HEPARIN INDUCED THROMBOCYTOPENIA: A REVIEW

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Abstract

Heparin-induced thrombocytopenia (HIT) is a rare but serious complication of heparin use. It is a prothrombotic, antibody-mediated condition in which thrombocytopenia associates thrombosis in a clinical picture that is often challenging for the clinician because of the difficulties of diagnosis and of therapy as well. In daily practice, HIT diagnosis relies mostly on clinical aspects and immunologic assays as the functional tests are not routinely performed, which along with the clinician`s fear not to miss the diagnosis have made this condition to be overestimated nowadays.

The aim of this article is to review the main diagnosis and management aspects of this dangerous complication in the light of the increasing use of heparin in a wider variety of clinical settings.

Rezumat

Trombocitopenia indusă de heparină (HIT) este o complicaţie rară, dar gravă a administrării heparinei. Este definită ca o condiţie protrombotică, mediată imun, în care trombocitopenia se asociază cu tromboze, realizând un tablou clinic greu de gestionat, datorită dificultăţii diagnosticului şi a alegerii tratamentului adecvat. În practica medicală zilnică, diagnosticul HIT se bazează mai mult pe elementele clinice şi pe testele imunologice, întrucât testele funcţionale nu se efectueaza de rutină, ceea ce, alături de teama clinicianului de a nu rata diagnosticul corect, duce adeseori la supraestimarea acestuia.

Scopul acestui articol este de a revizui principalele aspecte de diagnostic şi tratament ale acestei complicaţii periculoase, în condiţiile utilizării tot mai largi a heparinei, în diferite situaţii clinice.

Keywords: heparin-induced thrombocytopenia, thrombosis, alternative anticoagulants

Introduction

Heparin is the most used anticoagulant in clinical practice. Both unfractioned heparin (UFH) and low molecular weight heparin (LMWH)

can determine a very severe complication that is heparin-induced thrombocytopenia (HIT), associated with thromboses. This complication appears in 1-5% of patients receiving heparin [12].

Heparin is associated with two types of thrombocytopenia.

- Non-immune thrombocytopenia (previously known as type I or heparin-*associated* thrombocytopenia) that affects 10-30% of patients receiving heparin, with no significant differences between UFH and LMWH. Thrombocytopenia is due to heparin binding to the platelet membrane in a non-immune manner. It appears in the first 5 days of heparin administration, it is non-progressive and it does not associate hemorrhages or thromboses.
- Immune thrombocytopenia induced by heparin (previously known as type II or heparin-*induced* thrombocytopenia) appears in 0.2-3% of patients receiving UFH and 0-0.75% of patients receiving LMWH [4] and is a life threatening condition. It is defined as a prothrombotic drug reaction caused by platelet-activating IgG antibodies that recognize platelet factor 4 (PF4)/polyanion complexes [29]. It occurrence does not depend on the route of heparin administration (subcutaneously or intravenously) or on the heparin dose. It can appear during heparin administration, 5-14 days after the first heparin dose, with a maximum risk between day 10 and 14 and it is usually accompanied by moderate-severe thrombocytopenia and increased thrombotic risk.

Ethiopathology

Heparin is a negatively charged sulfated glycosaminoglycan with high binding affinity for platelet factor 4 (PF4). PF4 is a heparin-neutralizing protein contained in the platelet alpha granules and expressed on the surface of endothelial cells and platelets following their activation. Under normal conditions, once released into the blood flow, PF4 bind the glycosaminoglycan from the endothelial cell membrane. During heparin therapy, PF4 preferentially binds heparin and the PF4/Heparin complexes induce conformational changes that expose neo-epitopes and the immune response is initiated [17]. Only a minority of anti PF4/Heparin antibodies are platelet-activating. As Warkentin described in a recent publication [29], PF4/Heparin antibodies follow the so-called "iceberg model" of immunization in which the most of the iceberg remains below water and only $1/10^{th}$ protrudes above the waterline, and so do the PF4/Heparin antibodies because only 10% of the detected antibodies have platelet activating proprieties [11,33]. The antibodies bind by the Fab fragment to the PF4/Heparin complexes and by the Fc fragment to FcγIIa receptors expressed on the platelets surface and subsequently induce platelet

activation, calcium influx, thromboxan synthesis and releasing of procoagulant mediators (serotonin, histamine, adenosine 5^1 diphosphate - ADP) as well as prothrombotic microparticles [38]. Subsequently, new platelets are activated in a positive feed-back manner. PF4/Heparin complexes bind to monocytes, neutrophils and endothelial cells inducing cellular injury and releasing of tissue factor that promotes prothrombotic mechanisms. A procoagulant status associated with decreased platelets is thus generated, and defines the heparin induced thrombocytopenia that is clearly different from any other form of drug-induced thrombocytopenia.
Clinical studies showed that about 50% of patients treated with heparin develop HIT antibodies, but not all these antibodies are pathogenic and only a minority of patients have clinical consequences [30].

Epidemiology

There are several risk factors associated with HIT occurrence that include heparin-related and host-related variables. LMWH is associated with a 5- to 10-fold lower risk of HIT than UFH [16] and no difference were observed for the route of administration (subcutaneous or intravenous) or the dose used. Heparin exposure for more than 5 days significantly increases the risk of HIT compared to shorter duration administration (2.6% *versus* 0.2%) [16,23]. The age of recipients over 40 years seems to be associated with higher risks as well as the female sex. HIT is more frequently seen among surgical than medical patients, and especially in those undergoing surgery on cardiopulmonary bypass, probably related to the degree of platelet activation during different surgical procedures. The incidence of HIT is less than 1% in critically ill patients [22], in those undergoing hemodialysis [7] and in pregnancy [20].

Diagnosis

The diagnosis of HIT is based on clinical and serologic data and must be suspected whenever a patient treated with heparin has a significant platelet count fall in the first 5-14 days of therapy or when he or she develops a new thrombosis or extends a previous one being under heparin treatment. The diagnosis of HIT should only be made if the clinical picture is reasonably consistent with this diagnosis associated with the presence of platelet-activating anti-PF4/Heparin antibodies (demonstrated by laboratory assays) and without other explanation for thrombocytopenia.

Thrombocytopenia is usually moderate, the median nadir platelet count is usually 50-60 x 10^9/L but it can have any value between 20 and 150 x 10^9/L and it seldom falls below 20 x 10^9/L in the absence of concomitant disseminated intravascular coagulation - DIC [4]. A more appropriate evaluation of thrombocytopenia, especially in surgical patients in whom the

platelet count can increase in the first 72 hours following surgical intervention, is defined by the decreasing of the platelet count for at least 50% of the maximum level determined after surgery, even though this value does not fulfill the laboratory criterion for thrombocytopenia (e.g. below 150 x 10^9/L) [38].

Most often, in heparin-naïve patients, thrombocytopenia occurs between the 5th and the 14th day after exposure, but patients previously treated with heparin (within a 30 to 100 days interval) can develop thrombocytopenia in the first 4 days of treatment (*"rapid-onset"* HIT) as a result of sudden platelet activation by the pre-existing anti-PF4/Heparin antibodies. This is why platelet count monitoring is recommended in any patient previously exposed to heparin [20]. Rarely, thrombocytopenia appears after heparin cessation *("delayed-onset"HIT*) and can affect patients with only minimal previous exposure to heparin [14]. These patients present with new thrombotic accidents and heparin re-exposure rapidly induces thrombocytopenia, extension of the thrombosis or a new thrombotic event. When thrombocytopenia persists more than one week after heparin withdrawal (the median time to platelet recovery is 4 days), a "delayed-onset" HIT should be suspected [32]. Patients with "delayed-onset" HIT have intensely positive tests for anti-HIT antibodies.

The classic clinical picture of HIT associates thrombocytopenia with thrombosis but sometimes thrombocytopenia is not (at least initially) accompanied by thrombosis which is defined as *"isolated" HIT*. Approximately 30% to 50% of cases develop thrombosis within 30 days after heparin cessation if an appropriate anticoagulant therapy is not provided. These patients require venous compression ultrasound of the limbs even though the clinical signs are not obvious, as the thrombotic events might be silent.

Heparin induced thrombocytopenia is rarely accompanied by spontaneous bleeding, even when the platelet count is very low, because this condition is a prothrombotic state, hence petechiae or hemorrhage are considered evidences against HIT [4].

Thrombotic complications are the most feared and severe manifestation of HIT and may be limb- or life-threatening. Their occurrence is unpredictable at any time during HIT evolution. About 25% of thromboses appear concomitant to platelet decreasing, the rest of them being equally distributed before and after thrombocytopenia onset or even remote from heparin withdrawal ("*delayed-onset*" HIT) [5]. Any inexplicable thrombosis (defined as a new event or extension of a pre-existent one)

within 30 days following heparin exposure should rise the suspicion of HIT, even though it is not associated with thrombocytopenia (*"latent" HIT*).

HIT-related thrombosis can have any location, involving the deep veins of the lower limbs, the pulmonary circulation or the sites of the central venous catheter. Arterial thromboses are much rare, particularly after cardiovascular surgery. Seldom, thrombosis can involve adrenal veins with hemorrhage and adrenal failure, and if it develops bilateral, it results in death of the patient [19]. Other very rare locations are cerebral and coronary circulation.

Systemic anaphylactoid reactions: fever, chills, tachycardia, tachypnea, hypo- or hypertension, cardiovascular failure, neurologic signs (headache, global transitory amnesia) and digestive signs (diarrhea) that appear 5 to 30 minutes after intravenous *bolus* heparin or up to 2 hours after subcutaneous administration represents rare, unusual clinical manifestations of HIT.

Skin necrosis at the injection site is also a manifestation of HIT by contrast to the erythematous non-necrotizing injection-site lesions that are the result of delayed type IV hypersensitivity rather than HIT [21].

Laboratory diagnosis of HIT

HIT is caused by antibodies of the IgG class, that recognize large multimolecular complexes of PF4 bound to heparin, but only a minority of them are platelet-activating.

There are two types of tests used to identify anti-PF4/Heparin antibodies: functional tests and immunologic assays.

Functional tests detect heparin dependent antibodies that are able to attach to Fc receptors and to induce platelet activation.

- *Serotonin release assay* (SRA) is the "gold standard" in HIT diagnosis and it is based on the platelet capacity to activate and release serotonin following antibody attachment. This test has the highest sensibility (90-99%) and specificity (80-97%) [30,31]. Two concentration of heparin (therapeutic concentration of 0.1U/mL and high concentration of 100U/mL) and patient serum or plasma, depleted of residual heparin, are added to washed donor platelets radiolabeled with ^{14}C-serotonin. The test is positive if platelet activation with subsequently release of serotonin is induced by heparin in therapeutic concentration and not in high concentration. This test lacks standardization and its use is restricted to a small number of reference laboratories because of its technical requirements.
- *Heparin Induced Platelet Activation test* (HIPA) uses patient serum and donor platelets together with heparin and it is positive if platelet

aggregation appears. This test has a lower sensibility (39-81%) and specificity (69-94%) than the previous one [30].

Functional tests are important in confirming the presence of pathogenic antibodies, but are technically demanding in order to be performed and limited in guiding management in acute clinical setting [25]. They are superior to immunological assays in determining which antibodies are clinically relevant but they are not routinely performed, so using only the immunologic assay contributes to HIT overdiagnosis as only 10% to 50% of patients with positive immunologic tests have true platelet-activating antibodies.

Immunologic assays are enzyme-linked immunoabsorbent assays (ELISA) that detect HIT antibodies linked to heparin or to a polyanion. They have high sensibility (near 100%) but low specificity as they detect not only pathogenic antibodies but also clinical irrelevant ones. Increasing optical density (OD) values, a marker of antibody level, corresponds to a greater risk of HIT: for every 1.0 U increase in OD, the probability for a positive SRA increases by 40 [37] and a 1-unit increase in anti-PF4/H antibody level is associated with an approximate doubling in the odds ratio of thrombosis by 30 days [1]. An OD level >2U has a high probability of a positive platelet activation assay and hence, a true HIT while for low (0.45-0.99) or moderate OD levels (1.00-1.99) a functional assay is required [29]. The high sensibility of the test confers a strong negative predictive value: a negative test excludes HIT, but a positive result must be confirmed by a functional assay [31].

Ideally, both tests should be used in HIT diagnosis and they must correlate with the clinical picture. When laboratory tests are discordant, results of the functional assays are favored.

In order to better evaluate the diagnosis of HIT and to avoid overdiagnosis that can determine inappropriate therapeutic decisions, ***clinical scoring systems*** have been developed to assess the pretest probability of HIT. Warkentin [37] proposed a "4Ts" scoring system based on four criteria: *T*hrombocytopenia, *T*iming, *T*hrombosis and the lack of o*T*her explanations (Table I). Each characteristic feature of HIT is given a score ranging from 0 to 2 and the sum of each component is used to determine the pre-test probability score:

- Scores 0 to 3 indicate a low probability of HIT; antibodies are improbable;
- Scores 4 to 5 indicate a possible HIT; testing for antibodies is most useful in these patients;
- Scores 6 to 8 indicate a probability of HIT greater than 80%.

Table I
Pretest probability of HIT: the "4Ts" score (after Warkentin [37])

	2 points	1 point	0 points
Thrombocytopenia	>50% fall or platelet nadir ≥ $20x10^9$/L	30%-50% fall or platelet nadir 10-19$x10^9$/L	fall <30% or platelet nadir <$10x10^9$/L
Timing of onset of platelet fall	Days 5-10 or ≤ day 1 if prior heparin exposure within the last 30 days	>day 10 or timing not clear (missing platelet counts) or ≤ day 1 with prior heparin exposure within the last 30-100 days	< day 4 without recent exposure
Thrombosis or other sequelae	Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV UFH **bolus**	Progressive or recurrent thrombosis, erythematous skin lesions, or suspected thrombosis (not yet proven)	None
o***T***her cause of platelet fall	None evident	Possible	Definite

The role of this is to rule out the diagnosis of HIT, as a low score indicates a low probability of having a positive activation assay. Even with high scores, only 50% of patients have positive confirmatory tests.

Diferential diagnosis of HIT

Thrombocytopenia occurring in a patient receiving heparin in different clinical settings may be difficult to interpret but the diagnosis of HIT should be always kept in mind:

- The antiphospholipid syndrome (APLS) may present with low platelet counts and venous or arterial thrombosis as well as thrombotic microangiopathy that require heparin treatment.
- Hematologic neoplasms frequently associate thrombocytopenia due to bone marrow infiltration or therapy side effects and may complicate with thromboses whose best treatment is heparin.
- Non-hematologic malignancy-associated thrombotic microangiopathy may resemble HIT as it is frequently treated with heparin.
- Common causes of hospital-acquired thrombocytopenia include infections, medication other than heparin, disseminated intravascular coagulation (DIC) and intravascular devices are common in critically ill patients [6] and in those recovering from surgery on cardiopulmonary bypass. These cases may have various degrees of thrombocytopenia that are frequently accompanied by hemorrhagic manifestations. In a prospective study, only 0.4% of the intensive care unit patients that had thrombocytopenia and received heparin developed HIT [3].

- In nocturnal paroxistic hemoglobinuria (NPH), hemolitic anemia and thrombocytopenia are sometimes associated with thromboses that require anticoagulant treatment with heparin and this condition may predispose to confusion with HIT in a previously unknown patient, when the clinical picture is incomplete (e.g NPH without crises of hemoglobinuria).

Management

Several management principles are mandatory for a good outcome in patients with intermediate or high suspicion of HIT:

- Heparin therapy must be immediately stopped as well as any kind of heparin

exposure, including flushes of intravascular catheters. LMWH should also be avoided because of its high potential of cross-reactivity.

- As the risk of developing thromboses continues 30 days after heparin cessation, an alternative anticoagulant should be used in patients with "isolated" or "latent" HIT as well as in those patients with an already established thrombosis. Therapeutic options include direct thrombin inhibitors (DTI): argatroban, lepirudin, bivalirudin and factor Xa inhibitors (danaparoid and fondaparinux). The Chest guidelines recommend argatroban or lepirudin or danaparoid over other nonheparin anticoagulants in patients with HIT and thrombosis or "isolated" HIT who have normal renal function and argatroban in patients with renal insufficiency [13]. For patients with acute or subacute HIT who require urgent cardiac surgery, bivalirudin is recommended [13]. DTI have short half-lives that make their administration difficult, their effect must be monitored by aPTT (activated partial thromboplastin time) which may be elevated due to confounding factors (liver impairment, DIC) that may ultimately determine DTI underdosing and hence, anticoagulant treatment failure. They also increase INR (international Normalised Ratio) which complicate vitamin K antagonists (VKA) overlap. Other authors favor factor Xa inhibitors in HIT treatment [36,8] because of several advantages over DTI: longer half-lives with reduced risks of rebound hypercoagulability, direct monitoring through anti-Xa levels that reflect accurate drug levels, no significant effect on INR that simplifies overlap with VKA and inhibitory effect on platelet activation by HIT antibodies (a unique effect restricted to danaparoid [9]). The main limitations of factor Xa inhibitors are related to their renal clearance that makes them not suitable for patients with severe renal impairment and the reported potential of fondaparinux to induce or exacerbate HIT [2], although the attribution to fondaparinux in these cases remains uncertain [27]. The unavailability of DTI and the favorable risk/benefit profile of factor Xa

inhibitors have determined their frequently use in clinical practice, but randomized trials are still required.

- The non-heparin anticoagulant should be used until platelet recovery. A special precaution must be taken concerning DTI-induced INR prolongation while vitamin K antagonist (VKA) is still at an under-therapeutic level. Premature ceasing of DTI in these cases will determine the increase of the thrombotic risk.
- Patients receiving VKA at the time HIT is diagnosed must have vitamin K supplement (5-10 mg IV or 10 mg orally) in order to reverse their effect and thus to reduce the risk of skin necrosis and the possibility of underdosing DTI because of the ability of VKA to prolong aPTT [24].
- VKA can be started after platelet count reaches normal and stable values (>150 x 10^9/mL). Loading doses should be avoided. VKA must overlap with the alternative anticoagulant for at least 5 days and until the INR reaches its intended target. Patients with HIT associated thrombosis are generally advised to maintain the oral anticoagulant for 3-6 months, although the precise duration of anticoagulation is unknown. All patients with acute HIT must undergo limb compression ultrasound, even in the absence of clinical signs of deep vein thrombosis because silent thrombosis is common. For patients with "isolated" HIT, the cumulative incidence of thrombembolism at 30 days was 53% in a retrospective study [34] and some authors recommend prolongation of VKA until a stable plateau of the platelet count is reached and 1 month thereafter [4].
- Platelet transfusion must be avoided as it can precipitate thrombosis. Furthermore, very low platelet counts and bleeding complications are rare, so platelet transfusion is seldom required.
- Heparin re-exposure must be avoided although HIT immune response wanes over time. Anti PF4/Heparin antibody titers gradually decline and are no longer detectable in 60% of patients by day 100 [35] and do not invariably reappear with subsequent heparin use. Retreatment is possible for patients with a remote episode of HIT who require surgical procedures with cardiopulmonary bypass, but previously functional assays for anti-PF4/Heparin antibodies are recommented [18]. In patients with acute or sub-acute HIT and who require urgent cardiac surgery, bivalirudin is recommended [13]. Some recent studies suggest that rivaroxaban and dabigatran may be suitable for thromboprophilaxis in patients with a history of HIT and even for the treatment of HIT acute itself [10,26].

HIT prevention remains a challenging issue because even with the effective therapies now available, it is still a life threatening condition in severe cases with early onset before the hypercogulability state can be

controlled by an alternative anticoagulant [28]. Several new strategies have been recently proposed: a new low-sulfated heparin, called 2-O,3-O desulfated heparin (ODSH) that inhibits formation of PF4/Heparin complexes, disrupts them on platelets and other cells and inhibit HIT antibody-induced platelet activation, apparently could prevent HIT when it is co-administrated with heparin for the first 1 or 2 days of therapy (as it has only minimal anticoagulant effect by itself) [10].

Conclusions

Among the potential side effects of heparin, HIT represents the most serious one, whose mortality can be as high as 23-30%. Thrombotic events related to HIT can induce severe disability, by amputation of the affected limb, when the diagnosis is delayed. HIT recognition may be difficult in the context of polymorphic clinical manifestations, confounding comorbidities and difficult access to specific laboratory assays. All these factors along with the permanent fear of the clinician of missing a true case of HIT, led to overdiagnosis and to unnecessary exposure of some patients to alternative and sometimes potential harming anticoagulants. On the other hand, the diagnosis of HIT must be always kept in mind when exposing a patient to heparin, because of its high morbidity and mortality risk.

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