

HIT HAPPENS

by David Kissin, BS, RRT



In determining the topic for this issue's Blood Gas Corner, it was brought to my attention that the clinical practice protocol used at the hospital where I work is to have arterial line flush solutions sans heparin. When I first started working in the field of respiratory therapy, lo these 30+ years ago, heparin was a fundamental component of invasive line flush solutions. Why the norm has changed, I wondered. Many studies have taken place, and continue, to investigate a phenomenon called Heparin-Induced Thrombocytopenia (HIT).

Heparin sulfate is an intrinsically produced chemical synthesized by the endothelial cells. It is present on cellular membranes and is a potent anti-coagulant. Heparin prevents collagen and elastin cross-linking and decreases fibronectin synthesis. Heparin can also act as an adhesion protein as well. This latter property often causes HIT, along with the non-specific protein binding of heparin which results in antibody formation. The specific antibody for HIT is heparin/platelet factor 4. With the increasing use of anticoagulant therapy for patients undergoing treatment for everything from open-heart surgery, burns,

hemodialysis or deep-vein thrombosis, the prevalence of HIT has become a greater concern and comorbidity. Different timetables of HIT exist, with the typical onset usually occurring 5 - 14 days after initial heparin exposure. Rapid onset HIT develops within hours or days after initial heparin infusion and delayed onset HIT manifests 9 - 40 days after the discontinuation of heparin therapy. HIT is characterized by 2 types. Type-1 is seen as an early, mild drop in platelet count within the first 2 - 4 days after heparin dosing which usually has a return to normal levels without intervention or discontinuation of heparin therapy. This appears to be an effect of the heparin on platelet activation. Type-2 HIT is an immune-mediated problem causing severe thrombosis. It is usually a relatively rare complication of unfractionated heparin therapy as with central venous line heparin lock solutions. Heparin therapy comes in different preparations, as unfractionated heparin or low-molecular weight heparin (LMWH). Both are used to treat thrombotic syndromes and have shown the adverse effects of bleeding, osteoporosis and HIT. However, incidence of these sequelae has been shown to be lower with LMWH use.

Clinical diagnosis of heparin induced thrombocytopenia can be accomplished with measurement for heparin/platelet factor 4 immunoassay. HPF4 is an enzyme-linked antibody which disrupts platelet function and production. HPF4 immunoassay should not be used as a screening tool but as a confirmation assessment where there is clinical suspicion of HIT. This assay has few false negative results and, therefore, has good negative predictive value.

Clinical suspicion of HIT can be quantified using the 4 "T's" of HIT clinical diagnosis: thrombocytopenia, timing, thrombosis and other causes. Using a 2-point scale for these 4 parameters, risk can be ascertained as low, moderate or high. If the patient exhibits a relative drop in platelet count of >50% from post-operative baseline at least 4 days post-op, 2 points are assigned. Any drop of >50% gets assigned 1 point and <30% fall or a nadir of 10000/mcL is given 0 points. (Normal platelet count is at least 150000/mcL.) If the thrombocytopenia occurs 5 - 10 days after the initial dosing of heparin, the patient is assigned 2



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points, > 10 days 1 point and < 4 days 0 points. If thrombi are detected, the patient gets 2 points, if thrombi are suspected or possible without confirmation, the patient gets 1 point and if there are no thrombi, the patient gets 0 points. If other causes for the thrombocytopenia definitely exist, 0 points are assigned. If other causes are possible, the patient gets 1 point and if the only explanation for the thrombocytopenia is HIT, they are assigned 2 points. Risk assessment is then quantified as a patient score of 6 - 8 as high, 4 - 5 as moderate and 0 - 3 as low. Strong suspicion of HIT should be in patients treated with any heparin whose platelet counts are less than 100000/mcL. Up to 50% of patients with HIT develop some thrombosis, which includes pulmonary emboli and stroke, and may result in death or amputation. Clinical manifestation of thrombocytopenia, such as atypical bruising and/or petechiae are not usually found in HIT, though skin lesions at the heparin infusion site are strong indicators for HIT.

Delayed diagnosis of heparin induced thrombocytopenia increases morbidity and mortality. In order to treat a patient with any type of HIT, it is insufficient to discontinue the heparin therapy. Continuation of anticoagulation with low molecular weight heparin after unfractionated heparin has induced HIT is contraindicated. Though "safer" than unfractionated heparin in HIT, LMWH has the tendency to cause continued heparin/platelet factor 4 production and proliferation. Initiation of alternative, fast-acting anticoagulants is indicated, many studies have shown that the use of coumarins like warfarin are contraindicated for early intervention in HIT or as a lone treatment entity. Transfusions of platelets to replenish the patients' platelet count have also been shown to be inappropriate because this may increase platelet-mediated thrombosis. Vena cava filters have also been illustrated to increase thrombi, especially pulmonary emboli and inferior vena cava thrombosis.

The treatments of choice for heparin-induced thrombocytopenia include plasmapheresis, use of fast-acting direct thrombin inhibitors (DTI), such as argatroban, lepirudin and bivalirudin and addition of coumarins after platelet count return. Plasma exchanges have shown efficacy in removing HPF4. Antonijevic and his colleagues in Hungary have shown that plasmapheresis improves outcome for HIT patients resistant to alternative anticoagulants. The US FDA has approved argatroban and lepirudin for the treatment of HIT, to initially treat platelet deficiencies. Argatroban is the preferred treatment because it has a short half-life of < 1 hour, is metabolized and cleared in the liver. Argatroban is expensive as compared to heparin and contributes to INR making it difficult to transition to coumarin therapy and it can not be used with concomitant liver dysfunction. It is only available in intravenous preparation which makes compliance and administration an issue. Shapiro and his group at the University Of Illinois College Of Pharmacy have seen patients with liver failure and obesity exhibit anti-



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coagulation long after agratroban discontinuation and Scott and his colleagues from Harborview Burn Center in Seattle have shown increased bleeding complications requiring transfusions post-treatment. Hartman and his group in Belgium have looked at HIT and the systemic reaction to hemodialysis. They found patients treated and dialyzed with lepirudin recover from HIT and remain symptom-free. Bivalirudin is an alternative DTI for patients with liver disease, though the FDA has not approved its use in HIT. It has a longer half-life than argatroban (25 minutes) and is renally cleared and can be cleared through hemodialysis and plasmapheresis as well. It affects INR consistently but less than argatroban and can, therefore, ease transition to warfarin. Rice from Texas Medical Center in Houston has studied bivalirudin in patients with multisystem failure and HIT. Another heparin alternative is fondaparinux; a drug administered sub-cutaneously and is renally cleared. It has a long half-life (13 - 20 hours), is not reversible and should not be used in patients with moderate renal dysfunction.

HIT happens and requires immediate treatment with new thromboses occurring in 50% of patients. Treatments include discontinuation of heparin therapy and initiation of direct thrombin inhibitors, the choice of which depends on any concomitant organ dysfunction. First line therapies include argatroban, except in hepatic disease and bivalirudin for hepatic patients. These drugs should be given along with warfarin with care and only after the return of the patient's INR to normal range. Warfarin should never be given as an initial therapy. Fondaparinux can be used in patients who have a history of HIT as a treatment of or prevention of venous thromboemboli.