Heparin Induced Thrombocytopenia for the Perioperative and Critical Care Clinician

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Abstract
Purpose of Review This review will illustrate the importance of heparin-induced thrombocytopenia in the intraoperative and critical care settings.

Recent Findings Heparin-induced thrombocytopenia (HIT) occurs more frequently in surgical patients compared with medical patients due to the inflammatory release of platelet factor 4 and perioperative heparin exposure. Recognition of this disease requires a high index of suspicion. Diagnostic tools and therapeutic strategies have been expanded and refined in recent years.

Summary HIT is a condition where antibodies against the heparin/platelet factor 4 complex interact with platelet receptors to promote platelet activation, aggregation, and thrombus formation. Our review will focus on intraoperative and postoperative considerations related to HIT to help the clinician better manage this rare but often devastating hypercoagulable disease process.

Keywords Heparin · Thrombocytopenia · Surgery · Limb ischemia · Thrombosis

Introduction

Heparin-induced thrombocytopenia (HIT) is a prothrombotic disease where antibodies against the molecular complex of heparin-to-platelet factor 4 (PF4/H) interact with platelet receptors to promote platelet activation, aggregation, and removal from circulation [1, 2]. PF4 is secreted by platelet granules or displaced from the endothelium. HIT antibodies against the heparin/PF4 complex will trigger downstream thrombin generation and catastrophic thrombus formation. The prevalence of HIT is rare in both medical and surgical patients, and the incidence in most population-based studies ranges between 0.3 and 3.0%. However, the occurrence of HIT in the operating theater or the postoperative critical care setting can be swift and devastating. In this review, we will discuss standard definitions, scoring systems, epidemiology, and pathogenesis that is relevant to the perioperative and critical care environments. For our review, we will be referring to the type 2 variety of HIT, where an immune-mediated disorder emerges typically 4–10 days after heparin exposure to heparin and has life- and limb-threatening thrombotic complications [2, 3]. There will be a limited focus on the less clinically important type 1, which is a non-immune process that presents within the first 2 days after heparin exposure with correction of thrombocytopenia despite continuation of heparin therapy [3].

Definition and Epidemiology

Approximately 20–50% of critically ill patients present with thrombocytopenia in the intensive care unit (ICU), whereby a reduced platelet count below 150,000 platelets per microliter of blood is noted on laboratory testing [4]. Heparinoid exposure by syringe flush, subcutaneous prophylaxis, or therapeutic anticoagulation is common in the operative room (OR) and ICU environments [5]. Only a fraction of those with low platelet counts will develop HIT, which presents in approximately 0.3–0.5% of critically ill patients exposed to heparin [6]. These statistics suggest that around 1 in 100 ICU patients will develop thrombocytopenia due to HIT [1, 4, 7]. HIT is paradoxically linked to a high risk for arterial and venous thromboses. Almost half of the critically ill patients diagnosed with HIT will present with thrombotic events [5, 8].
HIT presents in the setting of higher concentrations of platelet factor 4 (PF4) leading to the formation of PF4/H complexes. Surgery can trigger the release of massive amounts of PF4 [9]. Therefore, the frequency of HIT varies with the type of surgery. Five percent of orthopedic surgical patients exposed to heparin for 10–14 days present with HIT [10–12]. Shorter courses of heparin treatment seem to decrease the risk of HIT development [13]. Preferential use of low molecular weight heparin (LMWH) as opposed to unfractionated heparin (UFH) is associated with lower rates of HIT [14•]. In cardiac surgery patients, the frequency of HIT is approximately 2% [15, 16•]. Although HIT is less frequent in cardiac surgical patients compared with orthopedic patients, cardiac surgical patients have a higher frequency of HIT immunization (positive antibody formation) [15], potentially due to the high intraoperative UFH doses required for anticoagulation on cardiopulmonary bypass [7, 17]. HIT presents in trauma patients with a frequency of around 2.2% [18]. Patients with major trauma showed higher rates of seroconversion compared with patients with minor trauma (OR 7.98 [95% CI 2.06–31.00]; \( P = 0.003 \)). In these patients, HIT incidence was lower when using LMWH versus UFH, although the difference was not statistically significant (LMWH 1.3% vs. UFH 0.3%; \( P = 0.37 \)).

HIT occurs more frequently in surgical patients compared with medical patients [19, 20]. Medical patients present a HIT prevalence of around 0.8–2.0% [20, 21]. Gender seems to be a risk factor for HIT and females are more affected than men (OR, 9.22 vs. 1.83; \( P = .020 \)) [19]. HIT is uncommon in obstetric patients [22].

The type of heparin used is a well-described risk factor for HIT. A small study with patients undergoing first-time CABG reported a seroconversion rate of 44.4% for bovine heparin and 30.6% for porcine heparin. Intraoperatively, bovine heparin is less frequently used compared with porcine heparin, and in the setting of HIT, both should be avoided [23]. Unfractionated heparin has been significantly associated with a higher incidence of HIT (almost 10-fold higher), [2•] compared with LMWH and selective factor Xa inhibitors like fondaparinux [9, 18, 19, 24] likely due to the difference of the polysaccharide chain lengths and the degree of sulfation of each medication [25]. Of importance, dosing seems to be correlated to the risk of developing HIT. Prophylactic UFH is more frequently associated with HIT compared with therapeutic UFH, due to the fluctuations in the PF4/H ratio. LMWH and fondaparinux are less likely to form multimolecular complexes with PF4 and, consequently, less likely to induce HIT.

The variability in the reported frequency of HIT is due to the multiple factors. Differences in the studied populations (medical vs. surgical) [15], type of heparin used [9, 24], duration of therapy, [10] and female over-representation [19] have been strongly correlated with such variability. Other limitations of the studies include selection bias, inconsistency in the definitions used for thrombocytopenia and HIT, discrepancy/inconsistency of tests performed for confirmation, and differences in baseline patient characteristics (including baseline platelet counts, inclusion of patients with early thrombocytopenia, and the failure to exclude patient whose platelet counts recovered during continue heparin treatment) [19, 26–28].

In the ICU, exposure to UFH occurs from flushes and heparin-bonded devices. Although rare, Swan-Ganz catheters and extracorporeal circuits may be heparin coated to avoid thrombus formation during routine standard use. Even minor heparin exposures can elicit the formation of HIT antibodies [29], but not all antibodies will trigger the development of HIT. The estimated frequency of catheter-associated HIT is around 0.4% [30]. Patients with central catheters and HIT antibodies are at a higher risk for both upper-extremity and lower-extremity DVT occurring at the catheter site [31]. The larger devices (i.e., VAD, ECMO, intra-aortic balloon pump) require high doses of systemic UFH, increasing the risk of seroconversion and clinically apparent HIT. Interestingly, the incidence of HIT in this population is around 8% [32], while the rate of seroconversion by immunoassay has been reported between 25 and 75% [15, 32, 33]. Such a wide range depends on the criteria used to define HIT, the populations included, and the difference in confirmatory tests used for diagnosis.

Pathogenesis

The binding specificity of heparin is determined by its negative charge, molecular size, molecular weight, and chain length [34••]. Heparin binding to the platelet surface can trigger the release of PF4, a positively charged chemokine secreted from the α granules of activated platelets [35]. PF4 readily binds negatively charged proteins on the endothelium and also to soluble proteins such as heparin [36]. Excess PF4 binding can alter the usual configuration of the endothelial proteins, expressing new antigens and inducing an immune response [34••, 37].

To be immunogenic, the PF4-heparin complexes must be soluble and sizable [25] to interact with the Fc γ receptors present on platelets and monocytes [38]. As a result of this interaction, these cells are activated and potentiate thrombin generation. In HIT, high-affinity IgG antibodies are produced soon after heparin exposure along with IgA and IgM antibodies [39]. In contrast to other conditions, HIT does not present with an initial IgM phase [40]. This rapid response with IgG might be related to exposure early in life to bacteria or host cells with PF4 bound to surface polyanions [41, 42]. Repeated exposure to heparin does not necessarily lead to recurrent episodes of
HIT (e.g., non-anamnestic), suggesting that these antibodies disappear within a short time [43–45] due to a lack of a robust increase in memory B-cells [45, 46].

The fine balance between molar concentrations of PF4 relative to heparin determines the immune response in HIT. Molar concentrations where one component exceeds the other will promote the formation of complexes that are non-immunogenic and that will not be favorable for platelet binding [15, 25, 42]. This may explain why seropositive HIT does not necessarily translate to clinically apparent HIT. The immunogenic ultralarge PF4-heparin complexes form in the presence of a 1:1 M ratio. The optimal concentration of PF4 needed to shift antigenicity to higher levels seems to be related to heparin dosing in the setting of platelet activation (i.e., surgery, trauma, diabetes, inflammation, etc.) [42]. Patients exposed intraoperatively to very high doses of heparin (e.g., cardiovascular surgery and cardiopulmonary bypass), where there is more heparin compared to PF4, are less likely to develop HIT [25]. Conversely, standard postoperative doses (e.g., orthopedic surgery) seem to produce a more favorable PF4/heparin ratio for clinically significant HIT [15].

HIT antibodies can develop even in the absence of heparin exposure, suggesting the presence of a group of B-cells that are triggered by inflammation and lack of immune regulation [47, 48]. Although rare, spontaneous or autoimmune HIT can occur through the binding of PF4 to other major anionic proteins including nucleic acids and bacterial lipopolysaccharides [41, 49]. Thrombocytopenia from autoimmune HIT may persist for weeks, even after the initiation of an alternative drug for anticoagulation [50].

HIT is characterized by thrombocytopenia or a fall of more than 50% in the baseline platelet count measured after surgery [11]. Around 85–90% of the patients diagnosed with HIT present with thrombocytopenia [51]. Thrombocytopenia (or the 50% fall in the platelet count) classically starts between 4 and 10 days of heparin exposure and more commonly between 6 and 15 days after the first heparin exposure in more than 90% of the patients with HIT [52]. By several reports, the platelet count reaches nadir values by day 8 and the first evidence of thrombosis usually starts by day 10. Some patients develop thrombocytopenia earlier (within 2 days of exposure), but those patients have usually been exposed to heparin before, typically within 2–3 weeks, yet sometimes within 100 days before heparin re-exposure [45, 50].

Thrombosis is common in HIT patients. It is estimated that around 50% of patients diagnosed with HIT in the postoperative period will present with thrombotic complications that might be a threat to life and/or limb [2]. Venous thromboembolic disease, such as deep vein thrombosis or pulmonary embolus, is more common than arterial thrombosis (two–fourfold higher), particularly in surgical patients [53]. Patients with vascular disease are an exception as they tend to have similar rates of venous and arterial thrombosis in the setting of HIT [54]. Arterial thrombosis is also common in cardiac surgery patients [55]. In vascular patients, postoperative HIT is associated with longer hospitalizations, higher cost of stay, and higher rates of non-routine home discharges [56].

Venous thromboembolism (VTE) occurs with a range of incidence between 17 and 55% in postsurgical cardiac, orthopedic, oncologic, and neurosurgical patients [53, 57]. If HIT goes untreated, then the frequency of thrombosis increases by 6.1% each day until cessation of heparin and the initiation of alternative anticoagulant therapy [58]. Other manifestations that may present with seropositive HIT include necrotizing skin lesions at heparin injection sites [59, 60], adrenal vein thrombosis with hemorrhagic necrosis [61], cavernous sinus thrombosis [62], acute systemic reactions within 30 min of an intravenous heparin bolus injection [60], and disseminated intravascular coagulation (DIC) [63–66]. DIC is perhaps the most feared complication if it were to occur along with a HIT diagnosis because clinical manifestations may be similar and the presence of DIC may often suggest HIT has progressed from localized thrombus formation to a systemic thromboinflammatory response [67].

**Screening Systems**

Multiple scoring systems can be used for HIT probability estimation. Only the 4 T score (4Ts) has been validated. The 4Ts comprises four variables evaluated and scored from 0 to 2 (Table 1). The positive (PPV) and negative (NPV) predictive values for this score were assessed in a pooled analysis from 2012 that included approximately 3000 patients. A low score (0–3) has a NPV 0.99 [95% CI, 0.99–1.00], which essentially rules out HIT. An intermediate score (4–5) has a PPV of 0.48 [95% CI 0.42–0.55], and a high score (6–8) has a PPV of 0.12 [95% CI 0.10–0.14]. Intermediate and high scores are not as reliable as only 48% of the patients with an intermediate score and 12% of patients with a high score will be accurately diagnosed with HIT with these criteria [6, 17, 68].

The HIT expert probability score (HEP score) was developed according to expert opinion to offer another option for guiding clinical decision making, as previous scores had limited predictive capacities [69]. The score showed good agreement with the serotonin release assay, but greater inter-observer variability. However, the predictive values were not different than the 4 Ts’ score (positive predictive value of 0.55 [95% CI 0.25–0.82] and a negative predictive value of 0.97 [95% CI 0.85–1.00] for a cutoff > 5). This score has not been prospectively validated.

The Lillo-Le Louët model [70] is intended for estimation of the likelihood of HIT in patients following cardiopulmonary bypass (CPB) for cardiac surgery. A low score (<2) suggests a low probability of HIT, while a high score (≥2) is associated with a high probability. The negative predictive value of this
model was comparable with both the HEP and 4 T scores (~97%), but this model has not been prospectively validated.

**Differential Diagnosis**

HIT is a challenging diagnosis in the ICU setting. Critically ill patients can often present with thrombocytopenia resulting from diagnoses other than HIT. The timing of thrombocytopenia is tremendously helpful in the diagnosis. The etiology of platelet depletion can be classified as consumptive and destructive (Table 2).

**Laboratory Tests**

HIT is a challenging clinical diagnosis as critically ill patients often present thrombocytopenia and are almost ubiquitously exposed to heparin. There are two varieties of laboratory tests for HIT: Immunoassays (ELISA, IgG) and functional assays (serotonin release assay-SRA, heparin-induced platelet activation-HIPA) [85].

Immunoassays detect anti-PF4/H antibodies (platelet-activating and non-activating) and have high sensitivity (> 95%) but low specificity (i.e., high rate of false positives) [12, 15, 19]. These tests are widely available. Enzyme immunoassays (EIA) identify antibody presence by days 4–5 reaching maximum reactivity on days 10–12 [40]. These assays use a solid surface with heparin coating to which the patient’s plasma is added. Antibody isotypes are measured using a combination of anti-immunoglobulins (Anti-IgG, -IgM, and IgA) or a single isotype (Anti-IgG) [66]. The main limitation of EIAs in HIT is the detection of antibodies that are not necessarily pathogenic (e.g., IgM and IgA antibodies). IgG-focused EIAs seem to be more specific but are likewise limited for identification of clinically relevant HIT antibodies [2*, 26].

Immunization (presence of PF4/H antibodies) does not necessarily mean the development of a clinical picture of HIT. In fact, seroconversion (or immunization) occurs frequently without thrombocytopenia or thrombosis [86]. A patient with a low pretest probability of HIT and a positive EIA requires confirmation with a functional assay [2*, 87, 88**]. The goal is to avoid over-diagnosis and over-treatment. A positive EIA does not automatically translate into a HIT diagnosis. Polyclonal immunoassays that detect IgA, IgM, and IgG isotypes can result in false positives for HIT, even when there are no clinical symptoms [89]. It is generally recommended to not pursue said test unless there is a high clinical suspicion of HIT. Treatment based on such results may be unnecessary and potentially harmful [90].

IgG-specific assays are more promising, but cutoffs for optical densities (OD) for HIT have not been clearly defined. OD values are arbitrary units and vary among laboratories.
Strongly reactive ODs (more than 1.0) are usually correlated with clinically apparent HIT [27, 28]. High ODs are also associated with positive functional assays [27, 28]. It has been suggested that an intermediate or high score on the 4 T’s plus a high OD (above 1.0) has a similar accuracy in diagnosing HIT compared with a functional assay, but validation studies are needed [87, 88]. An intermediate OD (0.4–1.0) should be confirmed with a functional assay [2, 87]. HIT assays should be used in the setting of an intermediate-high pretest probability of HIT [88••]. This level of pretest probability warrants transition to or the initiation of non-heparinoid anticoagulant therapy until serologic data returns (see below for Treatment).

Functional assays (i.e., SRA, HIPA) detect platelet-activating anti-PF4/H antibodies and have high specificity (80–100%) [92] but restricted availability due to technical requirements (i.e., require human platelets from known reactive donors, use of radioactive compounds) [92, 93]. SRA only detects antibodies that are capable of activating platelets and can detect antibodies by day 5 after heparin initiation [12]. The proportion of immunized patients who develop HIT is highest among the patients who have a positive SRA [94].

Titers of PF4/H antibodies decrease by 3–4 months [45]. These patients are still at risk for developing rapid-onset HIT on heparin re-exposure during this period unless the functional assays/EIA are negative [87].

### Treatment

HIT treatments aim to reduce thrombin generation, treat any thrombotic events, and interrupt platelet activation triggered by heparin. The mainstay of HIT treatment is the cessation of all forms of heparin and initiation of alternative anticoagulation (Fig. 1). Vitamin K antagonists should be avoided until HIT has resolved and the platelet count has recovered and plateaued. This is due to the increased risk of venous limb gangrene and limb loss with the inhibition of Protein C [2•].

There are options for alternative anticoagulation. Direct thrombin inhibitors (DTI), including argatroban, lepirudin, and bivalirudin, inhibit both free and clot-bound thrombin facilitating the action of antithrombin, preventing the conversion of fibrinogen to fibrin, and preventing the activation of factor XIII [95]. The inhibition is selective and reversible for argatroban and bivalirudin. These drugs have a short half-life (less than 2 h) and are monitored by PTT. However, there is a risk for falsely supratherapeutic PTT in the setting of coagulopathy (e.g., DIC, decreased liver function) leading to DTI underdosing [63–65]. DTIs (particularly argatroban) increase INR values and interfere with the protein C pathway [95], so transitioning to warfarin requires specific protocols with an overlap of the two drugs for 5 days to maintain an INR > 4 [16•, 87]. Argatroban is useful for patients with renal insufficiency due to its hepatobiliary excretion [4] and requires parenteral administration. Lepirudin has to be monitored by...
ecarin clotting time (ECT) during cardiopulmonary bypass and with unexpected bleeding [96].

Bivalirudin is a better option for cardiac surgery as it has a quick onset and short half-life and can be monitored with the activated clotting time (ACT) (Fig. 1). However, bivalirudin carries a risk for excessive bleeding as there is no specific reversal agent available to date. Monitoring its effect can be challenging due to a lack of standardized methods. Currently, ACT or aPTT are used as surrogates of the degree of anticoagulation. For surgeries that require the use of cardiopulmonary bypass, stagnant blood should be avoided at all times due to the increased risk of clotting as bivalirudin is cleaved by thrombin [97, 98]. Bivalirudin metabolism and clearance can be unpredictable with changes in renal function, core temperature, or repeated doses during a long procedure [99].

Indirect thrombin inhibitors (danaparoid, fondaparinux) work by enhancing the anti-Xa activity of antithrombin III. Danaparoid is not available in the USA since 2002, but it is available in other countries. Fondaparinux has a long half-life (17 h), requires monitoring with anti-Xa levels, has no effect on INR, and does not interfere with the activation of the protein C pathway [100]. These drugs undergo renal excretion [24, 101] and subcutaneously administered. Both direct and indirect thrombin inhibitors lack a reversal agent.

Platelet transfusions are not indicated in HIT unless the patient has uncontrolled hemorrhage or is undergoing an invasive procedure as it increases the risk of thrombosis [102]. IVC filters are also relatively contraindicated in HIT as there is an increased risk of IVC thrombosis, pulmonary embolism, and limb ischemia [103].

HIT patients with thrombosis or a moderate-high pretest probability should be started on a non-heparin anticoagulant while awaiting the results of confirmatory testing. These patients will require therapeutic anticoagulation for at least 3 months [2•].

**Treatment of Isolated HIT (Non-thrombotic)**

Patients with a strong suspicion of isolated HIT or with a confirmed diagnosis should receive therapeutic dose anticoagulation with a non-heparin alternative. The treatment should be continued until platelets recover to a stable plateau [104]. The risk of major bleeding with a DTI for HIT is around 1% for lepirudin (mean treatment period: 14 days) and 0.6–1% for argatroban (mean treatment period: 5 days).

**Treatment of Patients with a Low Probability of HIT**

Patients with a 4 T score of equal or less than 3 that do not have a reason for therapeutic dose anticoagulation should continue prophylactic treatment with heparin or an alternative [87]. Patients with an intermediate probability (4Ts score 4–5) without the need for therapeutic anticoagulation should continue prophylactic treatment with a non-heparin alternative.

**Adjuvant Treatments**

Intravenous immunoglobulin (IVIg) blocks the platelet Fc γ receptors at high doses (2 g/kg over 2 days) and, consequently, inhibits antibody-mediated platelet activation [105]. It can be an option in patients at high risk for autoimmune HIT or life-threatening thrombosis and bleeding (e.g., cavernous sinus thrombosis, pregnancy, severe limb ischemia) [106]. IVIG has been used successfully in the preoperative period. It was shown to reduce the activity of HIT antibodies and also decreased the risk of thrombosis while rapidly increasing the platelet count shortly after initiation of therapy [107].

Plasma exchange has been described as an adjunctive therapy for life-threatening HIT, particularly in the setting of urgent cardiac surgery requiring full heparinization. Its mechanism has not been fully determined, but it is thought to remove pathogenic immune complexes and potentially correct coagulopathy with FFP replacement [108]. In cardiac surgery, the
removal of prothrombotic complexes facilitates heparin use at high doses [16]. A single plasmapheresis session reduces EIA reactivity with a loss of SRA reactivity [109]. The anti-PF4/heparin antibody titer decreases by approximately 50–80%. In a case series describing 11 cardiac surgery patients with HIT managed with intraoperative plasmapheresis before heparin administration for cardiopulmonary bypass, none of the patients with reduced titers developed clinical HIT [108]. To date, only a few institutions are using plasma exchange for HIT antibody elimination [110].

Intraoperative TPE has been supported as a potential option for antibody removal in non-surgical patients [109]. Intraoperative TPE is a valuable adjunct in the management of antibody-mediated syndromes including HIT and is FDA-approved for the treatment of thrombotic thrombocytopenic purpura. TPE permits heparin use by removing immune complexes and HIT antibodies [113]. Intraoperative TPE can also allow for the routine reversal of post-cardiopulmonary bypass heparin reversal using protamine. In a retrospective study of 11 HIT or heparin/PF4 seropositive patients undergoing TPE in preparation for cardiac surgery, a single TPE treatment reduced heparin/PF4 titers by 50–84%, and 7 of 9 patients had normal anti-heparin/PF4 levels after treatment [108]. Following re-exposure to heparin, no serious adverse complications of HIT or to TPE were noted.

Conclusions

HIT is a devastating clinical condition that will lead to loss of life and/or limb if it is not quickly recognized, diagnosed, and managed in patients that have undergone surgery. The incidence of HIT development is higher in surgical patients than it is in non-surgical patients owing to the inflammatory milieu generated during surgery as well as the potential for heparin exposure, especially in select patients such as those that have undergone orthopedic or cardiac surgery. While the recognition and understanding of the pathogenesis of HIT has dramatically improved over the past several decades due to important basic and translational studies evaluating disease biology, there remains a paucity of information regarding optimal treatment modalities. Current therapy pivots on heparin avoidance and alternative non-heparinoid anticoagulation. Although therapeutic plasma exchange has been used as a means of quickly removing antibodies, comparative effectiveness studies have not been performed to assign a high level of evidence to the use of TPE in the setting of HIT management.

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Compliance with Ethical Standards

Conflict of Interest

Ingrid Moreno-Duarte declares that she has no conflict of interest.

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