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Peter's Painful Leg: HIT and Arterial Thrombosis

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Heparin-induced thrombocytopenia (HIT) is a common and important adverse effect of heparin seen in 1% to 5% of patients who receive standard, unfractionated heparin for one week to two weeks after surgery.[1] It is caused by heparin-dependent, platelet-activating antibodies. Ironically, a patient who develops HIT has an increased risk of thrombosis (odds ratio, approximately 40).[2,3] Both venous and arterial thrombosis are common complications. This review focuses on arterial thromboses in HIT, with its potential for serious and debilitating sequelae, such as limb loss and stroke.

Peter's Case

Peter, 6, underwent emergency heart surgery (Figure 1) where:

- An intra-aortic balloon pump was used perioperatively in the right femoral artery
- Atrial fibrillation occurred in the postoperative period
- Acute right limb ischemia, with absent pulses occurred on postoperative day 8
- Emergency surgical thromboembolectomy restored limb blood flow
- Intraoperative and postoperative heparin was given
- The platelet count, which was 309 x 10^9/L pre-embolectomy, fell abruptly to 74 x 10^9/L, the next day, at which time heparin-induced thrombocytopenia (HIT) was diagnosed

How can you manage Peter's case?
Go to page 28 to find out.

Clinical features

It takes at least five days for treatment with heparin to trigger sufficient levels of antibodies to cause thrombocytopenia or thrombosis. Thus, the most important clinical feature of HIT is this characteristic interval between initiation of heparin and the onset of a platelet count fall, symptomatic thrombosis, or both. Interestingly, there is a typically narrow onset of HIT that usually begins five days to 10 days (sometimes, up to 14 days) after starting heparin,[4] particularly when given after surgery. Indeed, as seen in Peter's case, postoperative thromboprophylaxis with unfractionated heparin is the most common scenario for HIT.[5]

About 50% of patients with HIT develop venous thrombosis, most often deep-vein thrombosis with or without pulmonary embolism.[2] However, about 15% to 25% of patients develop arterial thrombosis.[2,6] Characteristic arterial thrombosis, in descending order of frequency are:

- limb artery thrombosis,
- thrombotic stroke and
- MI.[6]

For unknown reasons, this rank order is the converse of that seen with typical atherothrombosis.

Sometimes, necrotizing skin lesions develop at the heparin injection sites of patients who develop HIT.[7] This complication, which was not seen in Peter's case, as it is associated with arterial thrombosis.[8]

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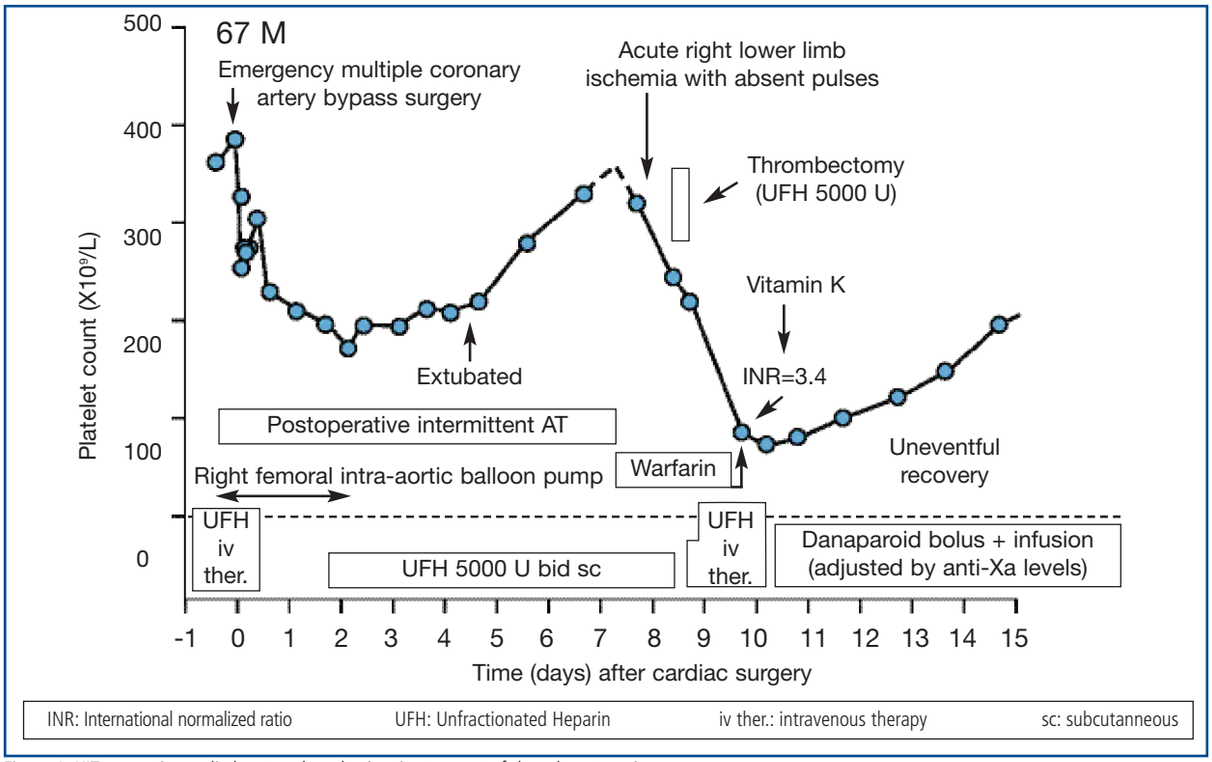

Figure 1. HIT presenting as limb artery thrombosis prior to onset of thrombocytopenia

Peter's Case Cont'd

- Peter developed acute right lower limb ischemia with absent pulses eight days after emergency heart surgery
- The platelet count (309 x 10^{9}/L) had fallen only minimally (from 330 x 10^{9}/L) and the limb ischemia was attributed to either a local right femoral injury (secondary to recent use of an intra-aortic balloon pump) or cardiac embolism (secondary to postoperative AF)
- After limb blood flow was restored by thrombectomy, with intraoperative use of unfractionated heparin, Peter received postoperative heparin
- Progressive decline in the platelet count by 78% to 74 x $10^{9/L}$ prompted the diagnosis of HIT, at which time the heparin was switched to danaparoid (an alternative, non-heparin anticoagulant)
- Vitamin K was given to reverse warfarin anticoagulation (Table 1)

Approach and differential diagnosis

A clinician should have high clinical suspicion for HIT whenever a platelet count falls and/or symptomatic thrombosis occurs five days to 14 days after starting heparin.[1,2] In Peter's case, arterial thrombosis, which manifested as limb ischemia with absent pulses, occurred within this characteristic time period. As the platelet count had not yet significantly declined, heparin was given emergently for intraoperative and postoperative anticoagulation. The limb artery thrombosis was attributed to either perioperative use of an intra-aortic balloon pump or postoperative atrial fibrillation, with risk for right femoral artery thrombosis or cardiac embolism, respectively. However, HIT was strongly suspected when the

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Table 1
Six treatment principles of HIT

Two Do's	Stop heparin
	Start alternative, non-heparin anticoagulant, usually in therapeutic doses
Two Don'ts	Avoid or postpone coumarin pending substantial platelet count recovery (give intravenous vitamin K if coumarin was already given when HIT is recognized*)
	Avoid platelet transfusions
Two Diagnostics	Test for HIT antibodies
	Investigate for lower-limb DVT (duplex ultrasonography)

* There are two reasons to give IV vitamin K when HIT is recognized after warfarin has been given. First, it may reduce the risk of warfarin-induced microthrombosis (venous limb gangrene and skin necrosis syndromes); second, it reduces the risk of underdosing of lepirudin or argatroban because of prolongation of the activated partial thromboplastin time by warfarin.

Take-home message

1. Suspect HIT if a platelet count fall and/or thrombosis occurs five days to 14 days after starting a course of heparin therapy
2. Arterial thrombotic complications of HIT most commonly involve limb arteries (risk for limb necrosis and amputation) and less often, thrombotic stroke or MI
3. Treatment principles of HIT (Table 1) include substituting heparin with a rapidly-acting, non-heparin anticoagulant and avoiding or postponing warfarin pending platelet count recovery

platelet count fell abruptly following the initiation of a therapeutic-dose heparin. This diagnosis was confirmed when blood tests revealed heparin-dependent, platelet-activating antibodies (strong positive platelet serotonin release).

Treatment principles

Table 1 lists the six treatment principles of HIT. When HIT is strongly suspected, it is important to substitute heparin with a rapidly-acting alternative anticoagulant. Three drugs that are approved to treat HIT in Canada are:

- danaparoid,
- lepirudin and
- argatroban.

Another important treatment principle is to avoid or postpone warfarin until after the thrombocytopenia has resolved. Warfarin is ineffective in treating acute HIT and worse, its use has been linked to the devastating syndrome of venous limb gangrene (*ie.,* limb loss in the setting of deep-vein thrombosis despite patent large limb arteries).

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References
1. Warkentin TE: Think of HIT. Hematology (Am Soc Hematol Educ Program) 2006; in press.
2. Warkentin TE: Heparin-induced thrombocytopenia: Pathogenesis and management. Br J Haematol 2003; 121(2):535-55.
3. Warkentin TE: Management of heparin-induced thrombocytopenia: A critical comparison of lepirudin and argatroban. Thromb Res 2003; 1102-(3):73-82.
4. Warkentin TE, Kelton JG: Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 2001; 344(17):1286-92.
5. Warkentin TE, Sheppard JI, Sigouin CS et al: Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006; 108(9):2937-41, Epub 2006, Jul 20.
6. Warkentin TE; Kelton JG: A 14-year study of heparin-induced thrombocytopenia. Am J Med 1996; 101(5):502-7.
7. Warkentin TE: Heparin-induced skin lesions. Br J Haematol 1996; 92(2):494-97.
8. Warkentin TE: Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia,* 3rd ed. Marcel Dekker, Inc. New York:2004, 53-106.