# Treating heparin-induced thrombocytopenia

## *The unconventional way!*

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## ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a potentially devastating complication of heparin therapy. The severe form of HIT has been associated with both venous and arterial thrombosis manifested by myocardial infarction, cerebrovascular occlusion, skin necrosis or limb ischemia. Several agents are now available as alternatives to heparin in patients with suspected HIT, including the thrombin specific inhibitors lepirudin and argatroban as well as the low molecular weight heparinoid known as danaparoid. When lacking these agents, here we report the use of plasmapheresis to create an artificial state of anticoagulation; exchanging patient's plasma with albumin rather than fresh frozen plasma, to allow the safe introduction of warfarin.

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Depending on the definition, severity of thrombocytopenia and the form of heparin used, the frequency of heparin induced thrombocytopenia (HIT) varies from 1-25%.[1] Heparin induced thrombocytopenia syndromes are 2 types; type I is usually associated with early onset thrombocytopenia (within 4 days) and usually leads to a mild decrease in platelet count (rarely <100 x $10^9$/L) and typically recovers within 3 days despite continued use of heparin, it results from non-immune-mediated mechanisms through direct platelet activation by heparin. This type is a benign form of HIT and is usually not associated with any major clinical sequelae.[2]

Type II HIT, is usually induced by immunologic mechanisms, typically occurs within 4-14 days after exposure to heparin, however, it may occur earlier in patients previously exposed to heparin. Substantial fall in platelet count (but usually >20 x $10^9$/L), can occur with any dose, by any route, and has the potential to develop life threatening thromboembolic complications.[2,3] HIT tends to occur more with bovine heparin, as compared to the porcine derived one, and more in surgical than medical patients.[4]

Patients with type II HIT, are at a high risk for thrombosis and should be treated with an alternative anticoagulant therapy to reduce thrombotic complications. The current treatment of choice is one of the approved direct thrombin inhibitors, Argatroban or Lepirudin. These drugs have been proven to be safe and effective in multicenter clinical trials.[5]

**Case Report.** A 56-year-old lady with diabetes mellitus and hyperlipidemia was admitted to another hospital for 5 days with an acute attack of

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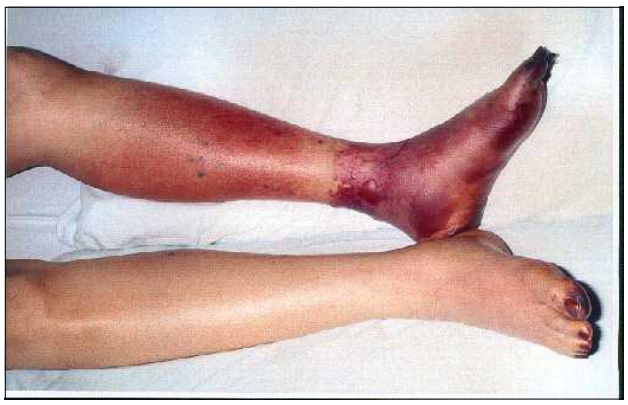

**Figure 1 -** Left lower limb ischemia

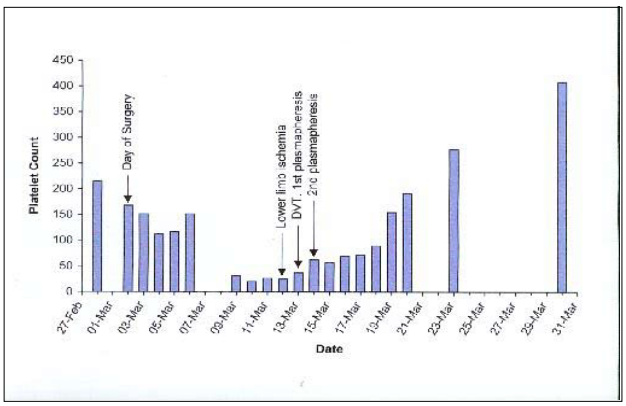


**Figure 2 -** Patient's platelet count

retrosternal chest pain, she was diagnosed as having subendocardial myocardial infarction and was treated with aspirin, intravenous nitroglycerin and heparin infusion. She developed post myocardial infarction angina and was referred to our hospital for cardiac angiography and possibly percutaneous transluminal coronary angioplasty.

On admission, her laboratory blood works revealed white blood cell 5.6 x $10^9$/L, hemoglobin 10.9g/dl and platelets 216 x $10^9$/L. She was continued on intravenous (IV) heparin infusion and had coronary angiography, which showed 3 vessels disease. Three days after admission, she had a coronary artery bypass graft procedure.

On the 7th postoperative day she had left lower limb pain, however, her clinical examination was unremarkable, but it was noted that her platelet count dropped from 168 x $10^9$/L on the day of surgery to 31 x $10^9$/L. As the left lower limb pain and thrombocytopenia persisted, hematology opinion was sought. Heparin was discontinued and aspirin was held. On the 10th postoperative day, she developed signs of left lower limb ischemia (**Figure 1**). A day later, she was noted to have a massive swelling of the left calf and thigh. Deep vein thrombosis (DVT) was suspected and confirmed by doppler ultrasound, which showed acute DVT in the left femoral vein and total occlusion of the left popliteal artery. A clinical diagnosis of Type II HIT was made. Lepirudin, Argatroban or Danaparoid were not available in the hospital during that day, and efforts to obtain any of these drugs were unsuccessful. Given the massive nature of DVT and the increased risk of progression of thrombosis with an added risk of pulmonary embolism, patient was commenced on plasmapheresis as the only option available. However, instead of giving her fresh frozen plasma, we opted to give albumin to create an artificial state of anticoagulation by factor depletion. Before commencing plasmapheresis her coagulation profile was normal. Following the first session of exchange, her partial thromboplastin time (aPTT) increased to 100 seconds and international normalized ratio (INR) to 1.95, with this coagulation profile, warfarin was introduced at a dose of 5 mg and aspirin was recommenced. After a second session of plasmapheresis, which was performed the next day, her INR was 3. Therapeutic range was maintained on adjusted dose of warfarin.

Her platelet count was followed on a daily basis and was noted to be increasing day by day until it reached a normal value on day 17 postoperatively, **Figure 2** shows the platelet counts during the course of her illness. Following recovery of her platelet count, the patient underwent left above knee amputation successfully and was discharged home after her condition improved.

**Discussion.** The pathogenesis of HIT is a complex one. The antigen in type II HIT, is thought to be a complex of a negatively charged heparin polysaccharide and a positively charged protein tetramer, known as platelet factor 4 (PF4). This PF4 is released from platelet storage granules during platelet activation. Immune complexes composed of heparin, PF4, and immunoglobulin G bind to platelet Fc receptors, resulting in strong platelet activation, and ultimate increase in thrombin generation.[6] In addition, binding of heparin to PF4 neutralizes the anticoagulant effect of heparin, therefore, HIT is considered a hypercoagulable state that may result in the progression of an existing thrombus or the development of a new venous or arterial thrombosis. In order to treat HIT, this circle should be interrupted, heparin has to be stopped and another method of anticoagulation has to be started.

The discontinuation of heparin and the initiation of warfarin alone in patients with HIT has been associated with venous limb gangrene.[7] The mechanism may be due to the transient initial decrease in protein C caused by warfarin, combined with ongoing thrombotic process. Warfarin has not been associated with gangrene or extension of

thrombosis when initiated while the patient is receiving thrombin specific inhibitors or Danaparoid. Current recommendations are to initiate warfarin at a low daily dose while the patient is also receiving an alternative anticoagulant.[8]

Several agents are now available as alternatives to heparin in patients with suspected HIT, these include the thrombin specific inhibitors Lepirudin (Refludan, Hoechst Roussel, Kansas City, MO, United States of America (USA)) and Argatroban (Glaxo Smith Kline, Research Triangle Park, NC, USA) as well as the low molecular weight heparinoid known as Danaparoid (Orgran, West Orange, New Jersey, USA).[5,9] Ideally, hospitals with active cardiac surgery service should have these alternative agents, unfortunately, sometimes none of these products are available to the treating physicians.

Plasmapheresis, intravenous gammaglobulin, aspirin and thrombolytic therapy were tried in the treatment of type II HIT.[10] Although, used historically, these options have not been tested in rigorous clinical trials.

Understanding the pathogenesis of HIT, one treatment modality would be removing the offensive antibodies via plasmapheresis. Several case reports and small studies have described this modality. In one study, patients diagnosed with HIT were divided into 3 experimental groups. Twenty-one patients received plasmapheresis within 4 days of onset of thrombocytopenia (early group), 7 patients received plasmapheresis 4 days after onset (late group), while 16 patients did not receive plasmapheresis (control). Most patients underwent a second plasmapheresis 24-48 hours after the first, when clinically indicated. The 30-day mortality rate was 4.8% among patients in the early group and 57% in the late group, as compared with 32% in the control group.[11] There were no adverse events related to plasmapheresis. Given the limitations of this study, these findings suggest that early plasmapheresis may be useful in the treatment of HIT.

The diagnosis of type II HIT in our patient was made solely on a clinical basis, as diagnostic assays were not feasible. Her HIT was complicated by both venous and arterial thrombosis. None of the heparin alternatives were available to us. A massive proximal deep vein thrombosis, with a very high risk for pulmonary embolism, encouraged us to use plasmapheresis, but instead of replacing patient's plasma with FFP, we administered albumin with the intention of depleting the patient's clotting factors, thus, creating an artificial state of coagulopathy, manifested by a prolonged aPTT and INR. It is true that this process of exchange may have resulted in removing some of her natural anticoagulants like protein C, protein S and antithrombin, but it also resulted in clotting factor depletion. This exchange process may have also helped in another way, by removing the heparin antibodies.

Though the patient lost her limb secondary to HIT related ischemia, we believe that our method of therapy prevented the progression of her massive DVT and helped in preventing pulmonary embolism. We are not recommending this method as a standard therapy, however, it is a possible alternative when pharmacological therapy is not available.

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