An anesthesia provider's perspective of heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a pathology manifested as clinically induced destruction of platelets. There are 2 forms of HIT, type I and type II; type II is the more serious. HIT type I is a transient, non–immune-mediated form manifesting with mild thrombocytopenia. Type II is a drug-induced, immune-mediated syndrome that may cause life- or limb-threatening thromboembolic events. Induction of general anesthesia for a person with HIT type II is no different from that for a person in the general population. Treatment modalities vary only if heparin will be used during the case. The initial indicator of HIT is decreased platelet count, with or without thrombosis. Clinical criteria and advanced serological testing are available for the definitive diagnosis of HIT. Clinical suspicion of HIT remains key to early cessation of heparin (all routes) and initiation of alternative treatments.

Key words: **Coagulopathy, heparin-induced thrombocytopenia, thrombocytopenia.**

Heparin has been the drug of choice for anticoagulation therapy for nearly a century. During the last 30 years, the activity of heparin-produced antibodies has been confirmed, with identification of a new syndrome: heparin-induced thrombocytopenia (HIT). The criteria for HIT, such as thrombocytopenia, resistance to heparin anticoagulation, and thrombosis, and assay tests, such as the serotonin release assay (SRA), heparin-induced platelet aggregation assay (HIPA), and enzyme-linked immunosorbent assay (ELISA) have been developed. Even with advanced testing, clinical suspicion of HIT remains the key to early cessation of exposure to heparin and to the initiation of alternative treatments. Through vigilance and a global understanding of HIT, complications related to this condition can be reduced.

Jay McLean, MD, discovered exogenous heparin in 1916 when he was a second-year medical student at Johns Hopkins University.[1] Since its discovery, heparin has become the drug of choice for anticoagulation. Exogenous heparin works by binding to antithrombin III (a circulating anticoagulant synthesized in the liver), neutralizing clotting factors in the intrinsic and final common pathways and, thus, substantially increasing the effectiveness of antithrombin III.

In 1958, Weisman and Tobin[2] suspected that thrombi were associated with the use of heparin. In 1964, Roberts and colleagues[3] reported unexplained arterial embolization associated with heparin administration. They theorized that the embolization might have been caused by an antigen-antibody reaction with production of antiheparin factors or platelet agglutinates. Rhodes and colleagues[4] later confirmed the hypothesis that heparin-dependent antibodies were responsible for the thrombocytopenia and thromboembolism associated with heparin. Originally, this disorder was termed *heparin-associated thrombocytopenia* due to the uncertainty of heparin being the causative factor. Today, it is understood that heparin is the causative factor for thrombocytopenia and thromboembolism; thus, the term *heparin-induced thrombocytopenia*, or *HIT*, is used.

Clinicians now recognize HIT as the most important immunologic complication of heparin therapy.[5] One third of hospitalized patients in the United States, or about 12 million people a year, receive heparin.[6] Approximately 5% of patients receiving unfractionated heparin or low-molecular-weight heparin (LMWH), by any number of routes, will develop immune reactions typical of HIT, and about one half of these patients (300,000) will have clinically evident HIT-associated thrombosis.[7]

Anesthesia practitioners are the primary providers of heparin during surgery. This places them in a unique position to minimize the adverse effects of heparin use by way of identifying patients at potential risk for HIT syndrome and then taking the appropriate measures to decrease adverse outcomes.

There are 2 forms of HIT: type I and type II (Table 1). Type I is a transient, non–immune-mediated form manifesting with mild thrombocytopenia (platelet count usually not $<100 \times 10^3/\mu L$) after 1 to 4 days of heparin therapy.[8] Thrombocytopenia usually resolves spontaneously, even with continued heparin use. Type I HIT is caused by heparin's ability to stimulate platelet aggregation, leading to increased platelet consumption and a drop in platelet count.[9] Thrombosis is not associated with type I.

Type II HIT is a more severe disorder, with delayed

Table 1. Classifications for heparin-induced thrombocytopenia

Type I
• Non–immune mediated
• Occurs 1-4 d after initiation of therapy
• Mild thrombocytopenia despite continued use of heparin
• Usually resolves spontaneously
• Occurs primarily with high-dose intravenous heparin
• Usually no clinical sequelae
Type II
• Immune mediated
• Occurs 5-14 d after initial therapy
• Thrombocytopenia is usually severe
• Occurs with any dose of heparin by any route
• Rarely causes bleeding problems
• May cause serious thromboembolic complications
• Heparin must be discontinued

onset of thrombocytopenia that is immunologically mediated.[9] Type II occurs 5 to 14 days after initiation of heparin therapy.[9] The resulting thrombocytopenia is usually more severe, with platelet counts dropping to $60 \times 10^3/\mu L$ or less and remaining there until heparin exposure is stopped.[9] Thrombocytopenia can occur even sooner in a patient who has been exposed previously to heparin.

Pathologic mechanisms

The pathologic mechanisms for HIT are distinctly different for types I and II. Introduction of heparin into the body by any route initiates the process of HIT in susceptible patients. Recall that type I is not immune mediated. High doses of heparin cause increased platelet binding to fibrinogen, leading to mild thrombocytopenia.[10] Type II is immune mediated and involves heparin, platelet factor 4 (PF4), immunoglobulin (Ig) G, and platelets. The heparin-associated antiplatelet antibodies are usually IgG, although IgA and IgM antibodies also have been detected.[10] These antibodies have inflammatory, thrombotic, and platelet-activating properties.[10]

The binding of PF4 to heparin causes a conformational change in heparin and PF4, to which heparin-associated antiplatelet antibodies develop.[10] These antibodies then bind to F_c receptors on the platelet surface, causing activation and degranulation; microparticles also are released at this time. Immune cells (monocytes) also become involved, binding to the endothelium after antibody formation.[10] These monocytes increase the expression of tissue factor (tissue thromboplastin) after exposure to antibodies from HIT serum.[10] In addition to monocyte expression of tissue factor, the binding of antibodies to endothelial cells causes tissue factor to be released from the endothelium.[10] The overall result produces a hypercoagulable state. Interestingly, heparin and PF4 occur naturally in the body; HIT antibodies have been demonstrated only in patients exposed to exogenous heparin.

Historically, a 30% drop in the platelet count created suspicion for HIT. Now, any decrease in the platelet count is considered significant for HIT.[11] Despite significant platelet decreases, patients do not commonly experience hemorrhage, spontaneous bleeding, or petechiae.[7] Type II HIT produces a hypercoagulable state, with clotting the primary threat, even in cases in which thrombocytopenia is severe.[7] Amputation and mortality associated with HIT type II are estimated to be 20% and 30%, respectively.[12]

Heparin-induced thrombocytopenia can occur in any patient at any age, even after only small amounts of heparin have been received (eg, in heparin flushes for intravenous catheters or heparin-coated central catheters). Venous thrombi occur approximately 4 times more often than arterial thrombi.[13] In approximately 5% of patients who undergo orthopedic surgery and 1% of patients who receive medical treatment for cardiac conditions, HIT will develop.[7] In approximately 50% of patients who undergo cardiac surgery, HIT antibodies will develop; thrombosis may or may not occur.[7] Patients at greatest risk for HIT type I are those receiving high doses of intravenous heparin. Patients at greatest risk for developing HIT type II are those receiving unfractionated heparin rather than LMWH or bovine rather than porcine preparations and surgical patients rather than medical patients.

Diagnosis of HIT

The diagnosis of HIT requires the clinician to systematically eliminate other possible underlying causes of thrombocytopenia. Various conditions noted to decrease platelet levels include infection, primary bone marrow disorders, disseminated intravascular coagulation, and sepsis.[7] Drugs known to cause thrombocytopenia other than unfractionated heparin and LMWH are quinine, antibiotics, histamine blockers, and sulfa drugs.[13]

Heparin-induced thrombocytopenia may manifest as a decrease in platelet count of greater than 50%, a falling platelet count, or an absolute platelet count of less than $100 \times 10^3/\mu L$.[10] Acute HIT may develop in patients who previously have received heparin, usu-

ally within 3 months. Clinical signs in such patients may include fever, chills, tachycardia, hypertension, flushing, chest pain, dyspnea, nausea, vomiting, diarrhea, or transient amnesia appearing within 5 to 30 minutes of heparin exposure.[13] Approximately 10% to 20% of patients with an IgG immune-based response to heparin will show skin changes, the most important of which is skin necrosis.[7] This necrosis can occur at the site of injection or at distant sites.[7] Other lesions typical of HIT include ecchymoses, hematomas, purpura, and blistering.[7] An important early manifestation of HIT may include the need to continually increase the rate of heparin administration to maintain therapeutic anticoagulation.

Two types of tests are used to detect HIT: physiologic testing and antibody detection.[10] Physiologic tests measure platelet activation by the ability of the IgG antibody to activate platelets in the presence of heparin and PF4. Two of the most commonly used physiologic tests are the SRA and the HIPA. Physiologic tests are limited by interference of thrombin and nonheparin immune complexes in plasma.[10] The ELISA identifies heparin-induced antiplatelet antibodies, based on the antibodies' reaction with immobilized heparin and PF4 complexes.[10] The "gold standard" for diagnosing HIT is the platelet SRA.[5] Sensitivity and specificity for the SRA have been reported up to 94% and 100%, respectively.[10] The sensitivity of the HIPA is reported to be more than 80%, whereas the ELISA has a sensitivity of approximately 90%.[7]

These tests are useful for the confirmation of HIT, but they have weaknesses. The HIPA has reduced sensitivity, the SRA has long turnaround times, and both are characterized by a lack of standardization. The ELISA has a high false-positive rate; results are positive in about 50% of patients who have undergone heart surgery, but HIT develops in fewer than 5% of these cases.[14] There is no ideal assay for HIT. A test that is easy to perform, inexpensive, and very specific and sensitive has yet to be discovered.[13]

Because HIT is a pathologic clinical syndrome, HIT should be considered confirmed when an adverse clinical event and a positive test result using a reliable laboratory assay are documented.[5] Optimal treatment of HIT involves interrupting the immune response and inhibiting thrombin generation.[7] Early cessation of heparin is not sufficient treatment for HIT. Antithrombotic treatment for HIT should be initiated before serologic confirmation is completed, even if no other indication for anticoagulation exists.[15] Table 2 summarizes "rules" and treatment recommendations from Warkentin and Greinacher,[15] editors of *Heparin-Induced Thrombocytopenia.*

Drugs for treatment of HIT

Currently, the only US Food and Drug Administration–approved drugs for the treatment of HIT are lepirudin (Refludan) and argatroban (Novastan).[13] Lepirudin and argatroban are direct thrombin inhibitors that do not resemble heparin and do not potentiate the procoagulant effects of HIT. Many other drugs, such as warfarin (Coumadin), ancrod (Viprinex), bivalirudin (Angiomax), and fondaparinux (Arixtra) are also options for the treatment of HIT.

Lepirudin is a recombinant hirudin.[10] In 1998, lepirudin became the first drug approved by the Food and Drug Administration for treatment of HIT.[14] Lepirudin is a derivative of natural hirudin, a direct thrombin inhibitor produced from leech salivary glands.[13] This drug is excreted in urine, and its effects are prolonged in patients with renal failure.[10] An intravenous bolus dose of 0.4 mg/kg followed by an infusion rate of 0.15 mg/kg per hour usually is effective in reducing new thromboemboli and death in patients with HIT.[14] When there is no acute thromboembolism, an infusion of 0.1 to 0.15 mg/kg per hour without a bolus often will suffice.[13] The dose of lepirudin must be reduced if creatinine clearance is impaired. The dosage is adjusted according to the activated partial thromboplastin time, which is recommended to be 1.5 to 2.5 times the control. The manufacturer does not recommend lepirudin when the creatinine clearance is less than 15 mL/min.[16] Presently, no direct antidote for lepirudin exists.

Lepirudin's interaction with spinal and epidural anesthesia is unclear.[17] The approximate half-life for lepirudin is 80 minutes.[14] The average daily cost of a lepirudin regimen for a 70-kg patient is $778.[14] Antihirudin antibodies have been observed in patients with HIT who were treated longer than 5 days with lepirudin. The presence of these antibodies has not been associated with any adverse effects or clinical resistance to lepirudin.[13]

Argatroban is a synthetic direct thrombin inhibitor approved for the treatment of HIT.[14] This drug undergoes hepatic metabolism and excretion.[10] A dose of 2 µg/kg per minute intravenously without a bolus provides adequate anticoagulation in 90% of patients.[14] The dosage is adjusted according to the activated partial thromboplastin time (recommended target, 1.5-3 times the control). Argatroban is the drug of choice for treatment of patients with HIT with renal insufficiency. Its approximate half-life is 40 to 50 minutes.[10] The average daily cost for an argatroban regimen for a 70-kg patient is $624.[14] Interestingly, the size of the argatroban molecule (527 d) compared with that of the lepirudin molecule (6,980 d) allows easier access

Table 2. Diagnosing and treating heparin-induced thrombocytopenia (HIT)

Ten clinical "rules" for diagnosing HIT

1. A thrombocytopenic patient in whom the platelet count fall began between days 5 and 10 of heparin treatment should be considered to have HIT unless proven otherwise. (First day of heparin use is considered "day 0").
2. A rapid fall in the platelet count soon after starting heparin is *unlikely* to represent HIT *unless* the patient has received heparin in the recent past, usually within the past 100 days.
3. A platelet count reduction of more than 50% from the postoperative peak between days 5 and 14 after surgery associated with heparin treatment can indicate HIT, even if the platelet count remains higher than 150×10^3/μL.
4. Petechiae and other signs of spontaneous bleeding are not clinical features of HIT, even in patients with very severe thrombocytopenia.
5. HIT is associated with a high frequency of thrombosis despite discontinuation of heparin with or without substitution by coumadin. The initial risk of thrombosis is about 5%-10% per day during the first 1-2 d; the 30-d cumulative risk is about 50%.
6. Localization of thrombosis in patients with HIT is strongly influenced by independent acute and chronic factors, such as the postoperative state, atherosclerosis, and the location of intravascular catheters in central veins or arteries.
7. In patients receiving heparin, the more unusual or severe a subsequent thrombotic event, the more likely the thrombosis is caused by HIT (eg, bilateral deep vein thrombosis (DVT), upper extremity DVT, multiple sites of thrombi).
8. Venous limb gangrene is characterized by (1) in vivo thrombin generation associated with acute HIT; (2) active DVT in the limb(s); and (3) a supratherapeutic international normalized ratio during warfarin anticoagulation.
9. Erythematous or necrotizing skin lesions at heparin injection sites should be considered dermal manifestations of the HIT syndrome, irrespective of the platelet count unless proven otherwise. Patients in whom thrombocytopenia develops in association with heparin-induced skin lesions are at increased risk for venous and especially arterial thrombosis.
10. Any inflammatory, cardiopulmonary, or other unexpected acute event that begins 5-30 min after administration of an intravenous heparin bolus should be considered acute HIT unless proven otherwise. The postbolus platelet count should be measured promptly and compared with prebolus levels, because the platelet count fall is abrupt and often transient.

Treatment recommendations for HIT type II

Discontinuation of heparin for clinically suspected HIT

- All heparin administration should be discontinued in patients suspected of having HIT.
- A clearly visible note should be placed above the patient's bed stating "NO HEPARIN: Heparin-Induced Thrombocytopenia."
- Heparin can be restarted safely in patients proven not to have HIT antibodies by sensitive activation or antigen assay.

Anticoagulation of patients with HIT with thrombosis

- Therapeutic dose anticoagulation with a rapid acting anticoagulant, such as argatroban or lepirudin, should be given to patients with thrombosis-complicated, acute HIT. Treatment should *not* be delayed pending laboratory confirmation in a patient strongly suspected of having HIT.

Anticoagulation of patients with HIT without thrombosis

- Alternative anticoagulation with an appropriate anticoagulant, such as argatroban or lepirudin, should be considered in patients with clinically suspected HIT, *even in the absence of symptomatic thrombosis*. Anticoagulation should be continued at least until recovery of the platelet counts to a stable plateau. Patients should be carefully assessed for lower limb DVT, especially those at highest risk for venous thromboembolism, such as postoperative patients.

Long-term anticoagulant management of patients with HIT with thrombosis

- The drug of choice for long-term anticoagulation is an oral anticoagulant of the coumarin class. However, in patients with acute HIT, oral anticoagulant therapy should be delayed until the patient is adequately anticoagulated with a rapid-acting parenteral anticoagulant. Ideally, warfarin should not be initiated until there has been substantial platelet count recovery.

Heparin reexposure of patients with acute or recent HIT

- Deliberate heparin reexposure of a patient with acute or recent HIT for diagnostic purposes is not recommended. Rather, the diagnosis should be confirmed by testing acute patient serum or plasma for HIT antibodies using a sensitive activation or antigen assay.

Heparin reexposure of patients with a history of remote HIT

- Heparin should not be used for antithrombotic prophylaxis or therapy in a patient with a history of HIT except under special circumstances (ie, cardiac or vascular surgery).

Management of patients with acute or recent HIT

- Heparin should not be used for heart or vascular surgery in patients with acute or recent HIT with detectable HIT antibodies. A direct thrombin inhibitor for intraoperative anticoagulation should be used, provided that rapid turnaround laboratory monitoring and blood product support to manage potentially severe bleeding complications are available.

Management of patients following disappearance of HIT antibodies

- In a patient with a history of HIT, heart or vascular surgery can be performed using heparin, provided the HIT antibodies are absent (by sensitive assay) and heparin use is restricted to the surgical procedure itself.

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to thrombins located within existing clots.[7,10] The primary disadvantage of argatroban is that it increases the international normalized ratio, which evaluates the extrinsic pathway.[13] If warfarin therapy is desired for long-term treatment and is given concurrently with argatroban, the argatroban infusion must be stopped for 4 to 6 hours (longer for cardiac or hepatic insufficiency).[13] This will allow the argatroban concentration to drop to insignificant levels and permit accurate reflection of the international normalized ratio based on the presence of warfarin.

Warfarin therapy deserves a special note of attention. Skin necrosis and venous limb gangrene have been reported in patients with HIT treated with warfarin.[13] Warfarin therapy alone should not be used to replace heparin because inhibition of the synthesis of protein C and protein S actually may accelerate the underlying procoagulant condition.[13] A direct thrombin inhibitor should be used until the return of normal platelet function, then warfarin therapy may begin if long-term therapy is desired.

Conclusion

During surgery, a key for anesthesia providers in decreasing the risk of HIT is vigilance. Being aware of the type of surgery, patient history, current medications, clinical manifestations of HIT, and the multitude of ways that a patient can be exposed to heparin will help minimize the risks associated with HIT. Before taking the patient into the operating room, one should know whether heparin is part of the regimen for the procedure to be performed. If heparin is to be used, previous patient experience with heparin must be explored, followed by an evaluation of the platelet count. A thorough review of the medications currently being taken by the patient, concentrating on those that would have an adverse effect on platelets, is necessary. If the patient is currently taking heparin, evaluate the platelet count from previous days; also assess subcutaneous injection and catheter sites.

Intraoperatively, be aware of acute HIT manifestations that may be revealed after a heparin bolus, such as hyperthermia, tachycardia, hypertension, and flushing. These symptoms can appear within 5 to 30 minutes of exposure. If acute HIT is suspected, obtain a postbolus platelet count to compare with the prebolus levels.

Heparin-induced thrombocytopenia is being recognized more frequently in the healthcare community. Of the 2 types of HIT, type II is the more detrimental. Early recognition of HIT remains key to cessation of heparin and the initiation of alternative treatments. Argatroban and lepirudin are direct thrombin inhibitors that have been used successfully as alternatives to heparin. As anesthesia practitioners, we must know and understand HIT, its causes, treatment modalities, and their implications related to anesthesia.

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