Meeting the Challenge of Heparin-induced Thrombocytopenia

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Introduction

Thrombocytopenia, defined as a platelet count of less than 150 x 10^9/L, is an important clinical problem most commonly encountered in hospitalized patients. Although the differential diagnosis is extensive (Table 1), it is essential to always consider heparin-induced thrombocytopenia (HIT) in patients with thrombocytopenia who are hospitalized or who have recently been in a hospital.[1,2]

HIT is an adverse drug reaction induced by exposure to heparin that is followed by thrombocytopenia, platelet activation and a dramatic increase in thrombosis risk. Although it is one of the most common and serious drug reactions in hospitalized patients, HIT is frequently not recognized until a major thromboembolic complication has resulted. However, if diagnosed and treated promptly, the outcome is generally favourable. With the widespread use of heparin in the elderly, geriatric patients constitute the largest population at risk of developing HIT. Therefore, clinicians providing care for the elderly must be able to recognize and manage HIT effectively and efficiently.

Pathogenesis

Heparin is associated with two types of thrombocytopenia. Occasionally, heparin binds to platelets directly, leading to a mild thrombocytopenia often within minutes of a bolus dose. This process, termed "non-immune heparin-associated thrombocytopenia", does not progress despite continuation of heparin, and is mild, transient and clinically benign. The platelet count will rapidly normalize, and no intervention is required.[3]

In contrast, immune-mediated HIT is the most frequent immune drug reaction seen in hospitalized patients.[1,3] Susceptible patients develop IgG antibodies against the complex of heparin and an endogenous protein called platelet factor 4 (PF4) that is found on the platelet surface. The HIT antibody, when bound to the heparin-PF4 complex, concomitantly binds to receptors on the surface of platelets, monocytes and endothelial cells, resulting in their activation.[3,4] This has several important consequences. Firstly, platelet activation releases procoagulant platelet microparticles while monocyte activation causes the expression of tissue factor; both responses activate the coagulation cascade, resulting in thrombus formation. Secondly, activated endothelial cells promote platelet binding.[4] Thirdly, activated platelets release more PF4 into circulation, which binds to and neutralizes heparin, thus inhibiting its anticoagulant properties and allowing the clotting process to extend.[3] Finally, the binding of the HIT antibody to platelets also leads to their removal from circulation,[4] resulting in thrombocytopenia which is associated paradoxically with thrombosis.

Frequency

HIT occurs in 1–3% of patients exposed to heparin for at least five days,[5] and is more likely to occur with full-dose heparin given intravenously than with lower, prophylactic doses. However, even tiny doses of heparin, such as those found in line flushes or heparin-coated catheters, may occasionally produce HIT.

Table 1
Differential Diagnosis of Thrombocytopenia

Pseudothrombocytopenia (due to platelet clumping)
Dilutional thrombocytopenia
Decreased platelet production: a. Drugs (including chemotherapy and alcohol) b. Aplastic anemia c. Leukemia d. Bone marrow malignancies or metastases to the marrow e. Infections
Increased destruction: a. Thrombotic microangiopathy (e.g., TTP, DIC) b. Sepsis/infection c. Autoimmune: primary and secondary (e.g., ITP, SLE) d. Drugs (e.g., valproic acid, glycoprotein IIb/IIIa antagonists) e. Post-transfusion purpura
Hypersplenism

TTP=thrombotic thrombocytopenic purpura; DIC=disseminated intravascular coagulation
ITP=immune thrombocytopenic purpura; SLE=systemic lupus erythematosus

Table 2
Definition of Heparin-induced Thrombocytopenia (HIT)

≥ 50% fall in platelet count from recent maximum
Occurrence ≥ five days after start of heparin exposure (may be <24 hours if heparin exposure within the previous three months)
Nadir platelet count 20–150 x10^9/L (median 50 x10^9/L)
Exclusion of other, more likely causes of thrombocytopenia

HIT is uncommon after exposure to low molecular weight heparin (LMWH) because the shorter chain length of LMWH is less able to form a complex with PF4.[3,5] Furthermore, LMWH is less susceptible to neutralization by the increased PF4 released by activated platelets. In a study assessing the frequency of HIT antibody formation, the rate of detectable HIT antibodies was 8% for patients given unfractionated heparin versus 2% for those who received LMWH.[5]

Despite advances in understanding the pathogenesis of HIT, it is still unclear why only a small fraction of patients receiving heparin develop the HIT antibody. Equally puzzling is the observation that only some patients who produce the HIT antibody develop thrombocytopenia, and even fewer still suffer thromboembolic complications.[3] Unfortunately, it is not currently possible to predict which patients will develop HIT or heparin-induced complications.

Clinical Features

The thrombocytopenia in HIT typically begins five to 10 days after heparin is started. However, if the patient has received heparin within the past three months, there may be a precipitous fall in the platelet count upon re-exposure to heparin.[6] There have also been recent reports of delayed-onset HIT occurring up to three weeks post-exposure.[7] The thrombocytopenia of HIT is generally not severe (to the 50–150 x 10^9/L range). Although the platelet count often falls by greater than 50% from the patient's recent baseline, it does not usually fall below 30 x 10^9/L (Table 2).[3]

Despite the presence of thrombocytopenia, bleeding is rarely encountered and it is actually the thromboembolic complications of HIT that can be devastating. When HIT is diagnosed, more than half of patients already have a thromboembolic complication, whether recognized or not.[1] Thromboses can occur at any vascular site (Table 3). While approximately 80% of thromboembolic complications of HIT are in the venous circulation,[8] arterial thromboses are usually more catastrophic. If a patient develops HIT during treatment for an acute thrombosis, there is often progression of the thrombosis. Venous and arterial thrombosis can sometimes present concomitantly—a scenario seen in only a few other conditions (malignancy, antiphospholipid antibody syndrome, disseminated intravascular coagulation). Patients with HIT may also develop skin lesions at sites of heparin injections.

The location of the thrombotic event may depend on the clinical setting. For instance, patients who develop HIT after heparin is given to prevent thrombosis following surgery or bed rest most often develop deep vein thromboses (DVT), whereas patients with HIT after cardiovascular surgery or acute coronary syndromes often develop arterial thrombotic events.[1] The overall mortality rate has been reported to be as high as 25%,[9] with a further 5% of patients requiring limb amputation.

Diagnosis

It is important to diagnose HIT promptly so that treatment may be commenced to minimize thrombotic events. We recommend daily platelet counts in patients receiving full doses of heparin. With low doses of heparin, or with LMWH, routine platelet count monitoring is controversial since the risk of HIT is much lower. Some authors suggest that the platelet count be monitored once or twice between day

Table 3
Clinical Manifestations of HIT-associated Thrombosis

Venous Thromboembolism a. Deep vein thrombosis b. Pulmonary embolism c. Adrenal infarction d. Cerebral thrombosis (cortical veins, venous sinuses) e. Warfarin-induced venous limb gangrene
Arterial Thrombosis ("white clot syndrome") a. Acute lower limb ischemia b. Thrombotic stroke c. Myocardial infarction, bypass graft occlusion d. Other arteries (e.g., mesenteric artery occlusion)
Skin lesions at sites of subcutaneous heparin injection
Acute systemic reactions a. Fever, chills, flushing, nausea, hypertension b. Disseminated intravascular coagulation c. Transient global amnesia

five and 10 in patients receiving either low dose heparin prophylaxis or LMWH, although this has not yet been supported with clinical evidence.

HIT should be suspected in any patient with an unexplained platelet count fall of at least 30% from baseline and current or recent use of heparin. In addition, HIT must be considered in any patient who develops a venous or arterial thrombosis while receiving heparin, or who has received heparin within the previous three weeks. Although these events may represent failure of the heparin therapy, they might also represent thromboembolic complications of the therapy itself.

When suspected clinically, HIT must be confirmed by laboratory testing. There are two main types of lab tests available.[1] Some laboratories use a functional assay in which patient plasma is added to normal platelets and aggregation or activation by the HIT antibodies is assessed using one of several methods. Other hospitals prefer an immunoassay for the HIT antibodies using the heparin-PF4 complex as the antigen.

Since thromboembolic complications are so common in HIT, some authorities advocate the screening of all HIT patients with ultrasonography of the lower extremities to exclude asymptomatic DVT.[10]

Treatment

The management of HIT involves a number of critical steps:[1,2]

1. Immediate withdrawal of all sources of heparin including subcutaneous injections as well as heparin used for line flushes or dialysis.
2. Platelet transfusions should be avoided; bleeding in HIT is rare and adding more platelets may "fuel the fire".[1,3]
3. Consult a hematologist or physician with an interest in thrombosis. Since HIT is uncommon, expertise in the investigation and management of this condition is important.
4. Consider whether the patient already has thrombosis.[1,10]
5. Due to the profound prothrombotic nature of HIT, thrombosis develops in about 50% of untreated patients despite recognition of this condition and cessation of heparin.[8,9] Therefore, alternate "HIT–safe" anticoagulation should be strongly considered for all patients (Table 4). LMWH must be avoided, as it is almost 100% cross-reactive in the lab tests for HIT.[1,3] Alternate anticoagulation should be given in prophylactic or therapeutic doses.[1,2,11] For patients who do not require therapeutic anticoagulation, our practice is to use subcutaneous prophylactic doses of danaparoid until the risk for thrombosis decreases. We use intravenous therapeutic doses of recombinant hirudin for patients with confirmed thrombosis or an ongoing need for therapeutic anticoagulation. Published dosing protocols for these agents can be found in several sources.[1,2]
6. Confirm the diagnosis with a sensitive laboratory test for HIT and, if positive, notify all relevant physicians, health record departments and the patient. Although the risk of recurrent HIT in patients who are rechallenged with heparin many months or years later is unknown, re-exposure should be avoided unless this has been approved by a thrombosis expert.
7. There are reports of warfarin–induced skin necrosis and limb gangrene in patients with HIT (due to warfarin-induced depletion of protein C and resultant uncontrolled thrombin for-

Table 4

Anticoagulants for Treatment of Heparin-induced Thrombocytopenia

Danaparoid (Orgaran®)
- a non-heparin heparinoid that inhibits Factor Xa
- long half-life (24 h)
- renal clearance
- cannot be monitored by PTT; need anti-Xa assay
- can be administered in prophylactic or therapeutic doses
- 10% *in vitro* cross-reactivity with heparin

Recombinant hirudin (Refludan®)
- direct thrombin inhibitor
- half-life <3 hours with normal renal function
- monitored using aPTT
- major bleeding in ~10%[13]
- can induce antibodies which prolongs its clearance

Argatroban
- synthetic, small-molecule direct thrombin inhibitor
- half-life <1 hour
- elimination by hepatic metabolism and biliary secretion
- may be monitored by aPTT
- no cross-reactivity with heparin

Fondaparinux (Arixtra®)
- synthetic pentasaccharide that inhibits Factor Xa in presence of antithrombin
- long half-life (~20 h)
- renal clearance
- no cross-reactivity with heparin
- not yet approved for this indication

mation).[12] Therefore, warfarin should not be given to a patient with HIT until an alternate, HIT-safe anticoagulant has been started and the thrombocytopenia has resolved.[1-3]

Conclusions

Heparin-induced thrombocytopenia is an uncommon but potentially fatal immune syndrome of platelet activation and thrombosis, the incidence of which is expected to increase as the population ages. HIT can often be recognized before thromboembolic complications develop, but this requires careful monitoring and a high index of suspicion. Once diagnosed, prompt treatment may be both life- and limb-saving. ◆

No competing financial interests declared.

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