# Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a complication of heparin therapy.

## Types

There are two types of HIT. Type 1 HIT presents within the first 2 days after exposure to heparin, and the platelet count normalizes with continued heparin therapy. Type 1 HIT is a nonimmune disorder that results from the direct effect of heparin on platelet activation.

Type 2 HIT is an immune-mediated disorder that typically occurs 4-10 days after exposure to heparin and has life- and limb-threatening thrombotic complications. In general medical practice, the term HIT refers to type 2 HIT.

HIT must be suspected when a patient who is receiving heparin has a decrease in the platelet count, particularly if the fall is over 50% of the baseline count, even if the platelet count nadir remains above 150 x 109/L. Clinically, HIT may manifest as skin lesions at heparin injection sites or by acute systemic reactions (eg, chills, fever, dyspnea, chest pain) after administration of an intravenous bolus of heparin.

Unlike other forms of thrombocytopenia, HIT is generally not marked by bleeding; instead, venous thromboembolism (eg, deep venous thrombosis, pulmonary embolism) is the most common complication. Less often, arterial thrombosis (eg, myocardial infarction) may occur. For that reason, the disorder is sometimes termed heparin-induced thrombocytopenia and thrombosis (HITT).

Diagnosis of HIT is based on the combination of clinical findings, thrombocytopenia characteristics, and laboratory studies of HIT antibodies [1].

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The incidence of heparin induced thrombocytopenia (HIT) in neurological patients continues to increase with expansion of indication for neurointerventional procedures. The pathophysiology of HIT is related to a hypersensitivity reaction against complex platelet factor 4. The diagnosis is mostly clinical and is often confirmed by laboratory testing. Patients with HIT have a higher rate of thromboembolic complications, both arterial and venous, and with worse neurological outcomes at the time of discharge. Early diagnosis and heparin cessation are essential in the management of those patients. Both immediate and prolonged alternative anticoagulation are necessary. Understanding of the mechanism of action, indication and drug interaction of the alternative anticoagulants (direct thrombin inhibitors, fondaparinux and danaparoid) and warfarin is essential during management of these patients [2].

Venous thromboembolism (VTE) is associated with heparin induced thrombocytopenia (HIT) infrequently (< 1%) in low molecular weight heparin (LMWH) treated patients, yet often (approximately one in eight cases) in unfractionated heparin-treated patients. Physicians should suspect the possibility of HIT if VTE develops during or soon after unfractionated heparin use; if thrombocytopenia is present, alternative anticoagulation should be used until HIT is excluded [3].

Heparin-induced thrombocytopenia type II correlates with a worse outcome and higher risk of thromboembolic complications in aneurysmal subarachnoid hemorrhage patients. In addition, HIT II

was strongly associated with the number of angiographic procedures performed during the same hospitalization [4].

The presence of HIT in SAH has adverse consequences and is more likely in female patients who have undergone aneurysm clipping and require multiple endovascular vasospasm treatments [5].

SAH patients with isolated heparin induced thrombocytopenia and heparin induced thrombocytopenia with thrombotic syndrome did not differ in the incidence of new thromboses, incidence of hemorrhage, or hospice/death. Patients with isolated heparin induced thrombocytopenia had fewer “poor treatment-related effects” than heparin induced thrombocytopenia with thrombotic syndrome patients [6].

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Studies reveal a high occurrence of overdiagnosis of heparin-induced thrombocytopenia in surgical patients with critical illness. The optimal criteria for diagnosis of heparin-induced thrombocytopenia remain unclear, contributing to unnecessary treatment.

## Treatment

Treatment of HIT begins with discontinuation of all heparin products (including heparin flushes of intravenous catheters). The patient should then be started on an alternative anticoagulant

Overtreatment of heparin-induced thrombocytopenia in the surgical ICU continues even with recent increased caution encouraging a higher antiplatelet factor 4/heparin enzyme-linked immunosorbent assay optical density threshold before initiating treatment. More stringent criteria should be used to determine when to order serologic testing and when the results of such testing should prompt a change in anticoagulant treatment. If antiplatelet factor 4/heparin enzyme-linked immunosorbent assay is used to consider immediate treatment, an optical density greater than or equal to 2.0 may be a more appropriate threshold [7].

## Case series

During a 3.5-year period (January 2000-June 2003), 389 consecutive SAH patients were treated at our center. We retrospectively reviewed their laboratory data and medical records and used accepted clinical criteria for the diagnosis of HIT II to determine the incidence of HIT II, thrombotic complications, management, and outcome.

Fifty-nine patients (15%) met the clinical diagnostic criteria for HIT II. The average platelet count nadir in the HIT II patients was 68,600 +/- 25,300/microl (mean +/- standard deviation). Female patients and patients with Fisher Grade 3 were more likely to develop HIT II ($P < 0.01$). Thirty-six patients (61%) underwent a neuroendovascular procedure. The rate of systemic thrombotic complications in the HIT II patients was 37 versus 7% in SAH patients without HIT II ($P < 0.001$), and the rate of new hypodensities on head computed tomographic scans was 66% in the HIT II patients versus 40% in the SAH patients without HIT II ($P < 0.001$). Clinical outcomes were worse in the HIT II patients. The outcome was favorable for 38% in the HIT II patients versus 52% in all SAH patients ($P < 0.05$), and deaths were more common (29%) in the HIT II patients than in all SAH patients (12%, $P < 0.001$).

The incidence of HIT II in SAH patients at a single center was 15%. The SAH patients with HIT II had significantly higher rates of thrombotic complications, new hypodensities on head computed tomographic scans, more deaths, and significantly less favorable outcomes. This is the first report of the incidence of HIT II in a neurosurgical patient population [8].

## Case reports

### 2013

A 63-year-old man with HIT and multiple medical comorbidities underwent emergent coronary artery bypass grafting, postoperative imaging revealed plaque at the origin of the left internal carotid artery with 80%-99% stenosis and minimal contralateral internal carotid artery disease. During the patient's evaluation to undergo CEA for symptomatic high-grade carotid stenosis, enzyme-linked immunosorbent assay revealed persistent platelet factor 4 antibodies.

The endarterectomy was successfully performed while the patient received argatroban, both as a continuous infusion and intermittent irrigation during dissection of the plaque. Postoperatively, the drip was continued for 24 hours, and the patient was discharged day 2 on a daily dose of 325 mg of aspirin. At the 6-month examination, Doppler ultrasound revealed normal anterograde velocities with no evidence of stenosis, and the patient noted no subsequent ischemic events.

Serrone et al., now recommend systemic intravenous and local argatroban irrigation to prevent thromboembolic complications in CEA cases with HIT and renal insufficiency. Bivalirudin for both systemic intravenous use and local irrigation may be safer in patients without renal insufficiency because of its shorter half-life [9].

### 2012

Kruljac et al., report a case of an elderly female who received prophylactic fractionated heparin therapy due to sepsis, consequent rhabdomyolysis, and overt disseminated intravascular coagulation. On the seventh day of heparin therapy, she reported sudden vision loss, ptosis, diplopia, and severe headache. Severe thrombocytopenia and positive antibodies to the complex of platelet factor 4 and heparin confirmed heparin-induced thrombocytopenia type 2 (HIT). Magnetic resonance imaging disclosed a homogenous pituitary tumor mass with pronounced sphenoid sinus mucosa thickening and two hypointense zones within the tumor mass on contrast-enhanced images consistent with focal ischemic necrosis. The tumor was confirmed to be squamous cell carcinoma with no signs of necrosis. Ischemic necrosis was found within marginal pituitary tissue. This is the first reported case of ischemic PA associated with pituitary metastasis and the first case in which HIT triggered PA. Our case demonstrates that prothrombotic states such as HIT can precipitate ischemic PA. Pituitary metastasis can present with ischemic PA, but radiological features differ from those described in pituitary neuroendocrine tumors. Segregated low-signal intensity zones within the tumor mass on postcontrast images indicate partial infarction of the tumor, which could be a special feature of ischemic PA in pituitary metastasis and has never been described in pituitary neuroendocrine tumors. These are all novel findings and might enlighten the pathogenesis of PA [10].

**2011**

A 58-year-old woman presented with right supplementary motor area glioblastoma multiforme and deep venous thrombosis in her legs. The tumor was resected after temporary inferior vena cava filter placement, considering that increased thrombosis during and after the operation would cause fatal pulmonary embolism. After anticoagulation with unfractionated heparin, thrombocytopenia was aggravated, and computed tomography showed filter catheter-related thrombosis in the inferior vena cava. The diagnosis was heparin-induced thrombocytopenia, and argatroban and urokinase were administered. Thrombolysis with urokinase was completed and the temporary inferior vena cava filter catheter was removed without complication [11)].

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A case of bifrontal intracerebral haemorrhage in a patient with heparin-induced thrombocytopenia type II (HIT II). HIT II was induced by treatment with low-molecular-weight heparin for recurrent deep vein thrombosis caused by essential thrombocytosis and accompanied by hepatic thromboembolism. This patient was treated with platelet substitution and neurosurgical haematoma evacuation. Anticoagulation with 2500 units danaparoid per day was sufficient for therapy of thrombosis and no rebleeding occurred [12)].

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A 61-year-old woman treated for cerebral venous thrombosis (CVT) leading to diagnosis of essential thrombocythemia (ET). During treatment with unfractionated heparin, after initial improvement of clinical state, signs of cerebral hypertension reappeared. Although the platelet count decreased, heparin-induced thrombocytopenia (HIT) was only suspected 2 days later when it dropped below the standard 150 × 10(9) L(-1) threshold. HIT diagnosis was confirmed by the presence of anti-PF4/heparin IgG. This late finding was the cause of the extension of CVT with worsening of cerebral hypertension necessitating decompressive craniectomy. Elevated basal platelet count due to ET can delay diagnosis and treatment of HIT. In this case, physicians should be more attentive to platelet count variations rather than thrombocytopenia threshold [13)].

**2009**

A patient with heparin-induced thrombocytopenia type II and pulmonary embolism who was anticoagulated with argatroban and, later, with fondaparinux. No intracranial bleeding was detected when anticoagulation was performed with argatroban and, later, fondaparinux [14)].

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A case of intratumor haemorrhage in the cavernous sinus 1 week after cardiac surgery. The pathogenesis may be venous thrombosis and haemorrhagic infarct caused by HIT following cardiopulmonary bypass surgery [15)].

**2007**

The development of cerebral sinus thrombosis as a complication of heparin-induced

thrombocytopenia is very rare. A 59-year-old patient with cerebral sinus thrombosis secondary to type II heparin-induced thrombocytopenia [16].

### 1986

Doty et al., report the clinical course of two patients who in the immediate postoperative period developed heparin-associated thrombocytopenia that resulted in significant morbidity. In these two cases, the origin of the heparin was in “flush” solutions used to maintain the patency of indwelling vascular catheters and was infused at a dose of 250 to 500 units/day. The minimal daily dose previously reported to result in thrombocytopenia is 9000 units/day administered in divided doses subcutaneously. The case reports indicate that heparin in “flush” solutions should be considered as a cause for unexpected thrombocytopenia and that platelet counts should be monitored in patients receiving heparin in any amount [17].

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