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Strategies in heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is an uncommon condition that may confront cardio-thoracic surgeons with difficult problems. The underlying cause of HIT is the formation of antibodies against platelet factor 4/heparin complexes, leading to platelet activation and intravascular platelet aggregation. HIT occurs following heparin administration usually with a time delay of 5–10 days. Clinical suspicion and laboratory tests for platelet-activating antibodies are the cornerstone of diagnosis. Appropriate strategies in HIT are stopping heparin and use of alternative anticoagulants. In addition, surgery with extracorporeal circulation (ECC) should be postponed whenever possible or alternative anticoagulants have to be used during ECC.

Keywords: Anticoagulation; Extracorporeal circulation; Heparin-induced thrombocytopenia

Introduction and clinical picture

The unexpected clinical picture of venous or arterial thrombosis in a patient on prophylactic or therapeutic doses of heparin for a variable period of time, combined with the laboratory picture of marked thrombocytopenia, is the hallmark of heparin-induced thrombocytopenia (HIT).

Therapeutic/prophylactic administration of heparin can lead to an immunological reaction usually with a time delay of 5–10 days [1]. Platelet activating immunoglobulin G (IgG) antibodies recognize heparin bound platelet factor 4 (PF)4. The resulting immune complexes cross-link platelets and lead to platelet aggregation leading to thrombocytopenia and venous and arterial thrombosis. Thrombotic events, such as acute peripheral occlusion of small and larger arteries, coronary bypass grafts, deep venous thrombosis and others may occur even with a low-platelet count. The platelet count usually falls below 50% of baseline in HIT (Schematic 1).

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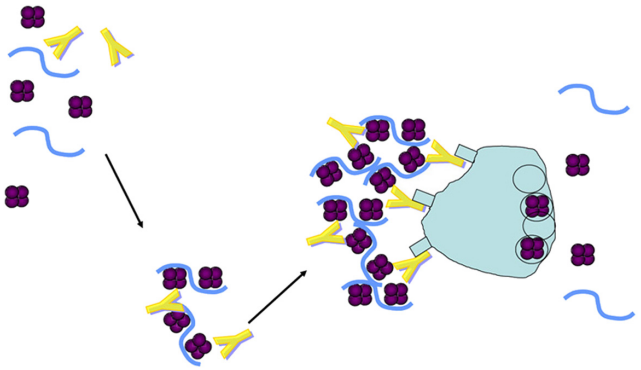
The development of HIT

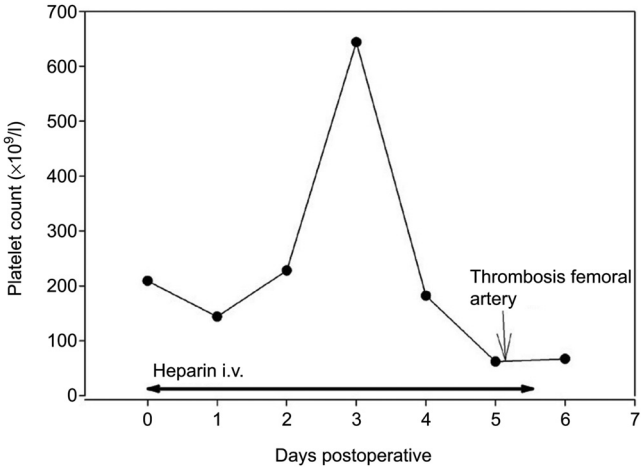
HIT is of particular relevance in the field of cardio-thoracic surgery due to the universal use of heparin [2]. Previous exposure to heparin prior to surgery may lead to rapid-onset HIT within a day of heparin re-exposure in the postoperative period.

It is important to appreciate the connection between thrombocytopenia, the development of HIT antibodies and the occurrence of clinical relevant HIT. Thrombocytopenia is common in patients following cardiac surgery with extracorporeal circulation (ECC), and a number of other clinical situations. Following ECC, the platelet count drops immediately and markedly due to haemodilution, adhesion of platelets to the circuit and postoperative haemorrhage. A further drop in platelet count several days later, often following a recovery of the platelet count, may be related to formation platelet activating antibodies and HIT (Graph 1).

Up to 20% of patients undergoing cardiac surgery were found to develop HIT-IgG antibodies [3]. The risk of developing the clinical picture of HIT is considerably lower and is estimated to be 1–3% [2].



Schematic 1. Pathogenesis of heparin-induced thrombocytopenia: heparin promotes release of PF4 from platelets. Heparin binds to PF4 and forms multimolecular structures. PF4/heparin complexes initiate IgG antibody formation. Several IgG molecules bind to serial PF4 molecules resulting in large immuno-complexes that cross-link platelet Fc receptors. This triggers release of PF4 from α granules which completes the cycle. PF4, platelet factor 4.



Graph 1. The platelet count profile in a patient is shown. The patient was subjected to emergency surgery due to pulmonary embolism. The platelet count recovered markedly on postoperative day 2 and 3. The platelet count fell dramatically on day 4 and 5 when clinical femoral artery thrombosis became clinically apparent.

Subclinical HIT

Patients considered for cardiac surgery and patients following cardiac surgery with a significant drop in platelet count need to be considered carefully. Although laboratory tests may be helpful in certain situations, the results often arrive too late. HIT is thus considered a clinical decision. HIT has to be suspected when the platelet count drops significantly later than five days but before 10 days following exposure to heparin [2]. The 4Ts scoring system described below may be very helpful in the evaluation of such situations.

Diagnosing HIT

Combining clinical and laboratory information is required to confirm the diagnosis of HIT in most patients [1]. Recently, the 4Ts scoring system, incorporating four typical features for HIT, has gained popularity to judge the patient's risk of having developed HIT [4]. A number of laboratory tests have been developed to facilitate diagnosing HIT. Usually, a positive-test result per se is not diagnostic for HIT.

Testing for HIT is performed by activation assays or antigen assays.

Both tests, the antigen assay and the activation assay, have in common that a strong reaction increases the probability of a clinical relevant HIT. Strong positive results in the enzyme immunoassay (EIA) with an optical density greater than 1.0 means that the likelihood of HIT is high [1].

Results of laboratory tests should be evaluated against the background of the pretest probability of HIT. The 4Ts scoring system aims at providing a risk assessment for HIT [4].

The 4Ts scoring system

The 4Ts scoring system is a simple risk assessment tool designed to help the clinician to judge the likelihood of HIT by weighing four key features associated with HIT. The scoring system (Table 1) comprises magnitude of thrombocytopenia, timing of thrombocytopenia, association with thrombosis and presence of another diagnosis to explain the thrombocytopenia.

Iceberg model of HIT

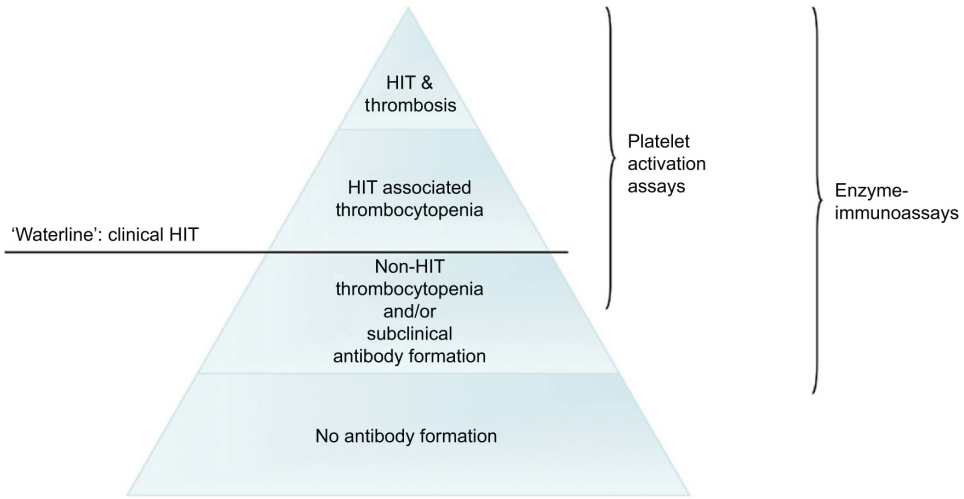
Apparently, clinically relevant HIT is less common than the formation of detectable HIT antibodies. The formation of antibodies in turn is less likely than thrombocytopenia of other causes (Iceberg model of HIT). The likelihood of over-diagnosing HIT is dependent on the type of laboratory test used, as depicted in Graph 2 [5].

Strategies for patients with HIT following cardiac surgery

In patients with suspected HIT all heparin should be discontinued and alternative anticoagulants have to be given. Previous studies show that termination of heparin without administration of an alternative anticoagulant carries a risk of up to 50% for development of new thrombosis in the follow-up period [6]. Individual strategies are summarized in Table 2.

Table 1. The 4Ts score (modified according to [4])

Category of Ts	Points		
	2	1	0
Thrombocytopenia	Thrombocytes fall >50% from baseline AND lowest count $\geq 20\times10^9$/l	Thrombocytes fall between 30% and 50% from baseline OR lowest count $10–19\times10^9$/l	Thrombocytes fall <30% from baseline OR lowest count $<10x10^9$/l
Timing of fall in thrombocyte counts	Onset between days 5 and 10 OR thrombocyte fall $\leq$1 day following heparin exposure within the 30 prior days	Fall in thrombocytes consistent with onset between days 5 and 10 but timing is not clear due to missing counts OR onset after day 10 of heparin exposure OR fall in platelet counts $\leq$1 day following prior heparin exposure between 30 and 100 days previously	Fall in thrombocytes <4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis, skin necrosis, or acute systemic reaction after unfractionated heparin exposure	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis	No thrombosis or thrombosis preceding heparin exposure
Other causes of thrombocytopenia	Not conceivable	Other causes possible	Other causes probable



Graph 2. The iceberg model of HIT depicts that thrombocytopenia and subclinical antibody formation are much more common than HIT with or without thrombosis. The diagnostic challenge lies in the fact that a laboratory test may indicate HIT in situations where detected antibodies are clinically irrelevant. HIT, heparin-induced thrombocytopenia.

Alternative anticoagulants

A number of anticoagulants can be used in HIT: the heparinoids with anti-factor Xa activity danaparoid (Orgaran) and fondaparinux (Arixtra) and the direct thrombin inhibitors lepirudin (Refludan), argatroban (Argatroban) and bivalirudin (Angiomax). No antidote is available for any of the commonly used alternatives to heparin. All of these alternative anticoagulants have a considerable half-life between 25 min and 24 h and all of them carry a significant risk of bleeding complications. They have different characteristics that make them suitable in different situations. A specific drug may be chosen accordingly and with respect to local experience, availability and laboratory back-up for adjusting of dosage. In patients with a high risk of bleeding and unconfirmed HIT, a reduced dosage (equivalent to a 'prophylactic dose') may be acceptable until HIT is confirmed. Details are outlined in Table 3. Orgaran is no longer available in the US. Monitoring of anticoagulation with direct thrombin inhibitors may be challenging especially in simultaneous

Table 2. Strategies in HIT

Discontinue all heparin
Administer alternative anticoagulant (consider prophylactic dose initially)
Avoid platelet transfusions
Withhold oral anticoagulants

HIT, heparin-induced thrombocytopenia.

Table 3. Anticoagulation in HIT with established thrombosis (modified according to [2])

Anticoagulant	Dosing	Monitoring	Metabolism	Half-life
Lepirudin	0.4 mg/kg bolus, 0.15 mg/kg/h infusion	aPTT	Renal	80 min
Bivalirudin	0.15–0.20 mg/kg/h infusion, no bolus	aPTT	Renal 20% Enzymatic 80%	25 min
Argatroban	2 μg/kg/min infusion, no bolus	aPTT	Hepatobiliary	40–50 min
Danaparoid	2500 anti-FXa units bolus, 200–400 anti-FXa units/h	Anti-factor Xa	Renal	24 h
Fondaparinux	7.5 mg/day	Anti-factor Xa	Renal	17 h

HIT, heparin-induced thrombocytopenia; aPTT, activated partial thromboplastin time.

administration of oral vitamin K antagonists. This may result in a falsely high activated partial thromboplastin time (aPTT), leading to a dose-reduction down to insufficient levels of anticoagulation. Thus, most authorities recommend the use of ecarin clotting time (ECT).

Strategies in patients with HIT diagnosed prior to cardiac surgery

PF4-reactive HIT antibodies disappear slowly from the bloodstream following HIT. They are usually undetectable after 100 days. A more rapid or amplified immune response does not occur in this situation [7]. It is therefore considered safe to use heparin as anticoagulant for ECC in these circumstances. It is recommended to perform antibody testing prior to heparin exposure.

Patients with a more recent onset of HIT and detectable antibodies in laboratory testing are at risk to develop a rapid and strong reaction at re-exposure to heparin. In this group of patients surgery with ECC should be postponed whenever possible.

Patients with a recent HIT, who are in need of a cardiac surgical procedure with ECC, should preferably be transferred to a unit experienced with non-heparin anticoagulation during ECC.

ECC with recombinant hirudin, bivalirudin and danaparoid are described in the literature [2].

Recombinant hirudin (lepirudin, desirudin)

The use of recombinant hirudin as anticoagulant during ECC has been described in a number of publications [2]. Lepirudin has a long half-life which is considerably prolonged in patients with renal failure. Measurement of ECT is mandatory for correct dosing. Moreover, lepirudin may induce antibody formation in a high-percentage of patients who are re-exposed to the drug. This may lead to a further prolongation of half-life [1]. Dosing of lepirudin is shown in Table 4.

Anticoagulation with bivalirudin (Table 5) is an alternative. It has a much shorter half-life of 25 min. Monitoring during ECC is probably most accurate with ECT.

Table 4. Lepirudin anticoagulation during CPB (modified according to [2, 9])

Pre bypass	
Initial i.v. bolus	0.25 mg/kg BW
Continuous i.v. infusion	30 ml/h (0.5 mg/min)
Lepirudin added to pump prime	0.2 mg/kg BW
Target plasma levels of lepirudin	>2.5 μg/ml before start of CPB If <2.5 μg/ml, give additional bolus (10 mg)
Dosing and monitoring during pump run	
Continuous infusion	30 ml/h (0.5 mg/min)
Lepirudin level monitoring	Every 15 min using ECT
Intraoperative dose adjustments based on ECT	
Lepirudin plasma level	Dosing modification
>4.5 μg/ml	Reduce infusion rate by 10 ml/h
3.5–4.5 μg/ml	No change in infusion rate
<3.5 μg/ml	Increase infusion rate by 10 ml/h
Special steps toward end of pump run	
Stop lepirudin infusion 15 min before anticipated termination	
After decannulation, administer 5 mg of lepirudin to the heart-lung machine (avoid clot formation)	

CPB, cardiopulmonary bypass; BW, body weight; ECT, ecarin clotting time.

Table 5. Bivalirudin anticoagulation during CPB (modified according to [2])

Pre bypass	
Initial i.v. bolus	1.5 mg/kg BW
Continuous i.v. infusion	2.5 mg/kg/h (42 μg/kg/min)
Bivalirudin added to pump prime	50 mg
Target plasma level of bivalirudin	>10 μg/ml before start of CPB If <10 μg/ml, give additional bolus (0.25 mg/kg and increased infusion rate by 0.25 mg/kg/h)
Dosing and monitoring during pump run	
Continuous i.v. infusion (adjusted as below)	2.5 mg/kg/h or greater (as above)
Bivalirudin level monitoring	Every 30 min using ECT
Intraoperative dose adjustments, based on ECT	
Bivalirudin plasma level (ECT)	Dosing modification
>15 μg/ml (>500 s)	Reduce infusion rate by 0.25 mg/kg/h
10–15 μg/ml (400–500 s)	No change in infusion rate
<10 μg/ml (<400 s)	Give additional bolus (0.25 mg/kg) and increase infusion rate by 0.25 mg/kg/h
Special steps at end of CPB	
Stop bivalirudin infusion at end of CPB, then either:	
(1) within 10 min of stopping bivalirudin infusion: first reinfuse appropriate portion of pump volume to patient, and then give 50 mg bivalirudin bolus to the circuit to prevent clotting; start an infusion of 50 mg/h into the circuit only and continue to recirculate; any subsequent reinfusion of remaining pump volume to patient should be processed through a cell-saver (which removes >90% of bivalirudin) or	
(2) promptly empty remaining pump volume into cell-saving device (replacing the pump contents with crystalloid), thus avoiding need for postseparation bivalirudin boluses to circuit; process blood for reinfusion with cell saver to remove bivalirudin	

CPB, cardiopulmonary bypass; BW, body weight; ECT, ecarin clotting time.

Danaparoid has been used for anticoagulation in ECC since 1990. Danaparoid is a low-molecular-weight heparinoid. Cross-reactivity with HIT antibodies is uncommon. Controlling the anticoagulation activity requires measuring anti-factor Xa levels. Danaparoid is unavailable in the US at present. The use of danaparoid is outlined in Table 6 [9].

Argatroban is a synthetic direct thrombin inhibitor with a half-life of approximately 45 min. Elimination is cor-

Table 6. Treatment protocol for danaparoid [9] (printed with permission)

Initial danaparoid dosing (preCPB)	
Initial i.v. danaparoid bolus*: 100 U/kg body weight	
Danaparoid added to priming solution: 3000 U	
Initial target anti-factor Xa level: >1.5 U/ml before start of CPB	
Additional danaparoid dosing if preCPB plasma anti-Xa level <1.5 U/ml	
Anti-Xa level	Dosing modification
<1.2 U/ml	Give extra 1500 U bolus
1.2–1.5 U/ml	Give additional 750 U bolus
Dosing and monitoring while on CPB	
Danaparoid infusion rate at start of CPB: 200 U/h	
Frequency of anti-Xa level monitoring: every 15 min	
Intraoperative dose adjustments, based on plasma anti-Xa levels	
Anti-Xa level	Dosing modification
>1.8 U/ml	Stop infusion until anti-Xa level <1.5 U/ml
1.2–1.8 U/ml	No change in infusion rate
<1.2 U/ml	Increase infusion rate to 300 U/h
<1.0 U/ml	Administer additional i.v. bolus of 3000 U
Special steps toward end of CPB	
Stop danaparoid infusion 30 min before anticipated end of CPB	

*The initial intravenous danaparoid bolus should be given 15 to 20 min before start of CPB (generally at the time the surgeon has opened the sternum). CPB, cardiopulmonary bypass.

related with liver perfusion and dose reduction may be required in patients with liver disease. Argatroban has been used in experimental cardiopulmonary bypass and its successful use is described in several case reports. In a recent review, it was concluded that other anticoagulants would be preferred until the role of Argatroban in HIT is better defined [10].

Other solutions have been described in the literature in special circumstances. It has been suggested to use heparin as an anticoagulant and prevent platelet aggregation with antiplatelet agents, such as iloprost, epoprostenol (Flolan) or tirofiban. The combination of heparin and tirofiban may be an attractive solution for a number of cardiac surgical units where ECT measurements are not available and who have experience with the glycoprotein IIb/IIIa (GPIIb/IIIa) antagonist tirofiban. Wadia and coworkers describe a patient who developed HIT while on an left ventricular assist device (LVAD). Lepirudin was discontinued and plasmapheresis was performed and heart transplantation was performed subsequently using a single dose of unfractionated heparin during ECC [11].

Ventricular assist devices and HIT

Patients in need for ventricular assist devices carry a high risk of developing HIT antibodies and probably have a higher incidence of developing clinical HIT. Thrombocytopenia is common in this group of patients. In addition, treatment with mechanical assist devices also predisposes for thromboembolism especially to the brain. Recent evidence confirms that HIT occurs in up to 10% of ventricular assist device (VAD) patients early after implantation. The use of routine non-heparin anticoagulation in this group of patients has been suggested in the literature [8].

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