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HEPARIN IN HIT: EFFECTIVENESS AS AN ANTICOAGULANT

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ABSTRACT: Heparin-induced thrombocytopenia (HIT), a devastating immune mediated adverse drug reaction, is triggered by the development of antibodies that stimulates the platelet activation in presence of heparin. Bleeding is infrequent in HIT patients regardless of thrombocytopenia; however, HIT is strongly associated with thromboembolic complications involving both venous and arterial systems. Numerous novel oral anticoagulants exist that may be beneficial for HIT, principally in cases refractory to standard therapies. However, these agents have not been fully evaluated for treatment of patients with HIT and hence none have FDA approval for use in HIT. Diagnosis of HIT is a bit challenging because of the routine use of heparin in hospitalized patients, which is one of the common consequences of thrombocytopenia. Numerous laboratory tests are available to confirm the diagnosis of HIT, but its clinical suspension remains crucial to the early cessation of heparin and initiation of alternative therapy. Treatment includes the initiation of alternative anticoagulants resulting in the reduced prevalence of HIT.

INTRODUCTION: Patients receive anticoagulants to prevent or treat blood clots. Heparin is frequently used as an intravenous therapeutic agent in thromboprophylaxis treatment in many clinical cases, including invasive procedures, acute coronary syndromes, cardiovascular surgery, venous thromboembolism, peripheral occlusive disease, and dialysis [1, 2].

Nevertheless, heparin-induced thrombocytopenia (HIT) is a serious and potentially life-threatening disorder associated with significant morbidity and mortality [3, 4, 5, 6]. HIT results in venous or arterial thrombosis and other rarely occurring congenital bleeding disorders [2, 3].

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In HIT, heparin acts as a confusing agent as it performs the opposite function than expected, *i.e.*, it forms new blood clots instead of preventing them [7]. Heparin generally acts as an anti-coagulant and does not affect the platelets.

However, HIT causes thrombocytopenia (low platelet count), which gets excited by immune system in response to heparin [8]. This complication can be defined as Type I HIT (non immune-mediated HIT) that results in the decrease in platelet counts during or shortly after the exposure to heparin.

There are significantly two types of HIT comprising immune and non-immune mediated conditions. The Type I or non-immune mediated HIT is a transient, benign, and self-limiting form of thrombocytopenia. In Type I HIT patients, a decrease in platelet count occurs in the first five days of the therapy due to the direct agglutinating impact of heparin on platelets [9, 10].

However, the development of thrombocytopenia in immune-mediated or Type II HIT appears within 5th to 14th day of the initiation of heparin therapy [9, 11]. In the immunologically mediated HIT condition, the antibodies are directed to heparin/platelet factor 4 (PF4) complexes that are formed during the heparin treatment [3].

Prevalence of HIT: HIT is termed as the most serious complication of the immune-mediated drug-induced thrombocytopenia, as reports have shown that up to 8 % of the heparinized patients are at higher risk of developing antibodies [12]. Moreover, it has also been reported that 1-5 % of the patients administered with heparin have more chances to develop HIT with thrombocytopenia [13, 14] by suffering from venous and/or arterial thrombosis in at least one-third of the cases [15, 16]. If thrombotic syndromes develop, limb amputation is prescribed in almost 20% of patients, whereas nearly 30% to 50 % of patients die [17]. Moreover, around 50% of patients are reported to develop deep vein thrombosis (DVT), and 25% develop acute systemic reaction and pulmonary embolism (PE), respectively [18]. Other HIT complications include acute limb ischaemia, skin lesions at the injection site, myocardial infarction, or acute thrombotic stroke [18]. The antibodies mostly occur in patients undergoing cardiovascular surgery compared to those subjected to orthopaedic surgery, and in post-surgical patients compared to medical patients. Furthermore, patients administered with unfractionated heparin (UFH) develop more HIT antibodies than those treated with low molecular weight heparin (LMWH) [19].

Pathophysiology of HIT: The mechanism underlying HIT is a reaction of the immune system to heparin [20, 21], which gets started with the binding of heparin to PF4 resulting in the formation of a highly immunogenic complex on the surface of the platelets. An IgG antibody to the antigenic heparin/PF4 complex develops in susceptible patients. The consequent antibody binds with the heparin/PF4 complex that in turn triggers the platelets activation through Fc receptors found on the surface of the platelets. Thrombocytopenia develops as the reticuloendothelial system and destroys its own activated platelets. Furthermore, platelet activation results in the production of procoagulant-rich microparticles, thereby, contributing to a thrombotic state [14, 22, 23].

Diagnosis of HIT: HIT diagnosis remains a challenging task, which should be suspected when thrombocytopenia or unexplained thrombosis occurs after the patient has recently been exposed to heparin therapy [12]. Misdiagnosis of HIT can be explained through three main issues. First, the name of the disorder creates confusion whether the clinically significant thrombocytopenia is present in all HIT patients. Second, thrombocytopenia in HIT patients is unexpectedly associated with thrombosis and not with bleeding. And finally, thrombocytopenia may arise from many other causes in hospitalized patients, including disseminated intravascular haemolysis (DIC), septicaemia, hypercoagulable states, multi-organ failure, and bone marrow disorder [24]. Therefore, other causes of thrombocytopenia should be excluded before HIT diagnosis.

A reference standard diagnostic laboratory test for HIT is not available till date. However, two types of laboratory assays are available, *i.e.*, the immunoassays and the functional assays. The immunoassay such as the enzyme-linked immune-sorbent assay (ELISA) is mostly used to diagnose HIT. ELISA has a sensitivity of almost 80% to 90% and can identify the antibodies against heparin/PF4 complexes. The functional assays comprise of several methods of platelet aggregation tests, the C-serotonin-release assay, and flow cytometric platelet activation assay [25, 26, 27] for the identification of antibodies that activate the platelets. Immunoassays can identify IgG, IgM, or IgA, even in low titers that have no clinical importance. Adversely, functional assays can detect the same antibodies but in higher titers [3, 9, 28].

Numerous score systems have been recommended for the estimation of the clinical probability of HIT type II because of the difficulties reported in reading the above serologic methods. These score systems are based on the severity of thrombocytopenia, the recovery following drug removal, beginning of thrombotic complications, and the elimination of the other varied causes of thrombocytopenia.

HIT type II diagnosis is low when the score is <1, intermediate within 1-3, and high when the score is >3 [3, 29]. It is important to have a frequent check on the platelet counts of the patients, thereby, verifying whether they are still in the high score level (>3) [30].

Inconclusive immunoassays can be confirmed using platelet activation tests, *e.g.,* the heparin-induced platelet activation (HIPA) assay or serotonin release assay (SRA). These assays are characterized by excellent specificity of 90% to 100%, and a positive analytical value of 89% to 100% [30]. Yet, those assays are available only in certain laboratories and they are time-consuming tests.

The diagnosis of HIT type II is primarily clinical, which is later confirmed by laboratory results. On conditions of thrombocytopenia or thrombosis, a positive test result is essential to confirm the diagnosis of HIT type II. An alternative assay is tested if the result of the selected initial test is negative and the clinical possibility of the syndrome is high; whereas the diagnosis is confirmed if the second test result is positive. In case the second test result is negative, the diagnosis is doubtful even if the clinical picture suggests the presence of the HIT type II disorder [3, 31]. Other disorders such as thrombocytopenia associated with pulmonary embolism (PE) and DIC, cancer associated DIC and thrombosis in which serologic assays are negative can strongly mimic HIT [29].

Management of HIT: The primary step of managing a patient with suspected or confirmed HIT is to stop all heparin infusions (UFH and LMWH), including the removal of heparin-coated intravascular catheters and heparin flushes [32]. The recommended guidelines for HIT management includes the use of alternative anticoagulant, whether HIT is complicated or not by thrombosis. As HIT is a risk factor for coumadin-associated microvascular thrombosis, oral suspension of vitamin K antagonists (VKAs) should be administered [33]. Platelet concentrate (PC) transfusions are contraindicated for the treatment of thrombocytopenia in acute HIT, unless there is evidence of clinical bleeding [34]. Direct thrombin inhibitors (DTI) including lepirudin, argatroban and bivalirudin are the drugs of choice for HIT treatment as they neither bind to blood platelets nor are neutralized by PF4. Furthermore, these drugs are administered by continuous intravascular infusion. However, the disadvantages of DTIs include the lack of possibility to routinely monitor their biological efficacy and the risk of substantial bleeding [30].

During the unavailability of DTIs, factor Xa (FXa) inhibitors should be administered because of the similarity between their mechanism of action and that of LMWH. The rate of thrombin generation decreases when the binding of the drug to antithrombin inhibits the FXa. As FXa inhibitors do not bind platelet or PF4, they are considered safe and effective for HIT treatment [35, 36].

CONCLUSION: HIT is a serious but rarely encountered complication of heparin therapy. HIT should be considered when the condition of the low platelet count increases and/or when an unexplained new thrombus occurs while or after a patient is subjected to heparin. HIT results from platelet activation and aggregation provoked by antibodies recognizing heparin/PF4 complex. Heparin should be withdrawn instantly and platelet concentrates in transfusions should be avoided when HIT is suspected or confirmed. Treatment includes the initiation of alternative anticoagulants resulting in the reduced prevalence of HIT. Initial detection of HIT and avoidance of suitable heparin treatment can aid promote a safe and efficient anticoagulation therapy

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