

Review

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Heparin-induced thrombocytopenia: an update

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Abstract

Heparin-induced thrombocytopenia (HIT) is the most important and most frequent drug-induced, immune-mediated type of thrombocytopenia. It is associated with significant morbidity and mortality if unrecognized. In this review, we briefly discuss the main features of heparin-induced thrombocytopenia, particularly analyzing the most recent advances in the pathophysiology, diagnosis and treatment of this syndrome.

Introduction

Heparin is a drug widely used for thromboprophylaxis or treatment in many clinical situations, including cardiovascular surgery and invasive procedures, acute coronary syndromes, venous thromboembolism, atrial fibrillation, peripheral occlusive disease, dialysis and during extracorporeal circulation [1,2]. However, it can cause serious adverse effects, including heparin-induced thrombocytopenia (HIT) which is a common, serious and potentially life-threatening condition [3-6]. Unfortunately, because thrombocytopenia is common in hospitalized patients and can be caused by a variety of factors [7], HIT often remains unrecognized.

Heparin-induced thrombocytopenia is defined as a decrease in platelet count during or shortly following exposure to heparin [8]. Two different types of HIT are recognized. The first, HIT type I (also called heparin-associated thrombocytopenia in the past), is a benign form not associated with an increased risk of thrombosis. The mechanism of HIT type I is still unknown but it is likely to be non-immune, probably related to its platelet pro-aggregating effect. This form of HIT affects up to 10% of

patients under treatment with heparin and is characterized by a mild and transient asymptomatic thrombocytopenia (rarely less than 100,000 platelets/ μ L) that develops early (usually within the first two days of starting heparin) and disappears equally quickly once the heparin is withdrawn. The second form of HIT, HIT type II, is immune-mediated and associated with a risk of thrombosis. It has recently been proposed that the term "HIT type I" be changed to "non-immune heparin associated thrombocytopenia" and that the term "HIT type II" be changed to "HIT" to avoid confusion between the two syndromes [9].

In this review we briefly analyze the main characteristics of the clinically relevant, immune-mediated, second type of HIT, focusing particularly on the epidemiology, pathophysiology, clinical manifestations and treatment of this syndrome. For simplicity and also in accordance with the new recommendations, in the following the term HIT refers to HIT type II.

Incidence

Heparin-induced thrombocytopenia is the most important of the immune-mediated, drug-induced

thrombocytopenias. Recent data show that up to 8% of heparinized patients will develop the antibody associated with HIT [10] and that approximately 1–5% of patients on heparin will progress to develop HIT with thrombocytopenia [11,12], suffering from venous and/or arterial thrombosis in at least one-third of cases [13,14]. In a recent analysis of 598 consecutive hospitalized medical patients treated with subcutaneous unfractionated heparin, Girolami and colleagues diagnosed five cases of HIT (0.8%) [15]. In general, the antibodies occur more frequently in patients undergoing cardiovascular surgery than those undergoing orthopedic surgery, and in post-surgical patients than in medical patients. HIT antibodies are also more frequent in patients receiving unfractionated heparin (UFH) than in those treated with low molecular weight heparin (LMWH) [16,17], although it must be highlighted that antibodies developing in patients receiving UFH frequently cross-react with LMWH [13]. In a study conducted on 665 patients undergoing elective hip arthroplasty who had been randomized to receive either UFH or LMWH for thromboprophylaxis, Warkenit and colleagues reported that HIT occurred in 9 of 332 patients who received UFH and in none of 333 patients who received LMWH (2.7% versus 0%, $P = 0.0018$) [10]. In addition, development of heparin-dependent antibodies and thrombotic events associated with thrombocytopenia were more common in patients treated with UFH than in those treated with LMWH.

Pathophysiology

The mechanism underlying heparin-induced thrombocytopenia is an immune response [18,19]. The principal antigen is a complex of heparin and platelet factor 4 (PF4). Platelet factor 4 is a small positively charged molecule of uncertain biological function normally found in α -granules of platelets. When platelets are activated, PF4 is released into the circulation and some of it binds to the platelet surface. Because of opposite charges, heparin and other glycosaminoglycans bind to the PF4 molecules, exposing neoepitopes that act as immunogens leading to antibody production. In fact, patients who develop HIT produce an IgG antibody against the heparin-PF4 complex, which binds to the complex on platelet surface through the Fab region [20]. The Fc portion of the HIT antibody can then bind to the platelet Fc receptor and this interaction triggers activation and aggregation of the platelets. Activated platelets release PF4, thus perpetuating the cycle of heparin-induced platelet activation. In addition, the platelet activation leads to the production of pro-thrombotic platelet microparticles which promote coagulation. Finally, as a result of the presence of heparin-like molecules (heparan sulfate) on the surface of endothelial cells, the HIT antibody-PF4-heparan sulfate complexes formed on the endothelial surface may induce tissue factor expression with further activation of the coag-

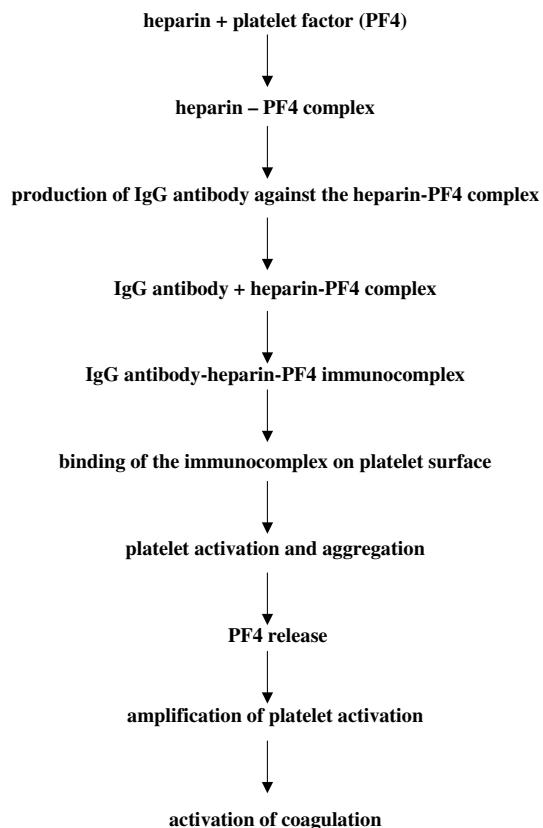


Figure 1
Pathophysiology of heparin induced thrombocytopenia.

ulation cascade and thrombin generation [21,22]. Thrombocytopenia in HIT is largely due to the clearance of activated platelets and antibody-coated platelets by the reticulo-endothelial system [1]. Figure 1 illustrates the pathophysiology of HIT.

Clinical features and diagnosis

The onset of heparin-induced thrombocytopenia may be rapid or delayed. The platelet count in patients with pre-existing heparin-PF4 antibodies from a previous exposure and sensitization to heparin may decrease within the first 3 days or even hours after re-exposure to heparin (rapid-onset HIT) [23]. However, in patients receiving heparin for the first time, the onset of thrombocytopenia usually occurs 5 to 10 days after the administration of the heparin. Conversely, in delayed-onset HIT, the thrombocytopenia occurs 5 or more days after heparin withdrawal [24].

The thrombocytopenia in HIT is usually moderate in severity, with a median platelet count being between 50 and $80 \times 10^9/L$, although the nadir platelet count can remain at a level considered normal (i.e. $> 150 \times 10^9/L$) but having dropped by 50% or more with respect to the pre-heparin value. The platelet count starts to rise 2 to 3 days after discontinuing heparin and usually returns to normal within 4 to 10 days. The antibody disappears within 2 to 3 months after cessation of heparin therapy [11]. Although HIT does not invariably recur during subsequent re-exposure to heparin, future use of heparin is contraindicated [25]. Despite thrombocytopenia, bleeding is rare [2]. Contrariwise, HIT is strongly associated with thrombosis, which frequently leads to the recognition of HIT [26]. Thrombosis in HIT is associated with a mortality of approximately 20–30%, with an equal percentage of patients becoming permanently disabled by amputation, stroke or other causes [27]. Thromboembolic complications can be venous, arterial, or both and include deep venous thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke and occlusion of limb arteries [28]. However, the type and site of thrombosis depends on the patient's clinical profile. For example, deep vein thrombosis and pulmonary embolism occur very frequently in postoperative patients who are already prone to developing venous thromboembolism [10]. In fact, Warkentin and colleagues reported that the incidence of deep vein thrombosis in orthopedic patients who received heparin for thromboprophylaxis was 17.8%, but that this incidence increased dramatically to 88.9% among patients who developed HIT [10]. Similarly, patients with central venous catheters and HIT develop upper limb venous thrombosis more frequently than those without HIT [1]. In some cases thrombosis of the cerebral venous sinuses can occur, giving rise to a clinical picture of severe headache and progressive neurological deficits [29]. In contrast, arterial thrombosis occurs more frequently than venous thrombosis in HIT patients receiving heparin for cardiovascular diseases [30]. Furthermore, areas of necrosis developing at the site of heparin injections can be a manifestation of HIT, and are not necessarily associated with thrombocytopenia [31]. Platelet activation and thrombosis due to heparin-dependent, platelet-activating IgG have been shown to be the underlying pathogenic mechanisms of this complication [31]. In some cases, thrombosis may be generalized leading to a syndrome resembling disseminated intravascular coagulation [32].

Finally, in some patients with HIT resistance to heparin may occur, meaning that an increasing dose of heparin dose is required to maintain the activated partial thromboplastin time (aPTT) within the therapeutic range [13].

The diagnosis of HIT remains a clinical one, supported by confirmatory laboratory testing [5,6]. The criteria include: a) thrombocytopenia (i.e., a drop of the platelet count to below $100 \times 10^9/L$ or a drop of > 50% from the patient's baseline platelet count); b) the exclusion of other causes of thrombocytopenia; c) the resolution of thrombocytopenia after cessation of heparin [1]. As regards the laboratory tests, HIT-antibodies can be demonstrated *in vitro* by functional tests and immunoassays [4,8]. Functional tests, which measure platelet activity in the presence of the patient's serum and heparin, include heparin-induced platelet aggregation (HIPA) and the serotonin release assay (SRA). Although the HIPA test is easier to perform and thus more commonly used, the SRA is more sensitive, albeit more complex, technically demanding and not readily available in most centers, and is therefore considered the "gold standard" [1]. The immunoassays utilize immunoenzymatic tests (enzyme-linked immunosorbent assay, ELISA) to detect the HIT antibody that binds to the PF4/heparin complex. Immunoassays are technically easier to perform than the functional assays and are also more sensitive [1]. On the other hand, comparative and prospective studies have demonstrated that functional tests are more specific than enzyme immunoassays and thus, being better at detecting the clinically significant HIT antibodies, are more helpful in the diagnosis of HIT [3].

Treatment

When HIT is suspected clinically, immediate cessation of all formulations of heparin is mandatory, but this will neither stop continuing thrombin generation nor avoid subsequent thrombotic events, which occur in as many as 40–50% of the patients over the next several days or weeks [33]. Interestingly, in a retrospective analysis of 113 patients with HIT, Wallis and colleagues [34] found that early heparin cessation (0.7 ± 0.6 days) was no more effective in reducing morbidity and mortality than was late heparin cessation (5 ± 3 days), thus indicating that heparin cessation alone is not sufficient treatment for HIT. In fact, the appropriate treatment for HIT requires immediate removal of the trigger (heparin cessation) as well as control of the thrombin storm of HIT (by providing appropriate alternative anticoagulation). Currently, three non-heparin anticoagulants that do not cross-react with HIT antibodies, danaparoid, lepirudin and argatroban, are available for alternative anticoagulation in HIT [35–41]. These drugs are immediately active and either inhibit thrombin directly or inhibit thrombin generation. As reported above, LMWH cannot be used in patients with HIT because of the strong cross-reactivity of the HIT antibody with the LMW heparin/PF4 complex. The duration of treatment for patients with HIT is not well defined. However, anticoagulation treatment is required for at least 2 to 3 months to prevent recurrence of thrombosis. Oral anticoagulation with warfarin should be initiated

until substantial platelet count recovery has occurred and while the patient is receiving danaparoid or a thrombin-specific inhibitor (an overlap of at least 5 days is recommended) [33]. In fact, it has recently become known that HIT patients who are switched to warfarin alone after the discontinuation of heparin may paradoxically have worsening thrombosis and develop venous limb gangrene and skin necrosis [42]. The mechanism appears to be a warfarin-induced marked decrease in protein C before prothrombin levels are adequately suppressed [2].

Danaparoid has been successfully used as a replacement for heparin in patients with HIT [43]. This anticoagulant is composed of a mixture of three glycosaminoglycans (heparin sulfate, dermatan sulfate and chondroitin sulfate) and, via antithrombin, inhibits anti-FXa activity. In a prospective randomized study conducted by Chong and colleagues [41], danaparoid was shown to be more effective than dextran 70 in the treatment of HIT-associated venous and arterial thrombosis. In a compassionate use program, more than 460 patients with HIT-associated thrombosis were treated with danaparoid with a success rate of over 90% [44]. For treatment of HIT, danaparoid is given as an intravenous bolus dose of 2500 U followed by 400 U/hour for 4 hours, then 300 U/hour for 4 hours and subsequently 200 U/hour until anticoagulation is no longer required, adjusting the dose to maintain plasma anti-Xa levels within 0.5–0.8 U/mL. Alternatively, danaparoid can be administered subcutaneously using a bolus of 1250 U followed by 2000 U twice a day [1].

Recombinant hirudin (lepirudin), an anticoagulant protein originally produced by the medicinal leech, inhibits thrombin directly [1]. In a meta-analysis of three prospective multicenter trials including 91 patients with laboratory-confirmed acute HIT treated with lepirudin, Lubenow and colleagues [45] found that the incidence of the combined end-point of death, new thromboembolic complications and limb amputation was significantly lower in the lepirudin-treated patients than in a contemporaneous control group not treated with lepirudin. Currently recommended doses are 0.4 mg/kg as a bolus followed by 0.15 mg/kg/hour adjusting the dose to achieve an aPTT of 1.5 to 3 times the baseline value [33]. In a retrospective study of 175 lepirudin-treated HIT patients and 126 danaparoid-treated HIT patients, Farmer and colleagues [46] found no significant difference in the same combined end-points between the two groups.

Argatroban, an arginine-based synthetic anticoagulant, is a direct inhibitor of thrombin that reversibly binds the catalytic site of thrombin [13,47]. A multicenter, prospective study conducted on 304 HIT patients receiving argatroban found that the above mentioned combined endpoints were significantly reduced in argatroban-treated

patients compared to in historical controls [40]. The recommended initial dose is 2 µg/kg/minute given intravenously and adjusted to achieve an aPTT 1.5 to 3 times the baseline value. Since argatroban is cleared by the liver, lepirudin, which is cleared through the kidneys, should be preferred in patients with liver disease. Vice versa, argatroban would be a better initial choice in patients with renal insufficiency. Thrombin-specific inhibitors also prolong the INR, but this effect is particularly pronounced with argatroban [48]. Thus, during the transition from argatroban to oral anticoagulation special precautions must be taken [49,50].

Finally, there is recent evidence that a novel synthetic heparin pentasaccharide, fondaparinux, which does not cross-react with HIT antibodies [51], can be successfully used for the treatment of patients with HIT [52,53]. However, additional controlled clinical studies are required to further evaluate the safety and efficacy of this agent in patients with HIT.

Conclusion

The analysis of the literature data reveals that heparin-induced thrombocytopenia is not only a common but also a serious complication of heparin therapy with a high rate of morbidity and mortality. Its prompt clinical and laboratory recognition is thus essential in order to stop heparin use immediately and commence an alternative anticoagulant. The low molecular weight heparinoid, danaparoid, and the thrombin-specific inhibitors, lepirudin and argatroban, have been shown to be effective in HIT patients.

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