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Heparin-induced thrombocytopenia: clinical manifestations and management strategies

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Thrombocytopenia is a relatively frequent and usually benign clinical complication of heparin therapy. However, some patients receiving heparin and heparin-based products experience an immune-mediated reaction due to the development of heparin-induced antibodies. This reaction leads to a highly specific and paradoxical form of thrombocytopenia, known as type II heparin-induced thrombocytopenia (HIT). Unlike other types of drug-induced thrombocytopenia, HIT promotes thrombosis rather than bleeding; therefore HIT should be suspected in patients who experience thrombotic events despite adequate anticoagulation therapy. Early identification and treatment of HIT can prevent more serious complications associated with this disorder (e.g., exacerbation of venous thromboembolism, limb gangrene, and skin necrosis). Both arterial and venous thrombosis can arise from a single episode of HIT. Routine assessment of platelet counts is necessary with heparin therapy, as a decreased platelet level is usually the only indication of HIT. Although compared with unfractionated heparin, low-molecular-weight heparin therapy is less likely to result in HIT, the use of these agents is contraindicated in HIT patients. Concomitant warfarin therapy is not contraindicated in such patients but must be carefully monitored. Treatment with a direct thrombin inhibitor, such as lepirudin or argatroban, is an effective strategy in reversing the thrombocytopenia associated with HIT and reducing its complications. This article discusses the clinical syndrome of HIT, including pathophysiology, diagnostic criteria, clinical presentations, and current available management strategies in the context of 2 case studies.

Heparin is a widely used anticoagulant drug for the prevention and treatment of venous and arterial thromboembolic diseases. Thrombocytopenia, a frequently occurring complication of heparin therapy and known as heparin-induced thrombocytopenia (HIT) may occur in 2 distinct types. The more common, type I (sometimes called heparin-associated thrombocytopenia), occurs in approximately 10% to 20% of patients receiving heparin,[1] and is a nonimmunogenic response to therapy. This mild thrombocytopenia is not progressive, nor is it associated with bleeding or thrombosis. No special treatment is required; the platelet count is usually $>100 \times 10^9$/L and gradually rises to pretreatment levels within a few days even if heparin therapy is not discontinued.[2,3]

The less-frequent but more severe form, HIT type II, is the subject of this article and henceforth will be referred to as "HIT." This is an immune response caused by the idiopathic presence of drug-related antibodies. It occurs in 1% to 3% of all patients exposed to unfractionated heparin (UFH)[1,4] and in 0% to 0.8% of patients receiving low-molecular-weight heparin (LMWH).[4,5] There is greater risk in those patients receiving heparin of bovine compared with porcine origin.[6] Although the main risk of thrombocytope-

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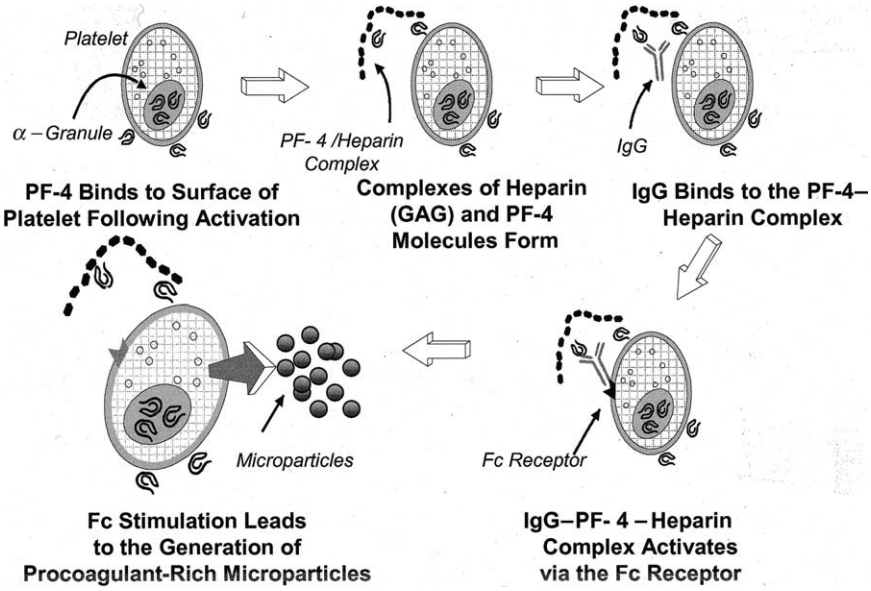

Figure 1 Pathophysiology of heparin-induced thrombocytopenia. Idiopathic production of antibodies after heparin exposure leads to interaction with platelet factor–4 (PF-4), a surface protein of epithelial cells. Patients then develop antibodies to the resulting activated PF-4–heparin complex upon subsequent heparin exposure, leading to platelet activation, thrombin generation, and clinical thromboembolic events. Fc = fragment crystallizable; GAG = glycosaminoglycan; IgG = immunoglobulin G. (Adapted from *Heparin-Induced Thrombocytopenia*.[15])

nia is bleeding, with HIT there is a paradoxical primary risk for thrombosis. HIT can lead to a systemic thrombotic response that can span both venous and arterial vascular beds, although venous events are 4 times more common.[7] The most frequent complications are deep venous thrombosis (DVT) and pulmonary embolism (PE).[8] In rare cases, patients with HIT may develop life-threatening thromboses such as thromboembolic occlusions of limb arteries, acute myocardial infarction (MI), and stroke. Other possible complications include warfarin-induced skin necrosis, acute systemic reactions, and transient global amnesia.[9]

Pathophysiology of heparin-induced thrombocytopenia

Given the severe sequelae associated with HIT, immediate recognition and efficient treatment are of the utmost importance. Typical presentation begins after ≥5 days of therapy (the minimum period required for pathogenic antibodies to reach clinically significant levels) but may clinically manifest much sooner if the patient has had previous exposure to heparin.[9–11] Recognition and diagnosis are complicated; however, because HIT has been reported up to 3 weeks after exposure to heparin, there also exists a phenomenon known as delayed-onset HIT. In order to fulfill this particular diagnosis, heparin treatment must have stopped for ≥5 days prior to the onset of symptoms, assuring that all heparin given intravenously or subcutaneously would have cleared the system at that time.[12,13]

The cellular interactions that lead to HIT begin with the formation of antibodies. Following heparin administration, platelet factor−4 (PF-4)—which is normally found on endothelial cells and the α-granules of platelets—and heparin bind together, forming a PF-4–heparin complex. Patients develop antibodies to this complex, usually in the form of immunoglobulin G, which results in platelet activation and the release of microparticles with procoagulant properties. These microparticles initiate thrombin generation and have been theorized to play a significant role in subsequent thrombotic events (**Figure 1**).[1,14,15]

Risk factors

Patients who have had recent major surgery represent 1 of the highest risk groups for development of HIT. The syndrome is more prevalent in patients receiving antithrombotic prophylaxis after peripheral vascular, coronary artery bypass graft, and orthopedic surgery.[16] The observed thrombotic complications are consistent with the baseline thrombotic risks that are more prevalent in each respective surgical population. (i.e., lower extremity DVT after hip or knee arthroplasty). A lower incidence of HIT is seen in medical patients and general surgery patients receiving prophylactic doses of UFH or LMWH. Medical and obstetric patients treated with prophylactic doses of LMWH represent the lowest-risk groups.[12]

However, because HIT is an immunologic reaction, it can potentially develop from exposure to any dose of heparin. Incidental exposure through heparin-coated catheters and heparin flushes to maintain an intravenous (IV) line can also provide an independent stimulus for HIT.[17,18] In a study of 12 patients, Laster and colleagues[17] found that the