A Review Paper

Heparin-Induced Thrombocytopenia and Thrombosis

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Abstract

Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT) are rare complications associated with use of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). HIT is a benign clinical condition characterized by a mild drop in platelet count with no clinical significance. HITT is an immune-mediated reaction associated with a widespread "hypercoagulable" state resulting in arterial and venous thrombosis. There is a higher incidence of HITT with UFH use than with LMWH use. Orthopedic surgery patients are at higher risk for developing HITT than are patients who receive prophylactic heparin for cardiovascular surgery or medical reasons. Therapy for patients suspected of having HITT should begin with immediate discontinuation of heparin in any form followed by pharmacologic inhibition with thrombin (eg, recombinant hirudin [lepirudin], argatroban, danaparoid sodium).

Heparin is a potent antithrombotic agent that has been used to prevent and treat venous thrombosis for more than 50 years. Heparin inactivates various coagulation factors by binding to a plasma cofactor, antithrombin III (Figure 1).[1] Administered to postsurgical patients in a fixed low dose of 5000 units subcutaneously every 8 to 12 hours, heparin resulted in a 60% to 70% risk reduction for venous thrombosis and fatal pulmonary embolism (PE).[2,3] Fixed low-dose unfractionated heparin (UFH), however, has been shown to be less effective than other pharmacologic agents after total hip arthroplasty. Orthopedic patients who received fixed low-dose UFH (3500 units every 8 hours) had a higher rate of venous thrombosis (39% vs 13%) than those who received an adjusted dose of heparin to maintain a partial thromboplastin time between 31.5 and 36.0 seconds.[4] In a meta-analysis of 70 randomized trials including more than 16,000 patients, incidence of fatal PE in patients given subcutaneous UFH every 8 to 12 hours was 0.3% versus 0.8% in control subjects ($P<.001$).[3]

Complications of heparin therapy include bleeding, allergic reactions, osteopenia, heparin-induced thrombocytopenia (HIT), and heparin-induced thrombocytopenia with thrombosis (HITT) (Table I).[5] HIT is an idiosyncratic reaction that occurs in 5% to 10% of patients who receive heparin and is a benign condition.[1,6-9] It is thought to result from a direct interaction between heparin and platelets rather than be an immune-mediated antibody response.[10] This reversible mild thrombocytopenia (100,000-130,000 platelets per milliliter) occurs within 4 days of heparin administration and resolves even with continued administration of heparin. HIT is not associated with thrombosis[10] or life-threatening thrombocytopenia and therefore has little clinical significance.

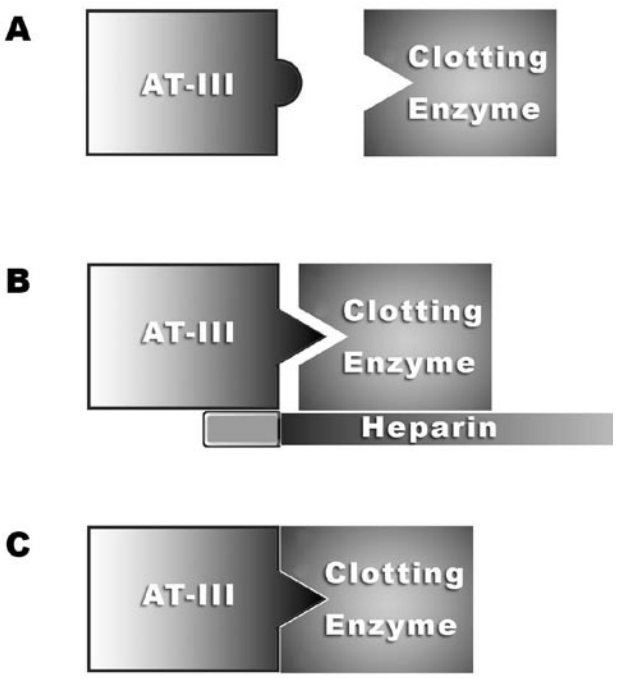

Figure 1. Mechanism of action of heparin. **(A)** In the absence of heparin, antithrombin III (AT-III) can exert only a mild inhibitory effect on clotting enzyme. **(B)** Heparin binds to lysine sites on AT-III through a pentasaccharide sequence. **(C)** AT-III is converted into a rapid inhibitor and binds covalently to clotting enzyme; the heparin subsequently dissociates and can be reused.

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HITT is a more serious complication. It is an antibody-mediated attack on platelets that results in platelet aggregation and a procoagulant environment.[10] It occurs between 4 and 14 days after starting heparin therapy and is associated with a severe thrombocytopenia (<100,000 platelets per milliliter). HITT can result in a widespread arterial and venous thrombosis, often leading to limb ischemia and even death.

Postoperative orthopedic patients seem to be at substantial risk for developing HIT and HITT. Studies have shown that HITT development is significantly higher in patients who undergo orthopedic surgery than in patients who receive heparin for medical prophylaxis or undergo cardiovascular surgery.[11-13] In orthopedic patients, risk for developing thromboembolic complications of HITT is about 0.5% for low-molecular-weight heparin (LMWH) and 3% for UFH.[12] Several issues may account for the particular susceptibility of patients who undergo orthopedic procedures. Orthopedic patients are predisposed to venous stasis secondary to long periods in the operating room and are often immobilized or delayed in their ambulation after surgery. Surgical trauma to soft tissues or deep veins, limb manipulation, and thermal injury (electrocautery or cement polymeratization) can all increase the risk for thrombosis caused by endothelial injury. Among postoperative orthopedic patients treated with UFH, heparin-caused thrombocytopenia occurs in about 5%, and at least half of these patients develop either arterial or venous thrombosis.[14,15] In a study of 665 patients who underwent hip surgery, Warkentin and colleagues[14] reported that HITT was more likely with UFH use than with LMWH use. Eight percent of patients who received UFH (vs 2% of patients who received LMWH) tested positive for HITT antibodies, and 3% of patients who received UFH (vs 0% of patients who received LMWH) developed HITT.

Pathophysiology

HIT results from direct heparin-platelet interaction and is not an immune response. The platelet-aggregating effects of high-dose heparin and the increased binding of fibrinogen seem to decrease the platelet count.[16]

HITT is due to the immune response of heparin-induced antibodies leading to a procoagulant environment. The principal antigen is a complex of heparin and platelet factor 4 (PF4), a small molecule normally found in platelets. When platelets are activated, PF4 is released into the circulation leading to antibody production that triggers activation and aggregation of platelets. Furthermore, this prothrombotic state is exacerbated by production of nonspecific prothrombotic microparticles by platelets and binding of antibody-PF4 to surface of endothelial cells. The mechanism underlying HITT can be understood by invoking the Virchow triad: stasis (result of being bedridden), hypercoagulable state (caused by platelet activation), and vascular injury (endothelium damage caused by immune-mediated injury, atherosclerosis, or surgical intervention leading to venous and arterial thrombosis).[17]

Incidence

The true incidence of HITT remains unclear because of the absence of a gold-standard diagnostic test. HITT was found to occur in 1% to 3% of patients who received UFH for 1 to 2 weeks and in 0.1% of patients who received LMWH.[16] A meta-analysis of 5 studies showed that bovine-derived UFH is significantly more likely to cause HITT than is porcine-derived UFH.[18] In contrast, another meta-analysis found no difference in HIT incidence between porcine and bovine UFH in which platelet counts were repeated, suggesting that the original observed difference may have resulted from inaccurate platelet counts rather than heparin type.[19] In orthopedic patients, there is a 7-fold higher risk for HIT with porcine-derived UFH than with LMWH (~5% vs 0.75%).[18] The reasons for these variations could be related to different heparin preparations, patient population-dependent factors, or even different laboratory techniques.

Clinical Presentation

HIT

Patients with HIT are asymptomatic when there is a mild decrease in platelet count (100,000-130,000 per milliliter), which is often encountered within 4 days of UFH or LMWH administration.[20] There are no serious sequelae, and the platelet count usually recovers to baseline despite continuation of heparin. It is important to distinguish between this early thrombocytopenia due to HIT and thrombocytopenia that may have resulted from the medical condition that prompted hospital admission (eg, septicemia, trauma) or even medical interventions that result in decreased platelet counts (eg, hemodilution from fluids or blood products).

HITT

HITT (sometimes referred to as *type II HIT* or *HIT II*) is the most devastating complication associated with use of heparin in any form. Patients with HITT are generally older

Table I. Characteristics of the 2 Types of Heparin-Induced Reaction*

HIT	HITT
Direct interaction of heparin and platelets	Antibody mediated
Early onset (within 4 days of treatment)	Delayed onset (day 4 to day 14)
Mild thrombocytopenia	Moderate to severe thrombocytopenia
Asymptomatic	Thrombotic complications (arterial and venous)
No need to discontinue heparin	Aggravated until heparin is discontinued

*HIT indicates heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia with thrombosis.

than patients with HIT alone and develop a more severe thrombocytopenia. Clinical conditions that increase HITT risk are sepsis, recent surgery, atherosclerosis, vascular instrumentation, and other conditions that result in endothelial damage. Patients with thrombosis usually develop thrombocytopenia earlier than patients without any thrombotic events.[21] Although HITT is typically associated with and occurs most commonly with intravenous (IV) infusion of heparin,[19,22] it may also occur with subcutaneous low-dose heparin, heparin flushes, heparin-coated catheters, and LMWH.[23] Warning signs of HITT include increased resistance to heparin[24] and abdominal or limb pain.[25,26] HITT may present in a variety of ways, from mild ischemia of extremities to limb-threatening gangrene, myocardial infarction, stroke, pulmonary emboli, disseminated intravascular coagulation, massive adrenal hemorrhage, shock, and skin necrosis (Table II).[20,27]

Among patients with HITT, venous thrombi are more frequent than arterial thrombi (4:1 ratio), and thrombosis usually occurs at a site of preexisting pathology. Venous complications of the disease include unilateral deep venous thrombosis (DVT) (50%), bilateral lower limb DVT (10%), and upper limb DVT (5%).[28,29] PE occurs in 5% of patients, is more common than all arterial events combined, and represents the most common cause of death in patients with HITT.[29] HITT may also present (rarely) with gradual neurologic dysfunction (cerebral dural sinus thrombosis) or adrenal hemorrhage (adrenal vein thrombosis).[27,30] Although such a presentation is uncommon, early diagnosis and intervention can be lifesaving.

Arterial complications include limb artery occlusion, stroke, myocardial infarction, and, rarely, paralysis secondary to spinal cord or plexus infarction. Patients with arterial thrombosis may present with an ischemic lower limb secondary to occlusion of large lower limb arteries. The most common sites of arterial thrombi are the distal aorta and the iliofemoral vessels.[31] Skin lesions, varying from painful erythematous papules to severe dermal necrosis necessitating skin graft, have been found at the injection site in approximately 10% to 20% of patients with HIT antibodies after subcutaneous heparin treatment.[32] Patients who develop a skin lesion and thrombocytopenia, however, are at significantly higher risk for developing arterial thrombosis.[32]

Table II. Clinical Presentation of HITT*

Venous
Pulmonary embolism (most common cause of death)
Deep venous thromboembolism
Adrenal hemorrhagic necrosis
Cerebral vein thrombosis
Limb gangrene

Arterial
Lower limb ischemia—
distal aorta and iliofemoral vessels most common
Myocardial infarction
Stroke
Transient global amnesia (rare)

Other
Disseminated intravascular coagulation—multiple organ failure
Skin necrosis
Erythematous plaques

*HITT indicates heparin-induced thrombocytopenia with thrombosis.

Diagnosis

HIT and HITT are primarily clinical diagnoses supported by laboratory tests. These syndromes are underdiagnosed, and recognizing them requires a high index of suspicion. Heparin administration and thrombocytopenia are common in hospitalized patients. Thus, a clinician must rule out other causes of thrombocytopenia (hemodilution, sepsis, disseminated intravascular coagulation, drugs, transfusion) in a heparin-treated patient with thrombocytopenia before considering a diagnosis of HIT or HITT.

HIT is diagnosed when there is a mild drop in platelet count (to 100,000-130,000 per milliliter) within the first 4 days of heparin administration. There is no clinical impact (bleeding or thrombosis) despite continuation of heparin.

HITT is characterized by (1) a moderate to severe decline in platelet count (>50% from baseline) usually between day 5 and day 14 after initiation of heparin treatment; (2) a new venous or arterial thrombotic event; (3) presence of heparin-dependent antibody; (4) return of platelet count to normal after discontinuation of heparin; and (5) absence of other thrombocytopenia causes, such as drugs, infection, malignancy, and autoimmune disorders.[20,33]

Platelet counts typically decrease by more than 50% of the highest value from day 5 but seldom fall below 30,000 platelets per milliliter and generally resolve within 5 to 7 days after heparin discontinuation.[34] HITT should be strongly considered whenever a patient's platelet count falls 50% from baseline during heparin therapy.[35] Although thromboembolic complications occur as platelet count decreases, many patients who experience these events have a platelet count higher than 100,000 platelets per milliliter. In fact, some patients experience their first thromboembolic event despite having a normal or mildly decreased platelet count.[36] HITT should also be considered and platelet count measured in patients who develop resistance to heparin or develop a new thrombosis while on heparin treatment. Studies have suggested that early recognition and intervention can reduce mortality in patients with HITT from more than 30% to less than 10%.[37] HITT may also occur within hours of heparin administration in patients who had received heparin therapy during the previous 3 to 4 months. This hypersensitivity is caused by circulating HIT antibodies from previous exposure.[38]

Given the poorly defined criteria for diagnosing HITT, several authors have developed clinical scoring systems to predict the probability of HITT onset in a variety of situations.[16,39] In one system, numerical values are assigned to a variety of factors, including the temporal relationship between heparin administration and platelet count (Table III).

Table III. Clinical Scoring System for Assessing Probability of HITT*

Platelet Count Evolution	Score
Normalization <10 days after heparin discontinuation	+2
Platelet increase >50x10^9/L (<2 days)	+2
Normalization between weeks 1 and 3	+1
Persistence of thrombocytopenia	-2
Recurrence of thrombocytopenia without heparin	-2
Recurrence of thrombocytopenia with heparin	+6
Normalization despite persistent standard heparin	-6
Normalization under low-molecular-weight heparin	0
Unknown follow-up	0

Development of Thrombosis	Score
Arterial without preexisting lesions	+4
Arterial without atherosclerotic lesions	+3
Extensive venous thrombosis (curative)	+3
Venous thrombosis (prophylaxis)	+2
Others (skin necrosis)	+1

Other Causes of Thrombocytopenia	Score
Excluded	+2
Likely (sepsis, cancer, disseminated intravascular coagulation)	-2
Potential by thrombocytopenic drugs	0

Total Score	Probability of HITT
<1	Unlikely
1-2	Possible
3-6	Probable
>6	Highly probable

*To be eligible for evaluation using this system, the patent must have thrombocytopenia with a platelet count decrease of more than 30% of initial value. HITT indicates heparin-induced thrombocytopenia with thrombosis. *Source:* Adapted from Samama and colleagues and used with permission of Elsevier.[39]

Laboratory Studies

HITT should be primarily diagnosed on the basis of clinical suspicion, and laboratory studies should be used to support the diagnosis. Two types of laboratory tests can be used to confirm the diagnosis of HITT: functional assays and antigen assays. Functional assays, which detect in vitro platelet activation after exposure to heparin and the suspected HITT serum, include the platelet aggregation test (PAT), the heparin-induced platelet aggregation test (HIPA), and the platelet ^{14}C serotonin release assay (C-SRA). Antigen assays, such as the enzyme-linked immunosorbent assay (ELISA), detect the presence of antibodies against the heparin:PF4 complex.[40]

Although ^{14}C-SRA is the gold standard for laboratory diagnosis of HITT (because of its high sensitivity and specificity, both >90%),[41] it is in limited use because it is very expensive, technically demanding, and time-consuming and involves use of radioactive material. PAT is used more often—it can be performed rapidly and is technically simple—but it has not gained wide popularity because of its low sensitivity (~50%).[42] HIPA can be performed rapidly and has high sensitivity (~91%), but its use is limited because of the required multiple normal donor platelets, which are difficult to obtain in most laboratories.

ELISA is the most sensitive of these tests. It can detect even some weaker antibodies that are not picked up by functional assays. However, false-positives have been found in 2% of normal controls, 4% of pregnant women, and 8% of disease controls who were heparin-free for more than 6 months.[43]

In a study comparing test effectiveness, HIPA, ^{14}C-SRA, and heparin:PF4 ELISA demonstrated sensitivities of 91%, 88%, and 97%, respectively, and specificities of 77%, 100%, and 86%, respectively.[44] As none of these tests is 100% sensitive, one approach is initially to use either a functional assay or ELISA and reserve the other assay for patients with strong clinical suspicion of HITT but with negative results in the first test.[40]

Treatment

The first step in HITT management is immediate discontinuation of heparin in any form, including IV catheter flushes, prophylactic subcutaneous flushes, LMWH, and heparin-coated indwelling catheters. Simply discontinuing heparin administration, however, does not eliminate the risk for complications in HITT patients. In a study of 127 patients with serologically confirmed HITT, a 50% risk for developing a thrombotic event existed despite discontinuation of heparin and platelet count recovery.[18] Therefore, in these patients with a prothrombotic tendency, an alternative anticoagulant is warranted immediately after heparin discontinuation. The most suitable agent for treating the thrombotic complications of HITT is a rapidly acting medication that inhibits either thrombin generation (eg, danaparoid sodium) or thrombin itself (eg, recombinant hirudin [lepirudin], argatroban). Warfarin is not recommended in the acute stage of HITT because of its slow onset of action (minimum 5 days) and its association with a paradoxical prothrombotic activity due to depletion of protein C and S.[45] However, warfarin may be desired for long-term therapy in patients with HITT once the prothrombotic process is controlled.[9] Aspirin and other antiplatelet medications are ineffective in patients who develop HITT, as platelet aggregation is the result of an antibody-mediated mechanism.[46] However, LMWH is contraindicated in patients with circulating HIT antibodies because of an 80% to 100% in vitro and in vivo cross-reactivity with UFH.[47] Newer anticoagulants, such as hirudin (lepirudin), argatroban, and danaparoid, have been used with varying degrees of success.

Recombinant Hirudin (Lepirudin)

Hirudin (lepirudin), a naturally occurring substance, is the most potent and specific thrombin inhibitor known. It irreversibly binds to thrombin, inhibiting all its proteolytic functions.[48] In a study of 82 patients with HITT, lepirudin administration resulted in a significant reduction in combined incidence of death, new thromboembolic complications, and limb amputations over historical controls (25.4% vs 52.1%). Furthermore, 90% of patients recovered their platelet count within 2 to 3 days of lepirudin treatment. Mortality was 8.6% in lepirudin-treated patients versus 22.3% in historical controls.[49] In a similar study, lepirudin

had a favorable outcome, with fewer deaths (9.8% vs 22%), fewer thromboembolic complications (17.4% vs 32.1%), and recovery of normal platelet count in more than 90% of patients.[49] The main drawbacks of lepirudin treatment are bleeding complications and lack of an antidote. Lepirudin must be avoided or given with extreme caution in patients with renal impairment, as its renal excretion rate is 90%.

Argatroban

Argatroban is a synthetic molecule that inhibits thrombin. Argatroban is unlike lepirudin in that its excretion is independent of renal function, and therefore lepirudin can be useful in patients with renal impairment and patients undergoing hemodialysis. Its elimination is reduced, however, in patients with impaired liver function.[50] A large prospective trial reported a 30% to 40% reduction in new thrombosis, deaths, and amputations in patients who received argatroban for HITT versus controls. In addition, in argatroban recipients, platelet count improved significantly and without significant bleeding complications.[51]

Danaparoid

Danaparoid sodium is an indirect inhibitor of thrombin with a half-life of approximately 24 hours. As no effective antidote exists, care must be taken in patients with bleeding tendencies and patients likely to need surgery. Danaparoid as treatment for heparin-induced thrombocytopenia must be given with caution in patients with renal failure. In a large study of 230 patients who received danaparoid, 92.5% responded favorably to treatment.[52] Of the 15 treatment failures, there were 2 cases of bleeding events, 9 cases of recurrent or persistent thrombocytopenia, and 4 cases of thromboembolic events. Danaparoid use was associated with a mortality rate of 3% and included episodes of bleeding, thrombosis, and septic shock.[52]

Other Treatments

In addition to the medications just described, thrombolytic therapy (streptokinase or urokinase),[53] thromboembolectomy, plasmapheresis,[54] high-dose IV IgG,[55] and GPIIb/IIIa inhibitors[56] have been reported as treatments for certain patients with HITT. Further studies are needed to prove the effectiveness of these treatments. In the absence of severe hemorrhage, prophylactic platelet transfusion should be avoided in patients with HITT because of the risk for precipitating thrombotic events. As long as there are circulating HIT antibodies and heparin, transfused platelets will be activated in the same manner as the patient's own platelets. In cases of severe hemorrhage, platelets may be transfused after discontinuing heparin for 24 hours.

Conclusions

Orthopedic surgeons must be aware of the potential complications of heparin, as orthopedic patients are at higher risk for HITT, and heparin use is highly prevalent in these patients. HIT and HITT receive less attention than they should given their attendant risks for morbidity and mortality. Prevention and early diagnosis are paramount in avoiding and reducing complications. In patients receiving heparin (including LMWH) by any route, it is important to obtain a baseline complete blood cell count, including platelet levels, before initiating heparin therapy. In patients with preexisting thrombocytopenia, other causes, including infection, malignancy, and autoimmune disease, must be investigated, and heparin should be used with caution. In addition to other studies based on clinical signs and symptoms, imaging of the lower limbs should be routine in patients with suspected HITT, as subclinical DVT occurs frequently in patients with HITT and will influence duration of anticoagulation.

Once the patient is started on heparin, platelet levels should be checked every 2 to 3 days during the hospital stay. Also, platelet count should be obtained whenever a patient on heparin develops a new thrombus or resistance to heparin. A low platelet count in a patient on heparin should be repeated to rule out a laboratory artifact. A diagnosis of HIT or HITT should never be made on a single unconfirmed platelet count. We do not recommend checking platelet counts on outpatients treated with LMWH, as doing so may be cost-ineffective. In that event, the patient should be informed about the warning signs. Because of the morbidity and mortality of HITT, discontinuation of heparin should not be delayed for laboratory results in patients with a high suspicion of HITT.

If platelets levels drop within the first few days, heparin should be discontinued, after which the platelet count should normalize in patients with HIT. In patients suspected of having HITT, heparin should be discontinued immediately, and a hematologist should be consulted. The patient should be tested for HIT antibodies to confirm the diagnosis, and antithrombotic treatment should be initiated immediately. The immediate use of warfarin or LMWH should be avoided in patients with suspected or confirmed HITT. It is important to document the complications of heparin in patients with HITT to avoid reexposure to heparin. Also, heparin should be avoided or delayed by at least 100 days in patients with a history of HITT to prevent any anamnestic response. Understanding and recognizing the onset of HITT will allow the orthopedic surgeon to differentiate thrombotic complications of HITT from those of inadequate heparinization. In patients receiving heparin, monitoring platelet levels at regular intervals and recognizing the early signs of HITT can lead to effective prevention of the complications associated with heparin use in orthopedic patients.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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This paper will be judged for the Resident Writer's Award.