Heparin-Induced Thrombocytopenia

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication of heparin therapy. The use of heparin to flush some vascular access devices makes HIT a concern for infusion nurses. This article reviews the risk factors for, pathophysiology of, and management of HIT.

Key words: heparin, heparin-induced thrombocytopenia, thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse response to heparin.[1–4] The widespread use of heparin makes HIT 1 of the most important adverse drug reactions in the United States.[2] The use of heparin to prevent clotting in some vascular access devices (VADs) makes HIT a particular concern to infusion nurses.

PATHOPHYSIOLGY

There are 2 types of HIT. Heparin therapy causes platelet aggregation, which can lead to a transient, mild drop in platelet counts 48 to 72 hours after initiation of heparin therapy. This transient thrombocytopenia is known as HIT type I. Because HIT type I is transient and mild, it is not clinically significant.[2,3]

HIT type II is an immune-mediated response and is clinically significant. In some patients, exposure to heparin leads to the formation of antibodies, which bind to the complex formed when heparin binds to platelets. These antibody complexes activate the platelets, which causes platelet aggregation and thrombocytopenia. Activation of platelets also leads to the release of substances that promote the formation of thrombin.[1,2,5] This article will discuss HIT type II, hereafter referred to as HIT.

CLINICAL MANIFESTATIONS

The primary clinical manifestations of HIT are thrombocytopenia and thrombosis.[1,2,4] Less common clinical manifestations include necrotizing skin lesions at heparin injection sites[1,2,4,6] and systemic reactions after intravenous injection of heparin.[1,6] Although patients with HIT have decreased platelet counts and have been exposed to an anticoagulant, bleeding is rarely seen in HIT.[1,2,5] Because thrombocytopenia and thrombosis are the clinical manifestations that infusion nurses are most likely to encounter, these will be discussed in depth.

Thrombocytopenia

HIT-associated thrombocytopenia is defined as a drop in platelet counts of at least 30% from the patient's baseline. Thrombocytopenia associated with HIT is usually moderate and not severe.[5] Most patients experience a drop in platelet count to below 150 000 mm^3, but some patients may experience a 30% or more drop in platelet count and yet maintain a platelet count above 150 000 mm^3.[1]

The timing of the drop in platelet counts is an important consideration to help identify HIT. Thrombocytopenia associated with HIT occurs 5 or more days following introduction of heparin.[1,2,5] Thrombocytopenia that develops within 4 days of heparin therapy is not likely to be attributable to HIT. There is 1 exception to this 5-day rule. Patients who recently have been exposed to heparin may have antibodies circulating and may develop HIT more rapidly. Patients who have been exposed to heparin within the previous 100 days may develop HIT $<$24 hours after the reintroduction of heparin.[1,2]

Thrombosis

Paradoxically, 1 of the common clinical manifestations of HIT is thrombosis.[1,2,4] The aggregation of platelets and release of procoagulant substances leads to the formation of multiple clots.[1,2,5] Venous thrombosis, including deep vein thrombophlebitis and pulmonary embolism, is the most common complication of HIT.[1,2] Arterial thromboses, including myocardial infarction, stroke, and limb artery thrombosis, may occur with HIT but are less common.[1,2] It is important to note that a drop in platelet count does

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The author has no conflicts of interest to disclose.

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DOI: 10.1097/NAN.0000000000000215

not always precede thrombosis. In 1 study, only 40.2% of patients who had HIT with thrombosis manifested thrombocytopenia before the thrombosis.[4]

Risk for HIT

Although HIT can occur in any patient exposed to heparin, some factors are associated with higher incidence of HIT.

Patient Factors

Ethnicity and gender may affect HIT. Women have approximately twice the risk of developing HIT as do men.[1,6] There are some data to suggest that women may be at more risk for HIT because of increased immune response.[2] Research has not established race or ethnicity as a risk factor for developing HIT. However, 1 study did find that although nonwhites had approximately the same risk for developing HIT as whites, once HIT developed nonwhites were 2 to 3 times more likely to develop thromboses.[7] Age has not been established to be a risk factor for developing HIT. However, 1 study did find that 66% of the patients with HIT were 60 years of age or older.[4] This may be attributable to elders having a higher prevalence of disease processes and surgeries associated HIT.

Disease Processes

Some conditions are associated with higher risk for HIT, although the reasons for these differences are not well understood. Surgery patients are more likely to develop HIT than medical patients.[6] Cardiac and orthopedic surgery patients are at especially high risk for HIT.[1,4,6] The severity of trauma also seems to influence the risk for HIT; more severe trauma is associated with a higher risk for HIT.[1] Cancer is also associated with a higher incidence of HIT.[1,6]

Type of Heparin Exposure

Unfractionated heparin (UFH) carries a higher risk of HIT than low-molecular-weight heparins (LMWHs).[1,6] This increased risk is thought to be attributable to increased affinity of UFH to the antibody complexes implicated in HIT.[2] Also, exposure to therapeutic doses of heparin (such as a heparin infusion) may carry a higher risk for development of HIT than prophylactic doses.[2] However, even though LMWH does pose a lower risk than UFH, HIT may still occur.[1,2] HIT has even been reported when the only heparin exposure was to heparin flushes of a VAD.[1,8,9]

Recognizing HIT

Monitoring platelet counts can help identify HIT. Clinical guidelines recommend that platelet counts be done every 2 or 3 days beginning on day 4 after heparin exposure for patients judged to have greater than a 1% risk of developing HIT.[1] Patients at 1% or greater risk of developing HIT include those on heparin infusions, cancer patients, and cardiac surgery patients.[1] In addition, because thrombosis may precede a drop in platelet counts,[4] any new thrombotic event in a patient who is receiving heparin could be a sign of HIT.

Diagnosis of HIT

Two categories of antibody assays are available to help diagnose HIT.[1,2,10] Antigen assays identify the presence of antibodies against heparin.[1] However, many patients do have antiheparin antibodies and do not have HIT.[1,2,5] A more definitive type of test is a functional assay that detects evidence of platelet activation by antibodies.[1] Unfortunately, functional assays are usually performed only at specialized laboratories and results can take several days to obtain.[1,10] It is important to identify HIT early in its course to minimize complications,[10] so vigilance is necessary. Relying on antigen assays may lead to overdiagnosis of HIT,[5] leading to unnecessary expense and risk.[1,6] Because treatment decisions have to be made before the results of functional assays are commonly available, they are of limited use in avoiding overdiagnosis. The 4Ts scoring system is a clinical tool to assist in diagnosis of HIT.[1,6,10,11] The 4Ts considers the degree of thrombocytopenia, timing of the thrombocytopenia, whether thrombosis or other sequelae of HIT have occurred, and whether any other explanations of the thrombocytopenia are present. Patients whose score on the 4Ts is in the "low risk" range are very unlikely to have HIT.[1,6,10,11]

Treatment of HIT

The most important treatment for HIT is to discontinue all exposure to heparin, including LMWH, heparin flushes of VADs, and removal of any heparin-coated device.[1,2,5,7,10,11] Patients with HIT need alternate anticoagulation to decrease the risk of HIT-associated thrombosis.[1,2,5,7,10,11] Argatroban, a direct thrombin inhibitor, is the recommended anticoagulant for most HIT cases.[1] There has not yet been adequate study of newer oral direct thrombin inhibitors and factor X inhibitors (apixaban, dabigatran, and rivaroxaban) to determine whether they are useful in HIT.[1,11]

Warfarin therapy requires special care in HIT. Warfarin inhibits some natural anticoagulants in addition to its intended effect of inhibiting clotting factors. The inhibition of the natural anticoagulants in patients with HIT—who have increased thrombin—can lead to thromboembolic complications, including limb gangrene.[2] Warfarin should not be started on patients who have HIT until the platelet count is at least 150 000/mm^3.[1,11] If warfarin had been started before HIT was recognized, it should be discontinued and vitamin K should be administered to reverse the warfarin.[1] In addition, transition from argatroban to warfarin requires care. Argatroban raises the prothrombin time/international normalized ratio (PT/INR), which may make it difficult to determine whether the warfarin has reached a therapeutic level.[1,2,11] The PT/INR should be checked 4 to 6 hours after argatroban is discontinued to ensure that the INR remains in the therapeutic range.[1,11]

Vascular Access Devices

When heparin is used to lock a VAD, 20% or more of the heparin may flow into the circulation, exposing the patient to heparin and possibly triggering HIT.[9] Minimizing the use

of heparin to lock VADs may help decrease the incidence of HIT.[12] In addition, patients who develop HIT from any type of heparin exposure will require vascular access for anticoagulation. However, it is critical to avoid using heparin to lock a VAD in patients who have HIT.[1,2,5]

Sodium chloride 0.9% is recommended as a VAD lock solution to prevent catheter occlusion.[12–14] Another alternative VAD lock solution is sodium citrate.[14] Sodium citrate may be a useful lock solution because of its antithrombotic properties.[9]

HIT is a potentially dangerous complication of heparin therapy. Infusion nurses armed with knowledge of HIT are well positioned to help prevent HIT and to help minimize the complications of HIT when it occurs.

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