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Heparin-Induced Thrombocytopenia (HIT)

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Abstract

Heparin-induced thrombocytopenia (HIT I) is a severe, life-threatening, and immunological drug reaction. According to the clinical-laboratory characteristics, there are two types of HIT: type I (HIT I) and type II (HIT II). HIT I is the result of non-immunologic, direct interaction of heparin with the platelet surface. Contrary, HIT II is immunologically induced (antibody-mediated) and life-threatening side effect of heparin therapy, often associated with thromboembolic complications. All patients receiving heparin are exposed to the development of anti-heparin antibodies, irrespective of the heparin dosage, type, and method of administration. HIT most commonly develops in intensive care patients, dialyzed patients, and cardiosurgical and orthopedic patients. It commonly develops after 5–10 days of heparin therapy. Platelet count decreases by more than 50% from the baseline and ranges from $20 \times 10^9/L$ to $100 \times 10^9/L$. In HIT II, thromboembolic complications usually include deep-vein thrombosis and pulmonary embolism, but they also include arterial occlusion of the extremities, myocardial infarction, stroke, and necrosis and organ damage. Clinical assessment of the HIT probability using 4T's score system, systematic monitoring of platelet number in heparin-receiving patients, and specific laboratory diagnosis of anti-heparin antibodies substantially contribute to the final confirmation of the diagnosis, enable timely administration of direct non-heparin thrombin antagonists, and reduce mortality from thromboembolic complications.

Keywords: heparin, heparin-induced thrombocytopenia (HIT), HIT type I, HIT type II, anti-heparin-PF4 antibodies, thromboembolism, direct thrombin inhibitors, argatroban, lepirudin, anti FXa, fondaparinux, direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban, danaparoid, IVIg

1. Introduction

Heparin-induced thrombocytopenia type II (HIT II) is a severe, life-threatening, immunological drug reaction. HIT II is an important side effect of heparin, the most commonly used anticoagulant agent. As opposed to bleeding caused by heparin overdose, some patients develop a paradoxical complication of heparin treatment – thromboembolism. According to the clinical-laboratory characteristics, there are two types of HIT: type I (HIT I) and type II (HIT II). HIT I is the result of non-immunologic, direct interaction of heparin with the platelet surface. It occurs in approximately 10% of the patients in the first several days of heparin treatment. Thrombocytopenia is mild and resolves within several days with the continuation of heparin therapy. Thromboembolic complications usually do not occur; therefore, it is of minor clinical significance. Contrary, HIT II is immunologically induced (antibody-mediated) and a life-threatening side effect of heparin therapy, often associated with thromboembolic complications [1]. The HIT may occur during the treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). All patients receiving heparin are exposed to the development of anti-heparin antibodies, irrespective of heparin dosage (prophylactic or therapeutic), type (UFH or LMWH), and method of administration (subcutaneous or intravenous). Since heparin is also used for flushing intravenous lines, it may lead to the development of anti-heparin antibodies in patients who do not receive subcutaneous or intravenous heparin [1, 2]. HIT most often develops in intensive care patients, hemodialyzed patients, and cardiosurgical and orthopedic patients, who usually receive heparin. Heparin-induced thrombocytopenia (HIT) is a clinical-pathologic syndrome diagnosed based on clinical findings and laboratory evidence of antibodies directed to the heparin and platelet factor 4 complex (H-PF4). HIT II may also be defined as a transitory, autoimmune, and heparin-induced thrombocytopenia. Reaching the diagnosis of HIT is a complex process, because thrombocytopenia in patients receiving heparin may be caused by numerous other factors. Although clinical assessment is very important in suspecting HIT, laboratory diagnosis plays the key role in providing evidence for the diagnosis of HIT II [3–5]. HIT II occurs in 0.1–5.0% heparin-treated patients, predominantly in those receiving UFH. It commonly develops after 5–10 days of therapy, but it may also occur earlier during the treatment course if the patient has been exposed to heparin within the previous 100 days (early form). HIT II rarely develops after 20 or more days from the start of the therapy (late form). In HIT II, platelet count decreases by more than 50% from the baseline and ranges from $20 \times 10^9/L$ to $100 \times 10^9/L$. HIT II patients are at high-risk of thromboembolic complications, venous and/or arterial, and allergic reactions. In HIT II, thromboembolic complications usually include deep-vein thrombosis and pulmonary embolism, but they also include arterial occlusion of the extremities, myocardial infarction, stroke, and necrosis and organ damage. Vein thrombosis may be found by duplex ultrasound in more than 50% of the patients with no clinical signs or symptoms of thrombosis [1–4]. In one-fourth of the HIT II patients, an allergic reaction may develop within 5–30 min after intravenous heparin administration (fever, chills, and respiratory distress). Rarely, an erythematous plaque or necrosis with pronouncedly painful skin may be observed. Complications related mortality rate was high (20–30%), but it has been significantly reduced in recent years due to the early diagnosis and treatment of HIT with heparin alternative [5, 6].

1.1. Heparin

Heparin is a polymer of varying chain size. Two forms of heparin are used as pharmaceuticals: unfractionated heparin (UFH) that has not been fractionated to sequester the fraction of molecules with low molecular weight, and low molecular weight heparin (LMWH), which undergone fractionation. Either UFH or LMWH can be used in the prevention of thromboembolic events LMWH is preferable. Heparin binds to the enzyme inhibitor anti-thrombin III (AT) via a specific pentasaccharide sulfation sequence contained within the heparin polymer. The formation of a ternary complex between AT, thrombin, and heparin results in the inactivation of thrombin, factor Xa, and other proteases. In contrast, anti-factor Xa activity requires only the pentasaccharide binding site. The highly negative charge density of heparin contributes to its very strong electrostatic interaction with thrombin. For this reason, heparin's activity against thrombin is size-dependent, with the ternary complex requiring at least 18 saccharide units for efficient formation. The rate of inactivation of these proteases by AT can increase by up to 1000-fold due to the binding of heparin. The size difference of heparin has led to the development of low-molecular-weight heparins (LMWHs) and, more recently, to fondaparinux as pharmaceutical anticoagulants. Fondaparinux is a synthetic pentasaccharide, whose chemical structure is almost identical to the AT binding pentasaccharide sequence that can be found within polymeric heparin and heparan sulfate. LMWHs and fondaparinux target anti-factor Xa activity rather than AT activity, with the aim of facilitating a more suitable regulation of coagulation and an improved therapeutic index [6].

2. Pathophysiology

The pathophysiologic mechanism of HIT II is mediated by the formation of heparin-platelet factor 4 (PF4) complexes. The PF4 is a positively charged heterodimer found in platelet alpha granules, and heparin is a negatively charged molecule. The formation of heparin-PF4 complex results in the change in the tertiary structure of the PF4 and exposure of neo-peptide, which elicits the formation of antibodies, usually IgG isotype. The immune heparin-PF4-IgG complexes activate platelets via Fc γ IIa receptors. The antibodies may bind to monocytes, which then release tissue factor, the most potent blood clotting factor. Activated platelets release procoagulant microparticles and PF4. Antibodies recognize the complexes, bind to the endothelial cells, and activate the coagulation cascade, which leads to the formation of thrombin and eventually thrombosis. The ability of HIT antibodies to strongly activate platelets even in the absence of heparin may cause heparin-independent HIT II [7–9].

HIT II is most often caused by IgG antibodies targeting heparin-PF4 complex. In patients with HIT antibodies present in the blood, re-administration of heparin causes a rapid decrease in the platelet counts (within hours) to extremely low values. In heparin-treated patients, platelet count should be monitored before and during therapy. Before the specific laboratory evidence of anti-heparin antibodies, the probability of HIT should be determined using clinical laboratory indicators.

3. Clinical diagnosis

Clinicians should assess whether the platelet count decrease is the result of anti-heparin antibodies or underlying disease. They should also be cautious not to over diagnose HIT, because some HIT antibodies are not pathogenic and will not necessarily lead to the clinical HIT syndrome. Before the specific laboratory evidence of anti-heparin antibodies, the probability of HIT should be determined using clinical-laboratory indicators. In heparin-treated patients, platelet count should be monitored before and during the course of therapy. According to the 2006 British Haematology Standards, platelet count should be determined in all patients on the day of the start of heparin therapy. In patients who received heparin within the previous 100 days, platelet count should be determined on the day of the start of heparin therapy and 24 h later. In patients receiving UFH, platelet count should be measured daily from day 4 to day 14, and every 2–4 days between day 4 and day 14 in patients receiving LWMH [10–13].

The clinical scoring system used for determining the probability of a HIT is the so-called “4 T score” - thrombocytopenia, timing of onset, thrombosis, and absence of other causes of thrombocytopenia (**Table 1**) [6]. Each of these symptoms is scored from 0 to 2 points. The total score of 0–3 indicates a low probability of HIT II, 4–5 indicates moderate, and 6–8 indicates a high

4Ts		Score
T1	(a) Platelet count decline by >50%, with lowest value of $20 \times 10^9/L$	2
Thrombo-cytopenia	(b) Platelet count by 30–50%, with lowest value of $10\text{--}19 \times 10^9/L$	1
	(c) Platelet count decline by <30%, with lowest value below $10 \times 10^9/L$	0
T2	(a) Occurrence of thrombocytopenia 5–10 days of initial heparin administration or <1 day (with previous exposure within 30 days)	2
Timing of platelet count decline	(b) Occurrence of thrombocytopenia >10 days of initial heparin administration or unknown or <1 day (with previous exposure within 30–100 days)	1
	(c) Occurrence of thrombocytopenia at <4 days (without previous recent heparin exposure)	0
	T3	(a) New thrombosis, skin necrosis, acute systemic reaction following bolus heparin
Thrombosis or other sequelae	(b) Progressive recurrent thrombosis, erythematous skin lesion, unconfirmed suspicion of thrombosis	1
	(c) No other causes of thrombocytopenia	0
	T4	(a) No other cause of thrombocytopenia
Other cause of thrombocytopenia	(b) Presence of other possible causes of thrombocytopenia	1
	(c) Definitive other cause of thrombocytopenia is present	0

Low, 0–3; Moderate, 4–5; High, 6–8.

Table 1. Clinical assessment of Heparine induced thrombocytopenia (HIT) by use of modified 4T scoring system according to Lo and Warkentin [6].

probability of HIT II. To confirm the diagnosis of HIT II, laboratory evidence of anti-heparin antibodies is needed. Anti-heparin antibodies may be confirmed in about half of the patients with clinically suspected HIT requiring laboratory investigation. The frequency of positive results depends on the clinical 4 T score and sensitivity and specificity of the test used [6–9].

4. Laboratory diagnostics

Laboratory investigation of HIT includes two categories of tests: immunologic assays for detecting circulating anti-PF4/heparin antibodies usually of IgG class and functional assays which detect antiplatelet antibodies capable to induce heparin-dependent platelet activation and thrombogenic potential (Table 2) [10–12].

In laboratory investigations of HIT II, anti-heparin-PF4 antibody tests are most commonly used in immunologic assays and serotonin-release assay (SRA) to determine anti-heparin antibody-induced platelet activation. In addition to, SRA heparin-induced platelet activation/aggregation assay (HIPA) is used when the thrombogenic potential of the present antibodies should be determined or *in vitro* effectiveness of heparin, alternative should be estimated. Enzyme-immunologic (EIA) method and gel method are most commonly used for immunologic assays. EIA is performed on a microtiter plate, and heparin-PF4 antigen complex is applied to the plate wells. Gel test is performed on gel-filled microcolonies, and the heparin-PF4 complex is added into a microparticle suspension. These tests have a similar sensitivity (80–90%) and specificity (89–97%). The most important advantage of gel test (quick screening test) is a high negative predictive value (>95%) for the exclusion of HIT II. In the other group

Method	Sensitivity	Specificity	NPV	PPV
Anti H-PF4 assays (antigen-antibody assays):				
(a) Gel-columns-micro-particle assay	High	Moderate	High	Low
(b) Lateral flow immunodiffusion assay-IgG	High	Moderate	High	Moderate
(c) EIA-IgG	High	Moderate	High	Moderate
Functional assays:				
(a) SRA-cr	Low/moderate	High		High
(b) SRA-HPLC				
(c) SRA-EIA				
(d) HIPA				
(e) HIMA				

H-PF4, heparin-platelet factor 4 complex; EIA, enzyme immuno assay; HPLC, high pressure liquid chromatography; SRA, serotonin release assay; HIPA, heparin-induced platelet activation/aggregation; HIMA, heparin-induced platelet activation/multilate aggregation; NPV, negative predictive value; PPV, positive predictive value; H-PF4, heparin-platelet factor 4 complex.

Table 2. Methods for anti-heparin antibodies detection.

of tests, heparin-induced platelet activation (HIPA), and serotonin-release assay (SRA) are the most commonly used tests. They have lower sensitivity, but higher specificity than the first group of tests. In addition to, EIA test result, OD value is also obtained. OD <1.000 indicates the presence of clinically significant antibodies and a high-risk of thromboembolic complications. OD ranging from 0.400 to 0.999 and low clinical 4T indicate low thrombogenic activity of the antibodies and subclinical HIT. Monitoring antibody titres using OD values is used in the preoperative preparation of patients with previously confirmed HIT II; the surgery in which heparin is given is performed after the antibody titer decreases or the test results become negative [14, 15].

To exclude other causes of thrombocytopenia, differential diagnosis should include pseudo thrombocytopenia (artifact), massive pulmonary embolism, disseminated intravascular coagulation (DIC), sepsis, other drug-induced thrombocytopenia (e.g. by GP IIb/IIIa inhibitors), autoimmune or alloimmune thrombocytopenia, post-transfusion purpura, diabetic ketoacidosis, and antiphospholipid syndrome with thrombocytopenia [16].

5. Treatment

Treatment of HIT patients is complex. In severely ill, heparin-treated patients who develop HIT II, there is often a misbalance of antithrombotic molecules including protein C, antithrombin III, thrombomodulin, and others. If there is a lack of these regulators, their substitution may increase the anticoagulant effect of heparin alternatives [16]. Clinical assessment plays a key role not only in discerning the platelet count decrease caused by anti-heparin antibodies from the platelet count decrease caused by the underlying disease but also in the selection of anticoagulant agent [17].

According to the clinical practice guidelines on antithrombotic therapy and prevention of thrombosis, if there is laboratory evidence of anti-heparin antibodies, heparin should be discontinued immediately, and replaced by some other non-heparin anticoagulant. Most commonly used alternative anticoagulants are: direct thrombin inhibitors, heparinoids, and factor Xa inhibitors (**Table 3**) [17].

Hirudin is a direct inhibitor of thrombin and acts independently of cofactors such as antithrombin. (19) Therefore, hirudin may be more effective in the presence of platelet-rich thrombi. Hirudin can also inhibit thrombin bound to fibrin or fibrin degradation products.

Direct thrombin inhibitors (DTI)	Hirudin, lepirudin, bivaluridin argartoban
Heparionoides	Danaparoid
Factor Xa inhibitors	Fondaparinux
Direct oral anticoagulants(DOACs)	Dabigatran, apixaban, rivaroxaban
Other	Intravenous gamma globulins (IVIG)

Table 3. Alternative anticoagulants for treatment of heparin- induced thrombocytopenia type II (HIT II).

Lepirudin is a recombinant hirudin and is a highly specific direct and irreversible inhibitor of thrombin. One molecule of lepirudin binds with one molecule of thrombin. Lepirudin is almost exclusively excreted by the kidneys and hence systemic clearance of lepirudin is dependent on the glomerular filtration rate. The drug should be avoided in hemodialysis patients and those with acute renal failure with creatinine clearance $<15 \text{ ml min}^{-1}$ (normally 120 ml min^{-1}) or serum creatinine $>528 \mu\text{mol liter}^{-1}$. The 2006 British Guidelines recommend lepirudin, recombinant protein, and direct thrombin inhibitor to be used as heparin alternatives [12].

Bivalirudin is a direct thrombin inhibitor and an analogue of the peptide fragment hirugen, which is a compound derived from hirudin. Unlike lepirudin, the binding of bivalirudin to thrombin is reversible. Bivalirudin binds specifically to the catalytic site and substrate-binding site of thrombin. The US Food and Drug Administration (FDA) has approved bivalirudin for use in patients undergoing coronary angioplasty with unstable angina who are also on aspirin therapy [18].

Argatroban is a direct competitive synthetic inhibitor of thrombin. It binds reversibly to the thrombin catalytic site and therefore, inhibits reactions that are catalyzed or induced by the presence of soluble and clot-bound thrombin. When given i.v. and is metabolized in the liver by cytochrome P450 enzymes it is 100% bioavailable. Unchanged drug is excreted in the urine (16%) and feces (14%). It is eliminated as its metabolite in the feces (65%), presumably through biliary secretion, and in the urine (22%) [17].

It should be taken into account that all non-heparin anticoagulants may also lead to anaphylactic reaction and bleeding. However, unlike heparin, there is no known antidote for these agents and laboratory monitoring of their effects and antibody cross-reactivity is difficult (anti-Xa activity and ellagic time are not standard laboratory tests for hemostasis), in addition to the high price of the substance.

Danaparoid is a low molecular weight heparinoid. It is a mixture of dermatan sulfate, glycosaminoglycans, and chondroitin sulfate. A favorable outcome in 90% of patients with HIT is associated with the use of danaparoid. The main activity of danaparoid is against factor Xa, with the anti-Xa: the anti-IIa ratio of 22:1 resulting in inhibition of fibrin formation. There is a 10–20% cross-reactivity rate with HIT antibodies in vitro although it is less common in vivo. [18].

Coumarin agents (e.g. warfarin) are contraindicated in acute HIT II, because they increase the risk of microvascular thrombosis, necrosis, and gangrene. Replacing UFH with LWMH is also contraindicated in the treatment of HIT II due to the antibody cross-reactivity [12, 13, 18].

Most guidelines suggest the use of argatroban over other nonheparin anticoagulants in patients with HIT and renal insufficiency, and the use of bivalirudin over other nonheparin anticoagulants or heparin plus antiplatelet agents in patients with acute HIT or subacute HIT who require urgent cardiac surgery (Grade 2C) [12, 18, 19].

Recently, the most commonly used agent has been fondaparinux, a synthetic and selective factor Xa inhibitor, which rarely causes anti-heparin antibody cross-reactivity. Clinical experience shows it has beneficial effects in the prevention of thromboembolic complications. The fondaparinux results are an important step in developing the recommendations for the use of alternative agents to heparin, although randomized studies are needed [20, 21].

The use of oral direct thrombin inhibitors in the treatment of HIT II (dabigatran, rivaroxaban, and apixaban) also holds promise. The effectiveness of rivaroxaban in HIT patients was assessed in several studies showing no cross-reactivity with anti-heparin antibodies. Moreover, there was no PF4 release from platelets, as opposed to enoxaparin-LWMH [22, 23]. HIT can be managed with danaparoid in post-cardiac surgery patients. However, in absence of any increase of platelet count after 3–5 days of danaparoid therapy and/or occurrence of a new thrombotic event, danaparoid cross-reactivity with heparin should be suspected and replaced with direct thrombin inhibitor [24].

There is a dozen of evidence that in some patients with severe HIT II refractory to standard treatment immediate and sustained respond could be achieved by the admission of intravenous gamma globulin (IVIg), most probably mediated by inhibition of platelet activation [25].

According to the literature data, prophylactic platelet transfusions in thrombocytopenic HIT patients are contraindicated. Since spontaneous bleeding in HIT is rare, and platelet transfusions may potentially increase the risk of thrombosis, their use is recommended in case of life-threatening bleeding. Contrary, there is not clear evidence suggested that platelet transfusions should be avoided in a critically ill bleeding patient with HIT. [26].

In a couple of studies, platelet transfusion was administered prophylactically to prevent bleeding in post-surgery patients. These patients experienced no new thrombotic complication but expected post-transfusion platelet count increment was not achieved. Furthermore, previous deep venous thrombosis progressed after platelet transfusion and subsequently led to death in one patient [27].

6. Conclusion

HIT II is immunologically-induced, a life-threatening side effect of heparin therapy associated with thromboembolic complications. All patients receiving heparin are exposed to the development of anti-heparin antibodies, irrespective of the heparin dosage, type, and method of administration. HIT most commonly develops in intensive care patients, dialyzed patients, and cardiosurgical and orthopedic patients. Clinical assessment of the HIT probability using 4T scoring system, systematic monitoring of platelet number in heparin-receiving patients, and specific laboratory diagnosis of anti-heparin antibodies substantially contribute to the final confirmation of the diagnosis, enable timely administration of direct non-heparin thrombin antagonists, and reduce mortality from thromboembolic complications.

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