CLINICAL VGNETTE

Heparin Induced Thrombocytopenia

Anh Kieu, M.D.

The patient is a 55-year-old woman who was admitted to the hospital with fevers and hypotension consistent with sepsis. Her initial complete blood count (CBC) revealed white blood cell count (WBC) of 20.44 x 10^3/uL and platelets of 290 x 10^3/uL. She was started on enoxaparin for deep venous thrombosis (DVT) prophylaxis and treated for her sepsis symptoms. During the hospitalization, her platelets were observed to decrease to a nadir of 43 x 10^3/uL at 7 days after starting enoxaparin. Enoxaparin was discontinued and she was started on fondaparinux for DVT prophylaxis. Evaluation was positive for Heparin associated platelet antibody. Three day after discontinuing enoxaparin, the patient's platelet count rose to 100 x 10^3/uL. One week after discontinuing enoxaparin, her platelet count recovered to her baseline level and she was started on warfarin. She developed no thrombotic events and was continued on fondaparinux while bridging over to warfarin. The patient stayed on warfarin for 8 weeks and did well without any thrombotic complications.

Heparin induced thrombocytopenia

Heparin induced thrombocytopenia (HIT) is a disorder caused by formation of antibodies to complexes of platelet factor 4 (PF4) and heparin. It is characterized by a low platelet count of less than 150 x 10^3/uL or a relative decrease of 50 percent or more from baseline. The time to develop thrombocytopenia is 5-10 days in patients with no prior exposure or who have a remote (greater than 100 days) history of exposure to heparin. There is a more rapid decline in people with more recent exposure. HIT is associated with the use of unfractionated heparin (UFH) or low molecular weight heparin (LMWH). UFH has 10 times the incidence of HIT versus LMWH. Antibodies can also be found in patients exposed to heparin without any clinical symptoms[1].

PF4 is a protein that is stored in platelets. At areas of endovascular injury, platelets release PF4. The PF4 then binds to heparan sulfate, a glycosaminoglycan on the endothelial cell surface. After binding of PF4 to heparan sulfate, antithrombin is released from heparan sulfate, changing the endothelial surface to a prothrombotic environment. Due to the higher affinity of PF4 for heparin compared to heparan sulfate, the presence of heparin causes complexes of PF4 –heparin to be released into the circulation. In 1-5% of patients, antibodies are formed leading to binding of HIT immune complexes[2]. The antibody-platelet factor 4-heparin complex activates platelets, increases thrombin generation which can cause venous and arterial thrombosis[3,4].

If HIT is suspected, a clinical scoring system can be used to estimate the pretest probability of HIT based on the level of thrombocytopenia, the timing of onset of thrombocytopenia, presence of thrombotic complications, and other etiology for thrombocytopenia. The score can range from zero to 8. Two points are given for each of the following: if the platelets fall greater than 50% of baseline; the onset of thrombocytopenia occurs between days 5-10 after exposure or within 1 day if there has been recent heparin exposure; new thrombotic event or skin necrosis occurs after heparin exposure; and there are no other reasons for the fall in platelet count. One point is given for each of the following: if the platelets fall between 30-50% of baseline; timing of thrombotic event in relation to heparin exposure is unclear; there is progressive or recurrent thrombosis; and there are other possible etiologies for development of thrombocytopenia. No points are given if there is less than 30% drop from baseline; timing of thrombosis occurs less than 4 days after heparin exposure; no thrombotic events and other definite causes of thrombocytopenia are present.

HIT antibodies are unlikely if the score is less than or equal to 3, and greater than 80% for high score greater or equal to 6. For an intermediate score of 4-5, lab testing is useful for diagnosis[3].

Testing methods include serologic assays to detect IgG, IgA, IgM antibodies or functional assays. Immunoassays are used more frequently due to rapid turnaround time, high sensitivity and ease of testing. A negative test rules out HIT[3]. The tests are highly sensitive but lack specificity (>99% sensitivity, 40-70% specificity) due to the detection of weak antibodies that are not associated with the presence of HIT[1,4]. PF4-heparin antibodies are detected in 8-17% of general medical and surgical patients treated with UFH, 2-8% with LMWH, 1-2% with fondaparinux. The highest rate of asymptomatic seroconversion is in cardiac surgery patients (27-61%) Functional assays have a sensitivity and specificity of >95% in experienced labs. Lack of assay standardization and limited widespread availability limits the use of functional assays[2].

Thrombosis risk in patients who develop HIT is greater than 30 times of controls. The incidence of thrombosis is higher in patients with higher levels of PF4-heparin antibody or with a drop in platelet counts of more than 70 percent[1]. Stopping heparin early does not reduce the risk of thrombosis. The risk stays elevated for 4-6 weeks after stopping heparin despite normalization of the platelet count. Thrombotic events are more often found in the venous circulation in medical and orthopedic patients and are in the arterial and venous circulation in cardiac or vascular surgery. The mortality rate is 8-20 percent[1,2]. Venous and line-related thrombotic complications are more common. Atypical sites of thrombosis such as bilateral adrenal hemorrhage, venous limb gangrene, skin necrosis should raise the suspicion for HIT[2].

Treatment of thrombosis in patients with HIT involves stopping heparin products and giving a non-heparin alternative. Monotherapy with LMWH or warfarin should be avoided. Warfarin can cause skin necrosis and venous gangrene in limbs if used in patients with HIT. If warfarin has already been started in a patient diagnosed with HIT, vitamin K should be administered to reverse the effects of warfarin. Warfarin can be used in HIT patients after the platelet count is above 150k and should be started with a low maintenance dose, no bolus dosing and should overlap with non-heparin anticoagulants. Warfarin can prolong aPTT and cause direct-thrombin inhibitors (DTI) underdosing[2,3].

Alternative anticoagulant therapies include DTI or heparinoids[1,4].

Direct thrombin inhibitors approved in the US for treatment of HIT include lepirudin and argatroban[2]. DTIs bind to thrombin and block thrombin's interaction with various substrates that are important in the coagulation cascade. Lepirudin is recombinant analogue of hirudin. In 3 prospective observational studies, patients with HIT treated with lepirudin had a 20% incidence of thrombotic events vs. 43% in historical controls at 35 days[2]. Lepirudin was associated with 14 % rate of serious bleeding versus 8 percent in controls. Anti-hirudin antibodies develop after 4 days or more of treatment in 40-74% of patients. Fatal anaphylaxis can develop in patients who receive repeat treatment of lepirudin within 3 months of prior exposure[4]. Patients with renal compromise should avoid use of Lepirudin or reduce the dose[3]. The target PTT is 1.5 to 2.5 of baseline level.

Argatroban has demonstrated reduction in thrombotic events as well, with 34-35% vs. 43% in controls in two prospective multicenter studies[2]. The bleeding risk with argatroban was 11% versus 6 %in controls. Argatroban does not seem to be immunogenic[4]. The target is 1.5 to 3 x baseline aPTT. The dose should be reduced by 75% in patients with liver dysfunction[3]. Argatroban prolongs the prothrombin time which can complicate conversion from argatroban to warfarin therapy[2].

Heparinoids inhibit anti-FXa activity via antithrombin. Danaparoid was used but was withdrawn from the market after fondaparinux became available in the U.S. Fondaparinux can occasionally cause the appearance of anti-PF4-

heparin antibodies but it was not thought to be associated with HIT. However, Warkentin et al. and Rota et al. have published reports of patients who had used fondaparinux and developed HIT. At this time, there is no conclusive answer regarding fondaparinux and HIT[5,6].

For patients with HIT but no thromboembolic events, a heparin alternative anticoagulant is used until the platelet count has returned to stable range. At that time, the option is to continue treatment with the same heparin alternative agent or bridge to warfarin for 4-6 weeks since the thrombosis risk remains high for 4-6 weeks. Patients with HIT who develop a thrombotic complication should receive a standard course of anticoagulation for that specific event.

HIT antibodies are transient and heparin can be used at a later time in selected patients[3]. Patients with a known history of HIT should not be re-exposed to heparin except during cardiac bypass surgery. The most commonly used agent is bivalidrudin. The other direct thrombin inhibitors are not used due to lack of reversibility. Prior to or after surgery, use other non-heparin anticoagulants for other indications[2].

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