

Drug & Innovation Updates

Heparin-Induced Thrombocytopenia

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The incidence of heparin-induced thrombocytopenia (HIT) in patients undergoing cardiovascular surgery is as high as 2.0% and appears to be rising.¹ While thrombocytopenia following cardiac surgery is common and up to 50% of patients develop heparin antibodies, only a fraction will develop HIT syndrome.² Unfortunately, when HIT does occur it is associated with a 40-80% incidence of thrombosis and a mortality rate of 28%.²

HIT is a transient, yet recurring, IgG antibody-mediated response directed against the platelet factor four (PF-4)-heparin complex.² It is more likely to occur with high dose, unfractionated heparin (UFH), but can occur with any exposure.³ The onset can be less than one day if a previous heparin exposure has occurred within 30 days.^{1,2} The risk of HIT can be lowered, but not eliminated, with the use of low molecular weight heparin.² HIT may continue for days to weeks, even after heparin discontinuation.^{1,2} Sequelae include arterial/venous thrombosis,^{1,2} skin lesions at heparin injection sites, or severe acute systemic reactions.⁴ The most common presentation following cardiac surgery is a >50% drop in the peak postoperative platelet count 5-10 days after surgery.^{2,3}

The diagnosis of HIT is made using both clinical and serologic findings. The most common test is the PF-4/heparin polyanion enzyme immunoassays.⁵ Recently, Warkentin has proposed the use of a scoring system to help establish the pre-test probability for HIT, which takes into account degree and timing of thrombocytopenia, extent of thrombosis and cause of platelet decrease (Table 1, website) to guide treatment while laboratory results are pending.⁵ A high clinical score indicates that HIT is highly likely (>80%) and avoidance of heparin exposure is warranted. Conversely, a low clinical score suggests the probability of HIT is low (<5%) and use of low molecular weight heparin or UFH would be reasonable if anticoagulation is indicated. The impact of laboratory testing has its greatest impact when the clinical risk score is moderate. In this range, physician judgment dictates which actions would be most appropriate pending the results of laboratory testing. Periodic reassessment of the HIT clinical score is critical as the clinicopathological picture evolves. If the diagnosis of acute HIT is made, then avoidance of all heparin exposure and treatment is indicated. Platelet transfusion should be avoided and used only in extreme situations after heparin has been discontinued for several hours.⁴

After confirming the diagnosis, treatment beyond heparin discontinuation may be necessary. Recommendations include: 1) UFH (intraoperatively only) for those with a history of HIT, but who are currently PF-4/heparin EIA negative; 2) delay surgery for those who have subacute (normal platelet count, positive PF-4/heparin EIA) or acute HIT for 100 days or until they

become seronegative; 3) for urgent or emergent surgery for patient with confirmed diagnosis or moderate to high suspicion of HIT, administer direct thrombin inhibitors (bivalirudin, lepirudin) or UFH with an antiplatelet agent.⁶⁻⁸ Additional antiplatelet medications can be administered as necessary either alone or in combination.

None of the commercially available direct thrombin inhibitors (lepirudin, argatroban, bivalirudin) (Table 2, website) are FDA-approved as an alternative (to heparin) for use in cardiovascular surgery. Most clinicians prefer the use of bivalirudin, based on its favorable pharmacokinetic properties (t_{1/2} ≈ 25 min) and on an emerging literature suggesting that it is a safe and effective alternate to heparin during percutaneous coronary interventions (PCI) and on- and off-pump cardiac surgery.^{4,9} Lepirudin is approved for the treatment of acute HIT, yet can be problematic, as it has a longer half-life (t_{1/2} ≈ 80 min) and is immunogenic (repeat doses are not recommended).^{2,10,11} Argatroban is also approved for the treatment of acute HIT and as an alternate to heparin during PCI and non-cardiac surgery (vascular).^{2,10}

Platelet hyperactivity plays a central role in the development of HIT syndrome. As such, the use of antiplatelet agents are included in the treatment of patients with a history of HIT.⁴ UFH can be used safely with infusions of potent antiplatelet agents (tirofiban or epoprostenol) in patients with both acute and subacute HIT.⁶⁻⁸

The inherent risk and complexity of managing patients with non-heparin anticoagulants during cardiac surgery suggests that each center should establish an institutional protocol using as few agents as possible. Bivalirudin has been administered during cardiac surgical procedures.⁹ For on-pump cases, dosing recommendations are 1 mg/kg bolus, followed by a 2.5 mg/kg/hr infusion.^{9,12} Fifty milligrams are added to pump prime. Repeat doses of 0.1-0.5 mg/kg are administered to maintain a target ACT ≈ 2.5 times baseline. The infusion continues until 15 minutes before cardiopulmonary bypass separation. Lower doses are employed for renal impairment. Although ECT monitoring is preferred, the use of the kaolin ACT appears to provide acceptable results.^{9,12} Of the direct thrombin inhibitors, bivalirudin has the shortest half-life due to enzymatic cleavage (slowed with hypothermia)^{2,9} and renal excretion, the latter of which can be increased with forced diuresis and ultrafiltration.¹³

In summary, the approach to patients with HIT includes initial confirmation or likelihood of HIT followed by elimination of heparin from all sites when appropriate. Then, based on the clinical picture, the decision to treat HIT with direct thrombin inhibitors and/or other antiplatelet medications can be made given the clinical score (platelet count, evidence of thrombosis, etc) and serological findings. Future work is needed to develop accurate monitors of direct thrombin inhibitors plasma levels and methods to reduce residual activity.^{13,14}

References and tables are on www.scahq.org