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REVIEW

Heparin Induced Thrombocytopenia – Pathophysiology, Diagnosis and Treatment: A Narrative Review

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Abstract: Heparin-induced thrombocytopenia (HIT) is a life-threatening, immune-mediated complication following heparin exposure and is considered to be the most severe adverse reaction to heparin treatment that is not associated with bleeding. Development of autoantibodies against platelet factor 4 (PF4) – heparin complex constitutes the basis of the pathophysiological changes in patients suffering from HIT, which then binds to the surface of platelets and monocytes, thus provoking their activation and subsequent aggregation, ultimately leading to the formation of thrombosis. Formation of arterial and venous thrombosis is aggravated by the simultaneous activation of platelets and monocytes with a substantial mortality rate. The incidence of HIT is reported to be significantly lower in pediatric patients compared with adults. Diagnosis of HIT in pediatric population remains a clinical entity supplemented by laboratory evaluation. The positive predictive value of laboratory evaluation is further elevated by the use of scoring systems and predictive models used for hastening the diagnosis of HIT. Use of alternative anticoagulants like direct thrombin inhibitors and factor Xa inhibitors form the mainstay of treatment in cases of HIT, however, more prospective studies would be required in the pediatric population to delineate definitive guidelines for proper management of patients in this age-group. This article delivers diagnostic and treatment approach in case of patients with HIT, wherein the pathophysiology, clinical manifestations, diagnostic approach and the management of patients with HIT has been described.

Keywords: heparin, induced, thrombocytopenia, paediatrics, patients

Introduction

Heparin induced thrombocytopenia (HIT) is recognized as an important type of drug induced thrombocytopenia which, if went undiagnosed, is associated with significant morbidity and mortality.[1] HIT is a pro-thrombotic, immune-mediated complication of unfractionated and low molecular weight heparin therapy usually seen following surgical treatment of patients for cardiovascular and orthopaedic ailments, invasive procedures, venous thromboembolism, atrial fibrillation and peripheral occlusive disease. HIT is characterized by moderate thrombocytopenia that usually develops during 5–10 days after the initial heparin exposure, presence of platelet-activating anti-platelet factor 4(PF4)/heparin antibodies along with an increased risk of venous and arterial thrombosis.[2,3] HIT is conventionally classified into two distinct variants namely, type I and type II HIT. Type I HIT (also known as heparin associated thrombocytopenia) is a non-immunological response to heparin treatment which is mediated by a direct interaction between the administered heparin and the circulating platelets thereby causing platelet aggregation followed by platelet clumping and sequestration. On the other hand, HIT type II is immune mediated and associated with a risk of thrombosis.[4]

The prevalence of HIT in case of adults who are on heparin therapy is reported to be 0.5–5%.[5,6] Numerous studies on HIT in adults have demonstrated the prevalence of thrombotic complications at the time of the diagnosis in 30–60% of patients.[2] The risk of thrombosis persists for several days even after heparin withdrawal while 50% of the remaining patients diagnosed with HIT subsequently develop a thrombotic event.[7,8] Prospective data on the prevalence of HIT in pediatric patients are

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lacking. However, published case series/reviews of children suffering form HIT indicate the prevalence of HIT in the pediatric population may be lower as compared to their adult counterpart. The prevalence can range from 1.5–3.7% and can be as low as 0.33% in non-neonates receiving cardiopulmonary bypass.[9–11] Owing to the fact that HIT is usually encountered in the hospital setting in case of admitted patients and can be caused by a multitude of reasons, HIT often remains unrecognised and undiagnosed.[12]

Paucity of data availability and the limited extent of reporting may be responsible for the low incidence of HIT in the pediatric population. Nonetheless, incidence of HIT in children is increasing mainly due to increased awareness regarding the condition and its associated complications.[13–15] Therefore, this review highlights the difference between HIT seen in adults and pediatric population as well as the management protocols specifically used for the treatment of HIT in pediatric population.

Pathophysiology

Heparin-induced thrombocytopenia is a fatal condition in the pediatric population due to its high morbidity and mortality, which is why it is necessary to understand its pathophysiology to identify its clinical condition early, to know its risk factors, to timely suspend the anticoagulation with heparin and to initiate alternative anticoagulants if necessary.[16]

HIT is an immunological reaction which can develop following exposure to heparin within hours or even after a few days.[17] Pathologically, the genesis of HIT involves the formation of antibodies against heparin, leading to the development of platelet activation and aggregation, subsequently giving rise to thrombin production.[18] Platelet factor 4 (PF4), a potent positively charged protein found in the alpha granules of the platelets, recognizes heparin upon administration. Following exposure to heparin, PF4 immediately recognizes heparin and neutralizes it. This PF4-heparin complex serves as the primary antigen for the antibodies of the immunoglobulin G (IgG) class, which identify the exposed epitopes on PF4 and bind to them.[19,20] This immune complex composed of IgG, PF4 and heparin further binds to and activates the circulating platelets via the Fc receptor. Platelets, following their activation, release more PF4 and various other prothrombotic mediators and agents that help to propagate the cycle of platelet generation, activation and aggregation which is ultimately followed by thrombosis.[21,22] Platelets aggregated in this way are then removed by the cells of the reticuloendothelial system, leading to thrombocytopenia.[23]

Increased platelet consumption arising out of extensive thrombosis is another theory put forward for thrombocytopenia in patients with HIT. In addition to this, the antigen-antibody complex causes endothelial injury by binding to the monocytes that give rise to increased production of the tissue factor and thrombin production along with propagation of the immune response.[20,24] Thrombin therefore plays a vital role in the pathogenesis of HIT.[25,26] Anionic polysaccharides can bind to PF4 and bring about conformational changes leading to platelet activation and aggregation followed by thrombocytopenia, depending on the chain length and degree of sulfation.[27,28]

Thrombocytopenia in Pediatric Patients

HIT is typically characterized by moderate thrombocytopenia with platelets in the range of 50–80 x 10^9/L.[29] The thrombocytopenia encountered in pediatric patients can be either absolute (<150 x 10^9/L) or relative in nature, which is defined as a drop in the platelet count of 50% or more as compared to the pre-heparin value. However, severe thrombocytopenia is unusual. Usually, the platelet count begins to fall 5–14 days after putting the patient on heparin, the onset of which may be rapid or delayed. If a patient has circulating heparin–PF4 antibodies resulting from recent heparin exposure, then the platelet count collapses within minutes or hours, resulting in rapid-onset HIT.[30] Conversely, in delayed onset HIT, the thrombocytopenia is delayed for several days that can even extend up to 3 weeks which becomes evident only after heparin treatment is withheld. The platelet count begins to improve within 2–3 days and usually returns to normal over a duration of 1 week following complete cessation of heparin therapy.[31] In patients presenting with persistent or worsening thrombocytopenia despite absolute discontinuation of heparin, other probable causes of thrombocytopenia should be considered and investigated.

Diagnosis of HIT in Pediatric Population

As in the case of adults, the diagnosis of HIT in pediatric patients remains a clinical entity which needs to be complemented by robust laboratory evaluation. HIT should be suspected in every patient who develops thrombocytopenia following heparin

exposure. Conventionally, clinical HIT characterized by thrombocytopenia with or without thrombotic sequelae, develops after 5–10 days of heparin exposure. Since thrombotic events may precede the development of absolute thrombocytopenia in patients with baseline thrombocytosis, a 50% decline in the platelet count during heparin therapy should raise an alarm for clinical suspicion of HIT. Rarely, clinical HIT develops within 24 hours of heparin therapy (acute HIT, that is thought to be associated with pre-existing HIT antibodies) or days after heparin is discontinued (delayed HIT). Whatever the timeframe involved in the genesis of HIT, discontinuation of heparin should be strongly considered followed by a confirmatory diagnostic evaluation. Prescription of an alternative anticoagulant should be based on the clinical suspicion of HIT by the treating physician considering the individual bleeding and thrombotic risk of the patient.

Predictive Scoring Systems

Several clinical prediction models have been developed so as to improve the accuracy of pre-test assessment for the likelihood of HIT diagnosis and to facilitate appropriate management. The pre-test probability assessment is crucial not only because the diagnostic test results for HIT assays are often delayed, but also the heparin-PF4 ELISA assay has a significantly higher false positive rate and the alternative anticoagulants used for treating HIT affected patients have a higher bleeding risk. The "4T score" pre-test probability model developed by Warkentin et al[32] is highly sensitive (sensitivity of 98.4%) and relies on the development of the clinical features of thrombocytopenia, particularly the degree and timing of thrombocytopenia in relation to heparin exposure, presence of new thrombosis and the exclusion of other etiologies of thrombocytopenia (Table 1). The presence or absence of other clinical manifestations like thrombosis and local skin reactions along with the presence of other potential causes of thrombocytopenia may also influence the likelihood of HIT. A low 4T score (0–3) was well correlated with a low incidence of HIT antibody test positivity rate (1.6%) among hospitalized patients at 2 centres and critically ill patients in 2 prospective studies

Table 1 4T Predictive Scoring System for Thrombocytopenia

4T's	2 Points	1 Point	0 Point
Thrombocytopenia	>50% decrease in platelet count and platelet nadir of >20 x 10^9/L No surgery within the preceding 3 days	>50% fall in platelet count but surgery within preceding 3 days OR Any combination of platelet fall and platelet nadir that does not meet criteria for a score of 2 points	<30% platelet fall OR Any platelet nadir <10 x 10^9/L
Timing of platelet count	Platelet count falls 5–10 days after start of heparin therapy OR Platelets fall within 1 day of start of heparin with exposure to heparin within the past 5–30 days	Onset unclear OR Platelet fall after day 10 OR Platelet fall within 1 day of starting heparin (if exposed to heparin within the past 30–100 days)	Platelet fall within 4 days without exposure to heparin in the past 100 days
Thrombosis	Confirmed new thrombosis OR Skin necrosis at injection site OR Anaphylactic reaction to IV heparin bolus.	Progressive or recurrent venous thrombosis OR Suspected thrombosis OR Red skin lesions at heparin injection site	Thrombosis not suspected
Other causes of thrombocytopenia	No other cause is present	Possible other cause is present	Probable other cause is present

Notes: Interpretation: ≤3 points: low probability for HIT. 4–5 points: intermediate probability (around 14% probability of HIT). 6–8 points: high probability (around 64% probability of HIT). Data from Lo et al.[34]

conducted in intensive care unit patients.[33,34] The incidence of HIT appears significantly lower in pediatric patients compared with adults.[35]

More recently, the HIT Expert Probability (HEP) score was developed as pre-test clinical scoring system that is based on the 4T scoring system but has been expanded further to include other clinical characteristics that influence the likelihood of HIT.[36] The timing and magnitude of thrombocytopenia in relation to heparin exposure and the presence of new thrombosis remain central to both scoring systems. Though the HEP scoring system is more extensive in terms of HIT diagnosis, the inclusion of additional clinical features of HIT may prove to be useful for clinicians for improvisation of their learning curve with respect to HIT diagnosis. A score of 2 was associated with 100% sensitivity but only 60% specificity for the diagnosis of HIT, whereas a score of 5 was 86% sensitive and 88% specific. The use of these clinical scoring systems may improve the accuracy of the diagnosis of HIT but will definitely require further study in the pediatric population.

In a cohort including 34 children (under 18 years) and 105 adults, adults mostly received heparins for thromboembolism prophylaxis and treatment (72.4%, n = 76), and were more frequently treated with low-molecular-weight heparin (LMWH). 4Ts scores were higher in children compared with adult patients for whom laboratory tests for HIT were obtained.[37]

Laboratory Testing

Since the diagnosis of HIT relies typically on clinical suspicion followed by laboratory evaluation, ELISA assay of the polyclonal antibodies to the PF4-heparin complex is the preferred laboratory test for diagnosis of HIT. These tests are highly sensitive but have a significantly higher false positive rate, hence useful in ruling out the diagnosis of HIT with a negative predictive value 95%. Immunoassays detecting only the presence of IgG antibodies appear to have greater specificity with sensitivity that is similar to the assays measuring IgG/IgA/ IgM antibodies.[38,39] Antibody titre as measured by ELISA is well correlated with the likelihood of clinical manifestations in adults.[40,41] Patients with a low antibody titre, have a 5% chance of having a positive serotonin release assay (SRA). It has been postulated that HIT may occur at lower antibody levels in pediatric patients, but the specificity and sensitivity of ELISA in this subset of patients have not been formally studied.[42]

SRA is a highly specific test that measures platelet activation by the release of radiolabelled 14C-serotonin by HIT antibodies in the presence of therapeutic concentration of heparin. As a result of this, the platelet activation is inhibited with excessive concentrations of heparin. A positive assay is defined as 20% release of serotonin, but higher levels of platelet activation are associated with a greater likelihood of thrombotic complications. The HIPA test is a functional test for heparin-dependent antibodies, the sensitivity of which may be affected by alterations in the reactivity of donor platelets. Both the SRA and the HIPA are more specific than the ELISA, however, they are performed only in a limited number of specialized laboratories.

Management of HIT

The mainstay of management for patients who have been confirmed to be suffering from HIT is immediate cessation of heparin therapy followed by administration of alternative anticoagulant treatment depending on the thrombotic status of the patient.[43] In patients who have been classified as having intermediate or high risk based on their 4T score, heparin therapy should definitely be discontinued. Cessation of unfractionated heparin is deficient to prevent the occurrence of thrombotic events and an alternative anticoagulant medication should be provided to the patient, with the exception of both LMWH or warfarin, which can conversely induce the generation of thrombin and further escalate the risk for thrombosis.[44,45] Pediatric pharmacokinetic data with nonheparin alternatives such as Direct Thrombin Inhibitors (DTIs) and Xa inhibitors are now available to guide dosing for the treatment of HIT.[11] DTIs such as Argatroban, Lepirudin and bivalirudin or factor Xa inhibitors such as Danaparoid and Fondaparinux.

Direct Thrombin Inhibitors

Argatroban

Argatroban, a direct thrombin inhibitor, is an arginine-based synthetic anticoagulant that reversibly binds with the catalytic site of thrombin. It has been approved by the US FDA for both prophylaxis and treatment of thrombosis and

during coronary angioplasty in patients with HIT.[46] A major advantage of argatroban is that it is metabolised by the liver which makes it the preferred therapy in case of patients with renal insufficiency. Argatroban has the shortest half-life among all alternative anticoagulants so it can be quickly discontinued if invasive procedures are mandated or if severe bleeding is encountered. There is no evidence of antibody generation to argatroban on prolonged or repeated administration, and no anaphylactic deaths have been reported.

Lepirudin

Recombinant hirudin, better known as Lepirudin, originally produced from the medicinal leech, is a 65 amino acid peptide with a molecular weight of approximately 7000 Da. It acts as a direct and irreversible thrombin inhibitor, binding to both the free and clot-bound thrombin. Since Lepirudin is eliminated via the renal route, it should be used with caution and in a reduced dosage in case of patients with serum creatinine values over 1.6 mg/dl (141.4 mmol/L). It is therefore contraindicated in patients who require haemodialysis or are suffering from acute renal failure.[47] Another issue with Lepirudin is the development of antibodies against the drug, ie, lepirudin–antibody complexes, encountered in approximately 50% of patients. The mentioned complex becomes too large for renal excretion, resulting in prolongation of the half-life, increased plasma lepirudin concentrations and the need for dose reduction. Anaphylaxis has also been reported in around 0.15% of patients receiving lepirudin. Omitting the bolus dose may reduce the severity of anaphylaxis and non-hirudin anticoagulants should definitely be considered for use in patients with previous lepirudin exposure.

Factor Xa Inhibitors

Danaparoid

Danaparoid is a mixture of heparin, dermatan and chondroitin sulphates which exerts its anticoagulant effect mainly by inhibiting factor Xa and to a much lesser extent by inhibiting thrombin. Though it has demonstrated in vitro cross reactivity to HIT sera in about 10–50% of cases, in vivo cross reactivity has been insignificantly encountered.[48] Danaparoid has a long half-life, near 100% bioavailability and is cleared by the kidneys. Danaparoid is approved by the US FDA for venous thrombosis prophylaxis following orthopaedic surgery but not for the treatment of HIT. Danaparoid in a high dose regimen is similar to lepirudin in the treatment of HIT with or without thrombosis.

Bleeding is an important safety concern with the use of direct thrombin inhibitors because no specific antidotes are available, though protamine sulphate is capable of neutralizing Danaparoid to some extent. Unintentional and excessive anticoagulation associated with the presence or absence of bleeding should be managed by either stopping the drug or reducing the dose of direct thrombin inhibitors. However, the anticoagulant effects decrease to baseline upon stopping the drug, typically within hours, as per the elimination kinetics of the drug and the patient's organ function. The half-life of argatroban (39–51 min) and lepirudin (1.7 h) are increased in patients with hepatic and renal impairment respectively. Since danaparoid has a long half-life (up to 25 h), one cannot expect rapid reversal after drug discontinuation. Haemodialysis or haemofiltration can sometimes reduce the plasma concentration of lepirudin, but dialytic clearance of argatroban by high-flux membranes is clinically insignificant.[49]

Warfarin Administration in HIT

When treatment with warfarin is indicated for some underlying medical condition or HIT-associated deep vein thrombosis (DVT), it must be delayed until adequate alternative parenteral anticoagulation has been administered to the patient and platelet counts have recovered substantially (to at least 100 x 10^9/L or preferably 150 x 10^9/L). Warfarin should be started with the maintenance dose and not at the loading dose. Parenteral anticoagulation should be overlapped with warfarin for a minimum of 5 days until the target international normalised ratio (INR) range has been achieved for a period of at least 2 days.[13] If warfarin has already been started when HIT is recognised, reversal of warfarin with vitamin K is recommended for two reasons, first to minimise the risk of microvascular thrombosis and consequent skin necrosis and second to prevent the under dosing of direct thrombin inhibitors.

Conclusion

Heparin induced thrombocytopenia in pediatrics is rare with estimated prevalence of 1.5 to 3.7%. It is caused by IgG antibodies against heparin-PF4 complex leading to platelet activation and thrombosis.

The diagnosis of HIT depends on a combination of clinical findings and laboratory testing. Clinical scoring systems to assess the pre-test probability of HIT improve the accuracy of HIT diagnosis, however, they have not been validated in the pediatric population. Also, management of HIT in children becomes challenging especially due to the paucity of studies on epidemiology, clinical presentation and treatment of HIT in this population. Whereas the clinical course of HIT in children appears to be similar to that in adults, relatively little data have been published in this regard and management for the same is largely based on extrapolation from adult studies. More studies should be carried out to outline the management algorithms in case of children suffering from HIT so that effective treatment with proven efficacy can be instituted at the earliest.

Disclosure

The author reports no conflicts of interest in this work.

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