Thoracic and Cardiovascular Surgery

Anticoagulation Management and Cardiac Surgery in Patients with Heparin-Induced Thrombocytopenia

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Unfractionated heparin (UFH) is the gold standard for anticoagulation during cardiopulmonary bypass (CPB). Of patients undergoing CPB operations, 25% to 50% develop heparin-dependent antibodies during the postoperative period, typically between day 5 and 10, if UFH is continued during the postoperative course. In 1% to 3% of all patients undergoing CPB operation with UFH anticoagulation, these antibodies activate platelets causing a prothrombotic disorder, known as heparin-induced thrombocytopenia (HIT), which can lead to life-threatening thromboembolic complications. If urgent cardiac operation with the use of CPB in patients with positive antibody titer is required, different anticoagulatory approaches are available, such as lepirudin, bivalirudin, and danaparoid or UFH in combination with platelet antagonists, such as epoprostenol or tirofiban. In patients with previous HIT but no detectable antibodies, UFH alone can be used only during CPB, but alternative anticoagulation has to be used pre- and postoperatively.

KEYWORDS heparin-induced thrombocytopenia, HIT, cardiopulmonary bypass, anticoagulation, cardiac surgery

In 25% to 50% of patients undergoing cardiac surgery with the use of cardiopulmonary bypass (CPB) and anticoagulation with unfractionated heparin (UFH), heparin-dependent antibodies are observed. If UFH is continued during the postoperative course, 1% to 3% patients develop a heparin-induced thrombocytopenia (HIT), an immune-mediated prothrombotic adverse effect of heparin (Fig. 1). In about 50% of these patients, a thrombosis will occur. Laboratory HIT testing typically becomes positive between day 5 and 10 after operation.[1]

Blood exposure to the great artificial surfaces of the heart-lung machine results in a considerable activation of the hemostatic system.[2,3] As the current anticoagulation with UFH during cardiopulmonary bypass cannot be used in patients with immune-mediated heparin-induced thrombocytopenia and active antibodies, there is the need for an alternative anticoagulant in these patients, which should ideally meet certain requirements: (1) the anticoagulant should minimize activation of coagulation during CPB, thus preventing thrombosis of the heart-lung machine, (2) a rapid and simple method of intraoperative monitoring should be available to avoid under- or overanticoagulation, and (3) a method for rapid and complete reversal of the anticoagulatory effect should be available to avoid postoperative bleeding complications.[4] Today, several different approaches to perform CPB anticoagulation in HIT patients are available: (1) thrombin inhibitors, such as lepirudin, bivalirudin and argatroban, (2) danaparoid sodium, (3) antiplatelet agents, such as epoprostenol or tirofiban in combination with UFH, and (4) the defibrogenating enzyme, ancrod. However, none of these alternative anticoagulants meets the above requirements.

This article reviews the different alternative anticoagulatory approaches for patients with acute or previous HIT undergoing cardiac surgery.

Pathogenesis of Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is an antibody-mediated disorder resulting in the production of immunoglobin G antibodies that recognize platelet factor 4 (PF4) on platelet surface when PF4 has formed complexes with heparin[5,6] Platelet activation in vivo and associated thrombin generation is induced by multimolecular complexes of heparin, PF4, and immunoglobulin G.[7] Platelet activation by HIT-IgG leads to the formation of procoagulant, platelet-derived microparticles,[8,9] and the risk of thrombosis. After the initiation

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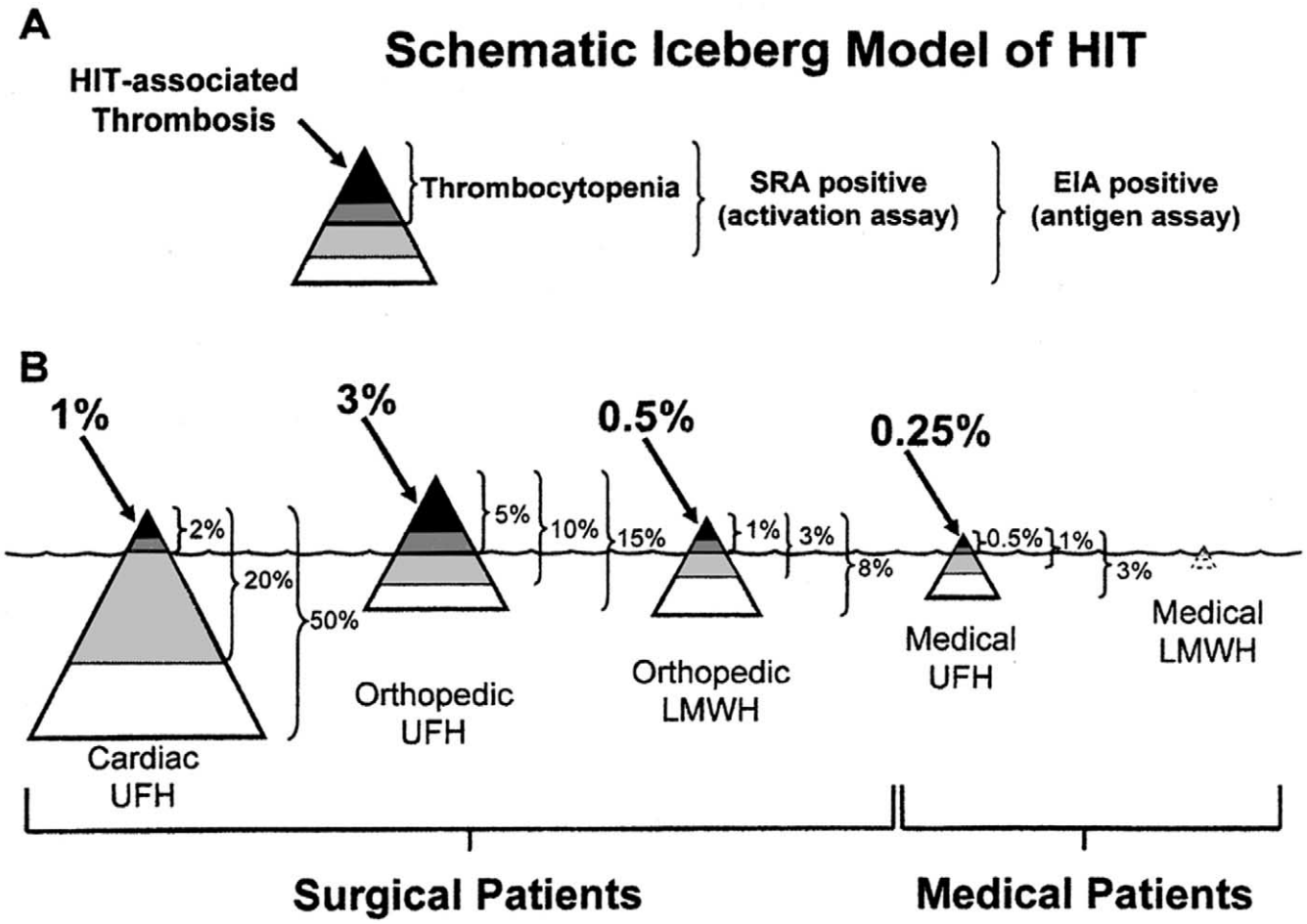

Figure 1 Variable frequency of HIT antibody formation and clinical HIT among different patient populations treated with UFH or LMWH. A schematic "iceberg", shown on upper line, illustrates the relation among HIT-associated thrombosis, thrombocytopenia, HIT antibodies detected by serotonin release assay (SRA), and HIT antibodies detected by enzyme-immunoassay (EIA). The size of the iceberg reflects the relative frequency of HIT antibody formation by EIA (i.e., the cardiac-UFH iceberg is about six times larger than the orthopedic-LMWH iceberg [50 versus 8% frequency of HIT antibody formation]). Noteworthy aspects include the observation that HIT-associated thrombosis is most common in orthopedic-UFH patients, even though HIT antibody formation is most common in cardiac-UFH patients, and the observation that orthopedic-LMWH has a higher frequency of thrombosis than does medical-UFH. *Source:* Lee and Warkentin[1]

of these procoagulant events, the risk for thrombosis remains for weeks, even after heparin has been stopped.[10]

Clinical Characteristics of Heparin-Induced Thrombocytopenia

Thrombocytopenia

In about 80% of patients suffering from HIT a platelet count nadir between 20 and 150 $\times$ 10^9/L (median 60 x 10^9/L) is observed.[5] In 10% of patients, platelet counts are measured below 20 $\times$ 10^9/L. Despite this significant thrombocytopenia, bleeding, especially petechial hemorrhage, is usually not observed. The remaining 10% of patients never had a platelet decrease below 150 $\times$ 10^9/L. They are detected as HIT patients because of thrombosis or skin lesions, or because of a decrease of platelet count of more than 50%.[11]

Onset of Thrombocytopenia

Most often, platelet count fall begins 5 to 10 days after surgery. In the minority of HIT patients, an abrupt fall in platelet count is observed when heparin is administered. These patients (rapid onset HIT) have received heparin within the past 100 days.[11] Rarely, HIT occurs several days or a few weeks after discharge from the hospital (delayed-onset HIT).[11]

Thrombosis and Other Consequences of Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia is strongly associated with thrombosis (odds ratio, 17 to 37).[11-13] In patients with HIT after cardiac surgery with the use of CPB, thrombosis