorized into two types: HIT type I and II. While HIT type I is a benign, non-immune mediated response presenting with mild self-limited thrombocytopenia, HIT type II is a severe, immune-mediated, potentially fatal complication that requires urgent diagnosis and management. Moreover, Type II is the most common form of HIT. Signs and symptoms may include a sudden onset of pain, redness, and swelling or ecchymosis in extremities. For diagnosis, the 4Ts score is a widely used clinical scoring system that can help assess the probability of HIT based on the timing of thrombocytopenia onset, degree of thrombocytopenia, presence of thrombosis, and other clinical factors. Diagnostic confirmation can be pursued with the help of immunoassays or functional assays such as ELISA and/or SRA. The first step in managing HIT is to discontinue all heparin exposure. Secondly, non-heparin anticoagulation medication must be initiated quickly. As a final step, it may be necessary to switch from parenteral to oral anticoagulation following the resolution of HIT.

Abbreviations: HIT: Heparin-Induced Thrombocytopenia; PF4: Platelet Factor 4; DIC: Disseminated Intravascular Coagulation; ELISA: Enzyme-Linked Immunosorbent Assay; SRA: Serotonin Release Assay; LMWH: Low Molecular Weight Heparins; UFH: Unfractionated Heparin; GAGs: Glycosaminoglycans; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; CVC: Central Venous Catheter; HEP: Heparin-Induced Thrombocytopenia Expert Probability; HIPA: Heparin-Induced Platelet Activation Assay; DOAC: Direct Oral Anticoagulant; IVIG: Intravenous Immunoglobulin

Keywords: Heparin-induced thrombocytopenia; Heparin; Prevention; Diagnosis; Treatment

Introduction

Heparin-induced thrombocytopenia (HIT) is a rare immune-mediated complication of heparin therapy, characterized by a decrease in platelet count by more than 50% of the baseline, typically occurring between 5 to 10 days after the initiation of heparin therapy. HIT is a rare but potentially fatal condition in approximately 0.2-5% of patients exposed to heparin. There are two types of HIT: type 1 and type 2. Type 1 HIT is a mild, non-immune-mediated thrombocytopenia that occurs within the first 2 days of heparin therapy and typically resolves spontaneously without any sequelae. Type 2 HIT is an immune-mediated reaction that occurs 5 to 10 days after heparin exposure and is associated with the formation of platelet-activating antibodies, which can lead to thrombotic complications. Several risk factors have been identified for HIT, including prolonged exposure to unfractionated heparin, recent surgery, female gender, and history of HIT. While

the exact etiology of HIT is not well understood, it is thought to be caused by the formation of antibodies against heparin-PF4 complexes, leading to platelet activation, aggregation, and thrombus formation.

Patients with HIT may present with various symptoms, including thrombocytopenia, skin necrosis, and thrombotic complications such as deep vein thrombosis, pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation (DIC), death. The diagnosis is based on clinical suspicion and laboratory tests, including platelet factor 4 (PF4)/heparin enzyme-linked immunosorbent assay (ELISA) and serotonin release assay (SRA). Prevention of HIT involves careful monitoring of patients receiving heparin therapy, particularly those with known risk factors. In addition, alternative anticoagulants, such as direct oral or fondaparinux, may be considered in patients at high risk of developing HIT. The mainstay of treatment for HIT is the prompt cessation of heparin therapy and the initiation of alternative anticoagulation. In addition, patients with thrombotic complications may require treatment with thrombolytics or mechanical thrombectomy. In severe cases, treatment with immunoglobulins or plasmapheresis may be considered. The purpose of this narrative review is to enhance the overall comprehension of this uncommon but potentially fatal medical condition utilizing current literature evidence.

Epidemiology

Heparin-Induced Thrombocytopenia is a rare but potentially life-threatening complication of heparin therapy. According to epidemiological studies, the incidence of HIT in the United States ranges from 0.2% to 3.0%, depending on the population studied and the diagnostic criteria used [1]. HIT is more common in patients receiving unfractionated heparin than those receiving low molecular weight heparin. HIT risk factors include prolonged heparin exposure, female gender, and underlying conditions such as malignancy and autoimmune disease. Early recognition and prompt management of HIT are critical to prevent complications such as thrombosis and bleeding [2,3].

Etiology & Pathogenesis

Heparin is a negatively charged sulfated glycosaminoglycan with a high binding affinity for platelet factor-4 (PF4) [4]. Low molecular weight heparins (LMWH), molecular weight 2000–10 000 Daltons (Da), are produced by chemical or enzymatic processes from unfractionated heparins (UFH). UFH is a heterogeneous mixture of negatively charged sulfated glycosaminoglycan (3000-30 000 Da) derived from animal sources [5]. PF4 is a positively charged, heparin-neutralizing protein synthesized by megakaryocytes and stored in platelet alpha-granules. When platelets are activated at sites of vascular injury, PF4 is released locally and binds to negatively charged heparin-like GAGs, such as heparan sulfate, on the endothelial cell surface [6]. When heparin binds with PF4, it undergoes a conformational change and becomes immunogenic, generating heparin–PF4 antibodies (HIT antibodies), most frequently IgG. The heparin–PF4–IgG multimolecular immune complex then activates platelets via their FcγIIa receptors, causing the release of prothrombotic platelet-derived microparticles, platelet consumption, and thrombocytopenia. These microparticles, in turn, promote excessive thrombin generation, frequently resulting in thrombosis. In addition, the antigen–antibody complexes also interact with monocytes, leading to tissue factor production, and antibody-mediated endothelial injury may occur. Both of these latter processes may contribute further to the coagulation cascade activation and thrombin generation [7].

Table 1: Comparison of HIT types.

	HIT Type 1	HIT Type 2
Severity	Typically mild and transient	A severe and potentially life-threatening reaction to heparin with an increased risk of thrombosis.
Mechanism	Non-immune mediated, direct platelet activation by heparin.	Antibody-mediated, with heparin-induced formation of antibodies against heparin-PF4 complexes.
Platelet count decrease	Mild to moderate decrease.	Moderate to severe decrease.
Onset	Within the first 2 days of heparin therapy.	It occurs 5 to 10 days after heparin exposure.
Thrombotic complications	Rare, usually asymptomatic.	Common, including DVT, PE, DIC.
Diagnostic tests	Clinical suspicion and laboratory tests (SRA and ELISA).	Clinical suspicion and laboratory tests. Serotonin-release assay (SRA) and the enzyme-linked immunosorbent assay (ELISA).
Treatment	Discontinue heparin.	Discontinue heparin and initiate alternative anticoagulation.
Prognosis	Excellent. Platelet count returns to normal within a few days without complications.	Poor, with a high risk of thrombotic complications and mortality without appropriate treatment.

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HIT has been categorized into two types: type I and II. HIT type I is a non-immune mediated response to heparin therapy. Its typical presentation includes mild thrombocytopenia (rarely below 100.000/mm3) within the first two days of treatment. It is a self-limited direct effect of heparin and normalization of platelet count occurring spontaneously without discontinuation of therapy [8]. On the other hand, HIT type II is an immune-mediated adverse effect. It represents a potentially catastrophic complication in which heparin administration must be discontinued as soon as possible at the time of clinical suspicion [9]. It commonly develops after five to ten days of treatment and manifests with more severe thrombocytopenia (<100.000 /mm3) or a decrease in platelet count to less than 50% of baseline values [10]. HIT type II occurs with a frequency of 0.5% to 5% of patients treated with unfractionated heparin. Risk factors for HIT type II can be categorized into drug- or host-related factors. Host-related risk factors include sex and age. According to Warkentin et al., there is a higher predisposition - twice the risk - for HIT development in females than in males [11]. An overview of the differences between HIT types 1 and 2 can be found in (Table 1).

Clinical presentation

Thrombocytopenia is the hallmark of HIT and is typically associated with exposure to heparin temporally. The most frequent indication of thrombocytopenia in HIT is a decline in platelet count, which occurs at least four days after heparin exposure and generally presents 5 to 14 days after exposure. In addition to thrombocytopenia, HIT causes a hypercoagulable state, and venous, arterial, or micro thrombosis may occur. Lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE), upper extremity central venous catheter (CVC)-associated DVT, splanchnic vein thrombosis, and cerebral vein/dural sinus thrombosis are all associated with HIT [12]. The signs and symptoms of HIT may include a sudden onset of pain, redness, and swelling in an arm or leg, as well as the development of ecchymotic lesions. Patients may also experience weakness, numbness, or pain with the movement of the affected limb. A rash or sore may also develop at the injection site following a heparin shot. Chills, fever, hypertension, tachycardia, shortness of breath, and chest pain may also occur [12].

Despite thrombocytopenia, bleeding is not classically associated with HIT. However, a recent study of 310 patients with suspected HIT found that significant bleeding occurred in 40.6% of patients and was no less common in HIT+ patients (40.9%) [13]. The most common type of bleeding is gastrointestinal, although intracranial hemorrhage, retroperitoneal bleeding, and other types of bleeding may occur. Less frequently, patients with HIT may develop heparin-induced skin necrosis, limb gangrene, or an anaphylaxis-type reaction following a heparin bolus. Rarer and perhaps under-recognized manifestations of HIT include adrenal failure/adrenal hemorrhage secondary to adrenal thrombosis and flap failure [12,14].

Diagnosis

Diagnosing HIT remains challenging due to the rising use of UFH/LMWH and the frequency of thrombocytopenia, especially among critically ill patients. Added to this are the difficulties caused by a poor understanding of the pathogenesis of this condition. Heparin-Induced thrombocytopenia cannot be diagnosed by clinical features or laboratory parameters alone but by combining both. A presumptive/suspected diagnosis can be established based on clinical findings (thrombosis, skin necrosis, etc.) and low platelet counts. Clinical manifestations of HIT can include a myriad of features- Thrombosis (DVT, PE, Cerebral veins, Dural thrombosis, Bleeding (less frequent than thrombosis), limb gangrene, Adrenal hemorrhage or insufficiency (often secondary to thrombosis), and occasionally even anaphylaxis type reactions [15]. The 4Ts score is a widely used clinical scoring system that can help assess the probability of HIT based on the timing of thrombocytopenia onset, degree of thrombocytopenia, presence of thrombosis, and other clinical factors [16-18]. Based on the clinical scoring of the 4Ts score/criteria, patients can be classified as low, intermediate, or high-risk categories [19]. Recently, a newer scoring system called the HIT expert probability (HEP) score has been developed by HIT experts and shown to have similar efficacy to 4Ts scoring [20,21].

In individuals with a presumptive diagnosis of HIT (positive pre-test score), confirmation can be sought with the help of Immunoassays or Functional assays [22]. These specialized biochemical tests can detect the presence of PF4 antibodies or antigen-antibody complexes that underlie the pathogenesis of HIT. Currently, the highest diagnostic sensitivity and specificity is awarded to Functional Washed Platelet Assays and Serotonin Release Assays (SRA)- tests that assess platelet activation in the presence of controlled fractions of patient serum, donor platelets, and heparin [23-25]. The SRA and ELISA are the most commonly used laboratory tests for HIT diagnosis. SRA is considered the gold standard, with a sensitivity and specificity of approximately 95% and 98%, respectively. However, it is a technically challenging and time-consuming assay and is not widely available. The ELISA is a more straightforward and widely available test, with a sensitivity and specificity of approximately 80-90% [16,17]. Other laboratory tests that can support the diagnosis of HIT include the heparin-induced platelet activation assay (HIPA), the platelet factor 4 (PF4)/heparin enzyme immunoassay, and the functional assay for heparin-induced platelet antibodies (HIPA-F). However, these tests have lower sensitivity and specificity than the SRA and ELISA [18].

Treatment & Prognosis

The suspicion index for diagnosing HIT is crucial in management since misdiagnosis raises the risk of bleeding and thrombosis. Using the 4Ts score helps us to classify individuals in different risk groups according to the likelihood of HIT [26,27]. For

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example, detecting HIT in patients with a low likelihood increases the risk of bleeding; failing to diagnose it when it is highly likely puts patients at risk of thromboembolic events [28]. The risk of thrombotic events following heparin withdrawal over the first 24 hours might range from 40% to 60%, posing a life-threatening situation [29,30]. A combination strategy using the 4Ts score and PF4/H-PaGIA is used to lessen the possibility of missing instances [27].

The first step in preventing HIT is to discontinue all heparin exposure; platelet transfusion may worsen the hypercoagulable state, resulting in additional thrombosis, and is thus not recommended until surgical intervention or severe thrombocytopenia is required [29,27]. Nevertheless, discontinuing heparin will not prevent antibody-mediated platelet activation leading to thrombosis [31]. Additionally, the time to discontinue heparin has shown no difference in the outcome since early heparin discontinuation is insufficient to prevent thrombotic events [30]. Non-heparin anticoagulation medication must be initiated quickly, which raises the question of which non-heparin anticoagulant is optimal for each patient. HIT has various treatment options, including direct thrombin inhibitors like argatroban, bivalirudin, fondaparinux, or direct oral anticoagulants (DOACs) like apixaban, rivaroxaban, or dabigatran [28,32]. Before prescribing an anticoagulant, there are some conditions to consider, as might affect the pharmacokinetics of the drugs, conditions such as chronic kidney disease, individuals that might need an invasive procedure, liver disease, or multiple organ dysfunction. Therefore, anticoagulant therapy will need a dose adjustment. (Table 2) depicts a summary of the different types of non-heparin anticoagulants. Argatroban, a thrombin inhibitor drug, is associated with a decrease in the occurrence of a thrombotic event and death from thrombosis [33]. It also has a short half-life, which means it can be discontinued quickly if required, either because of bleeding or the need to initiate invasive procedures [34]. However, this drug is metabolized in the liver, so it requires an adjustment in the initial dosage and multiple controls in patients with hepatic dysfunction whose serum levels of total bilirubin are higher than 1.5 mg/dL [35]. In patients with liver disease, another option, a hirudin analog called bivalirudin, has been shown to decrease the risk of subsequent thrombotic events. However, argatroban is associated with a lower risk of bleeding [36].

Table 2: Non-heparin anticoagulants.

Agent	Characteristic	Dosing	Special considerations
Argatroban	Method of administration: Parental Elimination: Hepatobiliary Half-life: 40-50 min	Normal hepatic function: 1-2 mcg/Kg per minute by continuous IV infusion. Hepatic dysfunction: 0.5-1.2 mcg/Kg per minute Renal dysfunction: < 2 m g/kg/min IV	Hepatic metabolism, it should be adjusted in hepatic dysfunction [44]. It is appropriate in critical ill patients and can be used in renal impairment [46].
Bivalirudin	Method of administration: Parental Half-life: 25 min Elimination: Renal (20%)	Initial dose: 0.15 mg/kg per hour Hepatic dysfunction and or renal dysfunction: 0.03 -0.05 mg/kg per hour	Careful in Renal failure and combined hepatic and renal failure [43]. Use in urgent cardiac surgery [46].
Danaparoid	Method of administration: Subcutaneous or intravenous Half-life: 24 h Elimination: Renal and possibly non-renal routes	Initial (IV) bolus: 2250 units at the rate of 400 units/hr for four hours, 300 units/hour for the next four hours and 200 units/hour thereafter	Challenges: measure anti-factor Xa levels and long half-life [39].
Fondaparinux	Method of administration: Subcutaneous Half-life: 17-20 h Elimination: Renal	5-10 mg per day (weight based)	Same efficacy as argatroban [47,52]. It can be used during pregnancy [49].
Rivaroxaban	Method of administration: oral Half-live: 5-9 h Elimination: Renal and liver	15 mg twice daily for three weeks; then 20 mg once daily [38,40].	Contraindicated in individuals with a mechanical heart valve, pregnancy or breastfeeding
IVIG	1g/kg per day for two days		Autoimmune HIT Severe HIT Refractory to other therapies [51].

Following the resolution of HIT, a transition from parenteral anticoagulant (thrombin or factor Xa inhibitor) to warfarin or DOAC must occur. Warfarin can be begun only after a non-heparin anticoagulant treatment has been initiated, and the platelet count is at least 150,000/microL [37]. The risk of warfarin generates a thrombotic condition upon its quick onset, resulting in significant adverse effects such as skin necrosis and gangrene. Furthermore, warfarin should be used with a non-heparin anticoagulant for at

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least 5 days or until the INR is within the desired range [28]. The risk of thrombosis in a patient with HIT can be extended until approximately 4 weeks after starting HIT treatment. Therefore, anticoagulant therapy with non-heparin anticoagulant or warfarin should be continued for up to 3 months in patients with thrombosis secondary to HIT and up to 4 weeks in patients with isolated HIT [38].

Some alternative treatments for patients with refractory thrombocytopenia are intravenous immunoglobulin administration and therapeutic plasmapheresis [39]. On the one hand, therapeutic plasmapheresis consists of removing antibodies against heparin/PF4 large molecular weight complexes and has been described in patients requiring immediate cardiovascular surgery. Moreover, it is a choice / indicated when anticoagulants are contraindicated due to a bleeding event or in the case of refractory HIT [40,41]. On the other hand, the administration of high doses of intravenous immunoglobulin is still under study. For the time being, it is associated with the inhibition of HIT antibody-induced platelet-mediated activation and shows some benefit in patients with refractory thrombocytopenia [42] [43-61].

Conclusion

Heparin-induced thrombocytopenia (HIT) is a severe immune-mediated adverse reaction in patients receiving heparin therapy. It is characterized by a rapid decrease in platelet count and an increased risk of thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis. This drug-induced reaction is typically caused by forming antibodies against heparin-platelet factor 4 (PF4) complexes, leading to platelet activation and thrombosis. While HIT type 1 is a non-immune-mediated response to heparin and does not typically lead to thrombosis, HIT type 2 is an immune-mediated response that can result in significant morbidity and mortality. In addition, type 2 HIT is the more severe form, accounting for up to 90% of cases of HIT. Clinical presentation may include a drop in platelet count, new thrombosis or worsening of existing thrombosis, and skin lesions. Therefore, the diagnosis of HIT is based on clinical suspicion and laboratory testing, which may include platelet count, functional assays for HIT antibodies, and imaging studies to evaluate thrombosis. Prevention of HIT involves avoiding heparin therapy in patients with a history of HIT or at high risk for developing HIT. Alternative anticoagulant therapies such as direct oral anticoagulants, fondaparinux, or argatroban may be used in these patients. The treatment involves discontinuation of heparin therapy and initiation of alternative anticoagulation. In addition, in severe cases, immune globulin or plasmapheresis may be considered. Therefore, early recognition and management of HIT are crucial to prevent morbidity and mortality associated with this condition. Future research studies are still needed to understand HIT's pathophysiology further and develop more effective diagnostic and treatment strategies. Improvements in our understanding of the immune-mediated mechanisms involved in HIT could lead to more targeted therapies with improved patient outcomes. Additionally, studies evaluating the long-term outcomes of patients with HIT are needed to guide management strategies and improve patient outcomes.

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