Heparin Induced Thrombocytopenia

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Abstract

Heparin induced thrombocytopenia (HIT) is a serious and life endangering complication of heparin therapy. It usually occurs after 5-14 days of continuous heparin therapy. It is immune mediated. Heparin, in the affected individual binds with platelet factor 4 (PF-4) and forms a highly antigenic Heparin PF-4 complex which leads to the generation of specific IgG Heparin PF4 antibodies (also called HIT antibodies). HIT antibodies may activate the platelets via Fcγ receptor causing the release of highly coagulable micro particles which promote thrombosis – both venous and arterial. However, all patients with HIT antibodies do not progress to HIT with thrombosis (HITT). HIT can present as asymptomatic thrombocytopenia. It can also present with alarming features of venous and/or arterial thromboembolism, for example, pulmonary embolism from deep vein thrombosis (DVT), limb gangrene warranting amputation, cerebrovascular attack (CVA) or myocardial infarction (MI). Rare manifestation of HIT includes necrotizing skin lesion, acute anaphylactoid reaction following IV heparin bolus and acute adrenal apoplexy due to massive adrenal vein thrombosis. The diagnosis is based upon the combination of unexplained thrombocytopenia, demonstration of HIT antibodies, clinical profile and outcome of the case following withdrawal of heparin and administration of non-heparin anticoagulant like Lepirudin, Argatroban or Danaparoid. The choice of alternative anticoagulant depends upon the availability, cost, monitoring facilities and administrative guidelines.

INTRODUCTION

Since the introduction in 1937, heparin has now become the anticoagulant of choice for the prevention and treatment of venous and arterial thromboembolism. Several millions of units of heparin are used world over. Major indications for heparin are acute coronary syndrome (ACS), embolism from deep vein thrombosis (DVT), embolism from atrial fibrillation, percutaneous coronary interventions (PCI), bypass surgery (CABG), cardiac valve replacement or repair, interventional radiology and hemodialysis. Bleeding and interpatient variability are known complications of heparin. Although first reported in 1973,¹ heparin induced thrombocytopenia (HIT) remains largely under-diagnosed and unrecognized. HIT is a serious complication of heparin therapy due to its prothrombotic state.² HIT is immune mediated due to heparin binding to platelet factor 4 (PF4) to form antigenic heparin PF4 complex. The antibodies to heparin PF4 (also called HIT antibodies) lead to thrombocytopenia and thrombosis in 30-50% cases.³ Thrombosis and not bleeding is the cardinal feature of HIT.⁴

Two type of heparin induced thrombocytopenia have been recognized (Breiger et al, 1998).⁵ Type I is relatively common (10-20%) non immune and benign. The platelet count falls within 1-3 days of heparin therapy to 100,000-150,000/cmm. There are no bleeding or thrombotic complications. Platelet count reverts to normal gradually without treatment. Type II is relatively rare (2-3%) and is immune mediated. Generally speaking HIT is associated with thrombosis. The platelet count falls to about 50,000/cmm although more important than the absolute platelet count is the relative fall of platelets by > 50% from the baseline. The fall in platelet count occurs 5-10days of heparin therapy. HIT/HITT are life threatening conditions due to associated thrombosis (Table 1).

HIT and Types of Heparin

HIT most commonly occurs after intravenous use of unfractionated heparin (UFH). The incidence is much higher with bovine lung heparin compared with porcine mucosal heparin.⁶,⁷,³⁸ HIT occurs less commonly with low molecular weight heparin (LMWH) (e.g. Enoxaparin, Deltaparin and Tinzaparin).⁹,¹⁰ HIT can however occur even after very small doses of heparin e.g. IV heparin flushes to maintain patency of IV line or central venous lines or with heparin coated catheters.¹¹

INCIDENCE OF HIT
The usual incidence of Type II HIT is 2-3%. However higher incidence have been reported after cardiac transplant surgery (11%),12 orthopedic surgery (4.8%),13 cardiovascular surgery (CABG, valve repair) (1.4-2.4%)14 and hemodialysis (3.2%).15 The incidence of HIT has been compared to a rising iceberg.14 With the present increase use of heparin in clinical practice, the incidence of HIT is likely to increase. Further old age population is on the rise and there are more chance of administration of heparin in old age to due to associated cardiovascular disease. In a recent study of Heparin (CATCH) Registry of prolonged heparin use and thrombocytopenia in hospitalized patients with or without cardiovascular disease, Oliveira et al (2008)17 reported data from 48 US hospitals on the complications of thrombocytopenia.

2420 patients with mean age is 65.2 yrs were enrolled. There were 1360 males and 1060 females. Thrombocytopenia developed in 881 patients (36.4%). 5.1% of thrombocytopenic patients died in comparison with 95% CI 2.1-5.6, p<0.001). Thrombocytopenia was associated of those without thrombocytopenia (Odds Ratio 3.4, 95% CI 2.1-5.6, p<0.001). Thrombocytopenia was associated with increased risk of MI (OR 2.1, CI 1.5-2.8, p<0.001) and heart failure (OR 1.3, CI 1.1-1.6, p<0.01). Thrombocytopenia developed in about 90% of 1132 CCU patients on heparin. 28.2% of 974 patients on LMW heparin and 34% of 1247 patients on unfractionated heparin developed thrombocytopenia. The authors concluded that prolonged heparin therapy is associated with thrombocytopenia and adverse clinical outcome in hospitalized and CCU patients. The American College of Chest Physicians (ACCP) guidelines suggest that platelet count monitoring should be done on alternate days in patients on prolonged heparin therapy.

**Temporal Pattern Of HIT**

Thrombocytopenia classically occurs 5 to 10 days of heparin therapy. However it could be earlier (or rapid) and delayed in few cases.18

Rapid Onset HIT – Thrombocytopenia may occur in a few hours to 3 days after exposure to heparin,19 if there is a recent past history of heparin administration within100 days. After IV bolus of heparin the clinical picture may simulate acute systemic disease resembling anaphylactic shock reaction with dyspnoea, tachypnoea, tachycardia and hypotension. Diagnosis is suggested by combined presence of thrombocytopenia and positive HIT antibody test. With an increasing number of cardiovascular patients requiring heparin repeatedly, the incidence of rapid onset HIT may become frequent.

Delayed Onset HIT – The onset of thrombocytopenia may be delayed for 2 -6 weeks. Rice et al (2002)20 have described 14 cases where the patient during first hospitalization were given heparin (CABG – 9, valve repair – 3 and knee surgery – 2) without any complications. There were re-admitted 9-40 days after discharge with new onset DVT with pulmonary embolism, CVA, MI or limb gangrene. The diagnosis of HIT became apparent during second hospitalization on finding thrombocytopenia and positive test of HIT antibodies.

**Hit Is A SeriouS Prothrombotic State**

In spite of thrombocytopenia, the most dangerous complication of HIT is thrombosis. This occurs when HIT antibodies triggers the formation of procoagulant micro particles from the activated platelets. The odd’s ratio for the risk of thrombosis in six commonly known prothrombotic states have been worked out by Ohmenn et al (2007)21 as HIT 36.9, antithrombin deficiency 24.1, Protein C deficiency 14.1, dysfibrinogenemia 11.3, Protein S deficiency 10.9 and SLE 5.4 respectively.

**Pathogenesis Of HIT**

In normal conditions, heparin is a potent anticoagulant and has very little effect on platelets. However in some persons, heparin binds to platelet factor 4 to form Heparin PF(4) complex which is antigenic and gets deposited on the surface of platelets and endothelial cells. The antibodies (IgG) to heparin PF4 interact with antigenic complex. Fc portion of IgG activates FcyRII receptors of the platelets and activates the platelets. Activated platelets release hypercoaguable micro particles which promote thrombin generation. The end result is thrombocytopenia and thrombosis. Thrombi could be venous, arterial or both. These may have devastating effect resulting in loss of life and limb. However, it is interesting to note that up to 50% patients with HIT antibodies do not develop thrombotic complications and there may be other factors involved in its pathogenesis.14

**Clinical Manifestations Of HIT**

1. Thrombocytopenia : Unexplained, asymptomatic, thrombocytopenia either absolute (Nadir 50,000/cmm) or relative fall of > 50% from the baseline may be the first manifestation of HIT.

2. Thrombosis : Thrombotic complications may be the first clinical manifestation of HIT/HITT (Greinacher et al, 2005).22 Venous thrombosis (DVT) can lead to fatal/serious pulmonary embolism or venous limb gangrene, warranting amputation. Arterial thrombosis can account for myocardial infarction (MI), cerebrovascular

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**Table 1 : Classification Of Heparin Induced Thrombocytopenia**

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
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<tbody>
<tr>
<td>Frequency</td>
<td>10-20%</td>
</tr>
<tr>
<td>Nadir Platelet/cmm</td>
<td>1,00,000</td>
</tr>
<tr>
<td>Timing of onset</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Antibody mediated</td>
<td>None</td>
</tr>
<tr>
<td>Bleeding</td>
<td>NIL</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>NIL</td>
</tr>
<tr>
<td>Treatment</td>
<td>NIL</td>
</tr>
<tr>
<td>Danger to life</td>
<td>None</td>
</tr>
</tbody>
</table>

Adapted from Brieger et al (1998)
accidents (CVA) and limb gangrene. Thrombosis in graft artery, renal artery, splenic artery and mesenteric artery have been reported.

3. Less common, yet specific manifestations of HIT include necrotic skin lesions at the site of heparin injection, acute anaphylactic reaction after IV bolus of heparin and adrenal hemorrhage due to adrenal vein thrombosis (Warkentin et al).23

4. Bleeding : Although rare, bleeding from intracranial, retroperitoneal, gastrointestinal and adrenal sites have been described. Patients with CABG and HIT are more prone to bleeding complications.

**DIAGNOSIS**

The diagnosis of HIT is not straightforward. It remains a clinico-pathological diagnosis depending upon a strong clinical suspicion and laboratory confirmation of thrombocytopenia with positive HIT antibody testing. Other causes of thrombocytopenia (e.g.: sepsis, drugs etc) must be carefully excluded. Warkentin et al (2004) have suggested “4-Ts” Assessment Point System for suspecting HIT (Table 2).

Steps in the diagnosis of HIT include the following:-

1. History of heparin administration for > 5 days
2. Exclusion of other causes of thrombocytopenia
3. Demonstration of HIT antibodies by functional and antigenic assays.24-27 Various assays are:-
   a. Elisa Assay
   b. Serotonin Release Assay (SRA)
   c. Heparin Induced platelet aggregation assay
   d. Flow Cytology – To demonstrate platelet triggered micro particles.

The sensitivity and specificity of various assays vary from 80–90%. Many assays remain in the domain of reference and research laboratories.

4. Recovery of low platelet count on cessation of heparin, usually within 4 – 14 days.

**MANAGEMENT OF HIT**

Recognition, treatment and prevention of heparin induced thrombocytopenia formed an essential part of seventh ACCP conference on Atherothrombotic and Thrombolytic Therapy (Warkentin and Greinacher, 2004).28 For the prevention of HIT, great stress was laid on the platelet count monitoring done daily or alternate days for 4-14 days of heparin therapy or till heparin was stopped which ever occurs earlier. In the presence of unexplained thrombocytopenia and clinical picture suggesting HIT, presence of HIT antibodies must be carefully evaluated.

Once HIT is diagnosed, all sources of heparin must be withheld, even in the face of thrombosis (HITT). Platelet count may take 4-14 days to recover. Platelet transfusion is not recommended. Warfarin monotherapy may result in cutaneous necrotic lesions or venous gangrene of limb. The risk of thrombosis is 38-76% within first month in spite of heparin being completely stopped (Hirsh et al, 2004).29 Patient should be investigated fully for any evidence of DVT or arterial thrombosis. Alternative nonheparin anticoagulants should be administered.

The choice between various nonheparin anticoagulants depends upon their availability, cost, monitoring facilities, presence or absence of renal and hepatic insufficiency, local administrative or legal guidelines.30-34 Two groups of alternative nonheparin anticoagulant are currently available:-

a) Direct Thrombin Inhibitors which reduce thrombin activity
b) Antifactor Xa which reduce thrombin generation.

Their actions, doses, monitoring methods and side effects are summarized in Table 3

(A) Direct Thrombin Inhibitors (DTI)

These do not generate or interact with HIT antibodies. These include Lepirudin, Argatroban and Bivalirudin. Only Lepirudin and Argatroban are approved by US/FDA for the treatment of HIT and its complications. None of the three

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Point</th>
<th>1 Point</th>
<th>0 Point</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt; 50% fall or Nadir 20-100 x10^9/L</td>
<td>30-50% fall Nadir 10-19 x10^9/L</td>
<td>&lt; 30% fall Nadir &lt;10 x10^9/L</td>
</tr>
<tr>
<td>Timing of platelet fall</td>
<td>&lt; 10 days</td>
<td>&gt; 10 days</td>
<td>&gt; 1 day with P/H heparin 31-100 days</td>
</tr>
<tr>
<td>Presence of thrombosis or other rare specific sequelae</td>
<td>Proven thrombosis</td>
<td>Progressive / silent thrombosis</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Skin Necrosis</td>
<td>Erythematous lesions</td>
<td></td>
</tr>
<tr>
<td>Presence of other causes of thrombocytopenia</td>
<td>None</td>
<td>Possible</td>
<td>Definitive</td>
</tr>
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Possibility of HIT
- High: 6-8
- Intermediate: 4-6
- Low: 0-3

Adapted from Warkentin et al (2003)24
DTI have any antidote. Hence caution is required in their dosing and administration. Bleeding may be a real problem as their side effect,

LEPIRUDIN is a recombinant protein analogue of leech Hirudin. It is eliminated from the body by the kidneys and the doses may require to be reduced/modified in renal insufficiency and those requiring dialysis. Lubenow et al (2005)\textsuperscript{35} have recently analyzed the results of three prospective studies HAT-1, HAT-2 and HAT-3 and concluded that 35day mortality and limb amputation were lower among those receiving Lepirudin than the control (20.3% vs 43%, p=0.001). However the bleeding episodes were more frequent with Lepirudin than the control (17.6% vs 5.8%). Bleeding was cause of death in 1.2% of treated patients. Being a protein, antibodies to Lepirudin develop in 30% patients after the first exposure and in about 70% after repeated exposure. Severe, even fatal, anaphylaxis has been reported after sensitization to Lepirudin (Greinacher et al, 2006).\textsuperscript{36} Hence the patient should not be treated with Lepirudin more than once in life. Further the antibodies to Lepirudin are polyspecific and recognize epitopes on Bivalirudin (Eicher et al, 2004).\textsuperscript{37} Hence, Bivalirudin is avoided in patients who has earlier received Lepirudin.

ARGATROBAN is a synthetic compound derived from L-arginine. It has been extensively studied in two multicentre prospective studies Argatroban-911 and Argatroban 915. In the Argatroban 911 study, 503 HIT patients were studies.\textsuperscript{38} 193 HIT patients did not receive Argatroban and acted as control. They were followed for 37 days. 166 HIT cases without thrombosis and 144 HIT cases with thrombosis (HITT) were administered Argatroban in standard doses for 14 day, monitored by aPTT and followed for 30 days. The incidence of composite end point of all causes of death, all causes amputation and new thrombosis was 25.6% vs 38.8% (p=0.014) in the HIT group vs. control and was 43.8% vs 56.5% (p=0.13) in the HITT group vs. control. The bleeding episodes were 6.9% in the treated group v/s 7.0% in the control group.

The authors concluded that Argatroban improved the clinical outcome in patients with HIT and HITT. The result of Argatroban 915 and the combined outcome of two studies were similar.\textsuperscript{39} Antibodies to Argatroban do not develop. Since it is metabolized in the liver, the doses require modification in hepatic insufficiency.

BIVALIRUDIN is a 20-amino acid polypeptide. Although reported to be safe and effective in the treatment of HIT,\textsuperscript{40} it has not yet been approved by US FDA. It has been recommended for use during percutaneous intervention (PCI) in place of heparin. Only 20% of the administered drug is excreted via kidney. However in dialyzed patients, smaller doses are advised. About 51% of Lepirudin treated patients with antilepirudin antibodies may cross react with

<table>
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<tr>
<th>Alternative anticoagulants in HIT</th>
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<tbody>
<tr>
<td><strong>(A) Direct thrombin inhibitors (DTI)</strong></td>
</tr>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Lepirudin</td>
</tr>
<tr>
<td>Argatroban</td>
</tr>
<tr>
<td>Bivalirudin</td>
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<tr>
<td>Danaparoid</td>
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<tr>
<td>Fondaparinux</td>
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*Adapted from Arepally and Ortel (2006)*\textsuperscript{33}
Bivalirudin. 

Hence there is a possibility of anaphylactic reaction in patients who were earlier given Lepirudin.

(B) Antifactor Xa Anticoagulants

Danaparoid and Fondaparinux are antifactor Xa drugs which reduce thrombin generation. These are not yet approved by US FDA for the treatment of HIT. DANAPAROID has been used in Canada, Australia, New Zealand and part of Europe with success. Its usefulness was first reported by Harrenberg et al. 

It has been used in Canada, Australia, New Zealand and part of Europe with success. Its usefulness was first reported by Chong et al (2001) in a prospective randomized open-label trial and its efficacy was later confirmed in a study of 750 HIT patients.

One serious drawback of Danaparoid is its cross-reactivity of Heparin and HIT antibodies in 3.2% cases. Magnam and Gallus (2006) have recently analyzed 1478 HIT patients treated with Danaparoid from 1982-2004. New thrombosis occurred in 9.7% of treatment episodes while bleeding occurred in 8.1% cases. The rate of cross-reactivity with heparin and HIT antibodies was 3.2% FONDAPARINUX.

Danaparinux is a synthetic pentasaccharide and is an indirect factor Xa inhibitor. It has been used as an anticoagulant for prevention of DVT, especially after orthopedic surgery. It is less likely to induce HIT, being smaller than LMWH. Harrenberg et al (2004) has reported its usefulness in six patients of HIT due to unfractionated heparin and 2 patients with LMWH induced HIT. Fondaparinux was administered in a dose of 2.5mg subcutaneously daily for 14 days without any bleeding or thrombotic side effects. US FDA has not approved it. There has been a case report of HIT associated with Fondaparinux.

**SUMMARY OF TREATMENT RECOMMENDATIONS ON THE USE OF ALTERNATIVE ANTICOAGULATION IN HIT**

Hassel et al (2005) divided the patients into three groups:

(A) Acute and Active HIT Patients with Thrombocytopenia, HIT Antibodies and Thrombotic Complications

1. Stop all sources of heparin
2. Do not give platelet transfusion
3. Nonheparin alternate anticoagulants should be given for at least 14 days. Preferred drugs are Lepirudin or Argatroban. Special monitoring facilities are essential. Doses should be appropriate and reduced in cases of renal and hepatic insufficiency depending upon the route of metabolism of the drug. Once the platelet count returns to 1,50,000/cmm or above, oral Warfarin may be initiated with careful overlapping with nonheparin anticoagulant for at least 5 days. Available guidelines on monitoring transition from Lepirudin or Argatroban to oral Warfarin should be followed.
4. If a life saving procedure like CABG, PCI or hemodialysis is required during acute HIT phase, the choice of nonheparin anticoagulant will depend upon the availability, monitoring facilities and local administrative and standing orders of the institution, besides the experiences of the user.

(B) Sub-acute HIT where Platelets have Recovered and are Stable (E* 1,50,000/Cmm) but the Patient Continues to have Detectable HIT Antibodies

Reintroduction of heparin is to be avoided for about 100 days since there is increased risk of thrombosis (repeat HIT) and acute anaphylactic reaction after IV heparin bolus. Alternative nonheparin anticoagulant may be required to tide over the life saving situation (e.g.: CABG, PCI, hemodialysis)

(C) Those with a Remote Past History of HIT but with a Normal Platelet Count and Negative HIT Antibody Test

Short term exposure to heparin may be safe in emergency procedure like CABG and PCI. However Bivalirudin may be considered as drug of choice for PCI.

**REFERENCES**


