ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 8, Issue – 3, May - 2025, Page No.: 154 – 160

Heparin Induced Thrombocytopenia (HIT) in A Patient Undergoing Pulmonary Valve Replacement for Cardiac Surgery

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How to citation this article: Dr Mayur S Kumar, Dr Manoj Kumar Chauhan, Dr Rajkumar Vishwakarma, Dr Rajvee Gala, Dr Kunal Khera, "Heparin Induced Thrombocytopenia (HIT) in A Patient Undergoing Pulmonary Valve Replacement for Cardiac Surgery", IJMACR- May - 2025, Volume – 8, Issue - 3, P. No. 154 – 160.

Type of Publication: Case Report

Conflicts of Interest: Nil

Introduction

Heparin-induced thrombocytopenia (HIT) can be defined as a prothrombotic disorder caused by platelet-activating antibodies that attack complexes of platelet factor 4 (PF4) and heparin. Since almost all patients who undergo cardiopulmonary bypass (CPB) are exposed to heparin and encounter a platelet count fall postoperatively, it is not uncommon that HIT is commonly suspected in this subgroup.[1]

It is an immune complication triggered by antibodies targeted to complexes containing heparin and an endogenous platelet protein, platelet factor 4 (PF4). Although the immune reaction is relatively common (8% to 50%), clinical complications encompassing thrombocytopenia and thrombosis are much less frequent.[2,3,4,5]

Type I HIT encompasses a transient, nonimmune complication of heparin therapy. It can be attributed to the agglutinating effects of heparin on platelets.

Type II HIT is a more serious, immune complication form of Heparin therapy.[6]

Components seen are:

1. Both thrombocytopenia in addition to thrombosis during heparin therapy,
2. Improvement in platelet counts post stoppage of heparin therapy,
3. Heparin-dependent antibody positivity using platelet aggregation assays in the acute phase, and
4. Recurrence of thrombocytopenia with a repeat heparin rechallenge during the acute phase of illness.

Here we report the case of a patient who underwent successful pulmonary valve replacement (PVR) with a

bioprosthetic valve and Pulmonary artery plication along with tricuspid Valve repair.

Keywords: Heparin, Thrombocytopenia, PVR, Platelet

Case Presentation

Presenting a case report of a 38 year old male, presented with shortness of breath on exertion since the past 6 months. He is a known case of intracardiac repair for tetralogy of fallot in 1992. He is also a case of Juvenile rheumatoid arthritis since 1991 and epilepsy detected in 2008. There is no history of need for a pacemaker, and he has no history of narcotic medication dependence or alcoholism.

At hospitalization to our hospital, his blood pressure was 110/80 mm Hg, other vitals within normal range.

His 2D echocardiography 2 months ago revealed free pulmonary valve regurgitation, grade 3 tricuspid regurgitation, ejection fraction 52%. Now cardiac MRI reveals a dilated right atrium, dilated right ventricle and RVOT, free pulmonary regurgitation with a right ventricular ejection fraction of 36%. Mod-severe Tricuspid regurgitation is also seen.

Initially planned for transcatheter pulmonary valve replacement but was abandoned due to very large area of regurgitation. He is now being planned for redo sternotomy pulmonary valve replacement.

On the day of surgery, patient was shifted to operation theatre after an 8 hour NBM guideline and oral premedication policy as per our institute. The standard ASA monitors including ECG, saturation probe was applied. Right radial artery cannula was transduced, and a general anaesthesia was administered to the patient. Pulmonary artery catheter with was inserted through right internal jugular venous access under GA. Central venous access with a 7Fr triple lumen catheter was also obtained.

The patient underwent Redo-median sternotomy. After systemic heparinization with intravenous Heparin of 4mg/kg and achieving an ACT OF >400 S, cardiopulmonary bypass was instituted with aortic and SVC and IVC cannulation.

Findings observed were a dilated pulmonary artery with a pulmonary annulus of 37mm and severe pulmonary regurgitation (PR). Tricuspid valve was severely regurgitant with an annulus of 41mm. Pulmonary valve replacement was done using 29mm inspiris Resilia tissue valve along with pulmonary artery plication and tricuspid valve repair done using 28mm contour 3D ring.

Patient was then slowly weaned off CPB successfully with minimal inotropes. Transesophageal (TEE) echocardiogram revealed well-functioning pulmonary prosthetic valve and trivial TR. He received 5 packed cell transfusions as well as 6 FFP and 1 single donor platelet transfusion in the OR.

In the ICU, patient was received sedated, intubated and on inotropic supports. On POD1, patient was extubated and started on physiotherapy. Tapering of ionotropes was also started.

Hematologist and gastroenterologist reference were sought in view of:

- deranged LFT,
- raised serum Bilirubin levels (Direct 8.8 and indirect bilirubin 7),
- persistent anaemia with Hb below 10 g/dl,
- Low platelets of 28,000/mm^3 and advice was followed.

Following investigations were carried out:

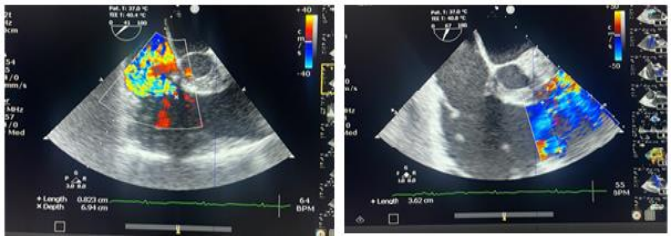
• PT, APTT	Deranged coagulation
• Fibrinogen levels	Biliary obstruction, chronic liver diseases
• LDH Reticulocyte counts	Elevated in hemolytic anemias
• HIT Antibody	Positive for heparin induced thrombocytopenia
• Peripheral smear for Schistocytes	Rule out malaria
• antimitochondrial and antinuclear antibodies	Rule out autoimmune disorders
• serum ceruloplasmin levels	Rule out genetic disorders
• 24 urine copper level tests	Wilsons disease, obstructive liver disease
• CT abdomen	Rule out obstructive pathology

Blood transfusions to maintain Hb above 7, maintaining adequate urine output and adequate hydration were advised. On POD 5 arterial line and remaining invasive lines were removed and patient was made to walk with support.

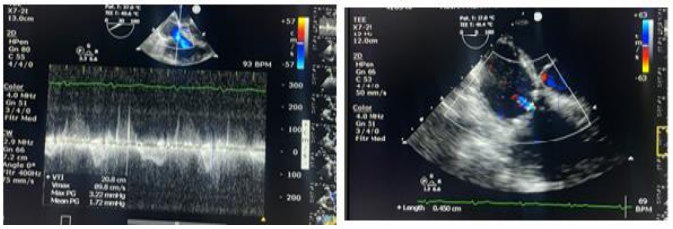
Patient was found to be positive for HIT antibody. Inj Clexane was discontinued and replaced with LMWH. Haemoglobin levels, LFT and platelets began to normalise POD 6 onwards. He was shifted to wards on POD7 for further observation and management.

Postoperative transthoracic echocardiography demonstrated a max pressure gradient of 16 mm Hg across the prosthetic valve, trivial trace tricuspid valve regurgitation, and a normal left ventricular ejective fraction of 55%. The patient recovered well and was discharged on postoperative day 25 without other complications.

The patient remained in good condition at a 3-month outpatient follow-up visit. Below images are Intraop TEE imaging showing severe PR and Tricuspid regurgitation.



Below are the TEE findings post-surgery showing reduction in the regurgitant fraction at the tricuspid area.



Discussion

It has now been understood that the immune response trigger to PF4/heparin occurs far more frequently than clinical manifestations of thrombosis or thrombocytopenia.[7]

The incidence of antibody generation in general medical and surgical patients treated with Unfractionated Heparin is 8% to 17%, for LMWH and fondaparinux is 2%to 8%,[7,8] and reaches upto 50% in patients undergoing cardiac surgical procedures.[4]

Once an immune reaction occurs, a subgroup of seropositive patients develop thrombocytopenia and may progress to life-threatening complications of thrombosis.

The chief cellular target point for HIT antibodies is platelets, which carry FcgRIIa receptors. Platelet activation in HIT takes place along with intense thrombin generation. The mechanisms underlying thrombin generation in HIT are not fully understood, but recent studies show that a cellular activation of monocyte FcgRIIA facilitates tissue factor expression, which in turn causes platelet activation via thrombin.[9]

The clinical diagnosis of HIT depends on:

- Thrombocytopenia in temporal relation with heparin therapy while removing other causes of thrombocytopenia.
- Thrombosis and
- The timing factor of complication relative to the heparin therapy.

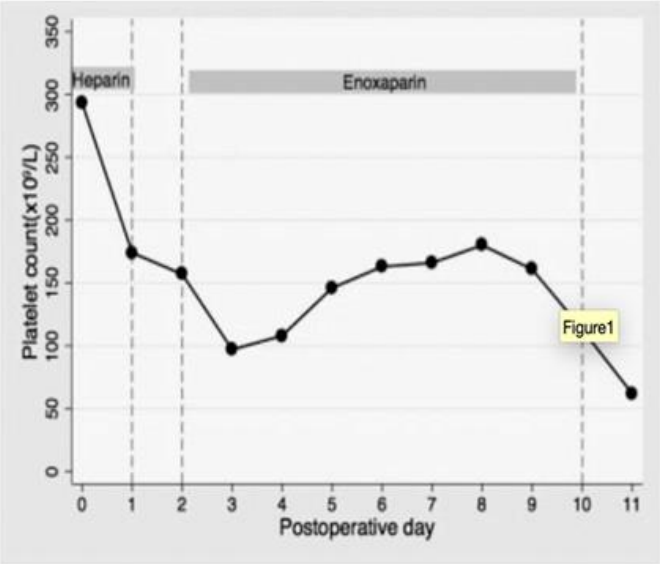
The main cardinal manifestation of HIT is the presence of thrombocytopenia, which occurs in 95% patients in temporal association with heparin therapy.[10]

- Absolute thrombocytopenia in HIT is more often moderate (50-70 x10^9/L) and typically unassociated with bleeding complications.
- Severe thrombocytopenia (20 x 10^9/L) can occur as a more grave manifestation of fulminant thrombotic disease and consumptive coagulopathy.[10]

Thrombosis is the most life threatening complication of HIT and contributes to disease morbidity and mortality.[11]

- Venous thromboses are common, mostly at sites of vascular injury from catheters.
- Uncommon presentations, such as bilateral adrenal hemorrhage, venous limb gangrene, and skin necrosis should point to diagnostic consideration of HIT.

The most important diagnostic criteria of HIT is the time sequence of complications relative to heparin therapy. A Biphasic platelet count is typical in this scenario.



Above image shows an example of biphasic platelet count characteristic of HIT after cardiopulmonary bypass surgery. A 77-year-old woman was operated for elective aortic valve replacement under cardiopulmonary bypass (CPB) as on postoperative day 0. She was given unfractionated heparin during surgery and later prophylactic dose of enoxaparin beginning on postoperative day 2. Her preoperative lab platelet count was 294 × 10^9/L. As anticipated, her platelet count fell post CPB to a nadir of 97 × 10^9/L on postoperative day 3 and later on started to recover. Beginning on postoperative day 9 (9 days post the initial heparin exposure), she had a second platelet count fall. Two days later, patient became hypoxic and pulmonary embolism was diagnosed. An anti-PF4/heparin enzyme-linked immunoassay was done and shown to be positive at 2.80 optical density units and a serotonin-release assay was positive. This case showcases the characteristic biphasic platelet count pattern which is typical of HIT post-surgery with CPB.[1]

In cases unexposed to prior heparinisation, PF4/heparin antibodies can be picked up by laboratory tests at an average time of 4 days from the beginning of therapy with heparin. Clinical manifestations of thrombocytopenia and/or thrombosis start 5 to 14 days after start of heparin therapy, and on average ~2 days (range 1-5 days) after antibody detection.[12]

Platelets rise up back to the normal range within 1 week of discontinuation in ~65% of patients. Even after platelet count recovery, patients still remain at risk for thrombosis for around 4 to 6 weeks post diagnosis due to presence of circulating anti-PF4/heparin antibodies

Laboratory investigations

A diagnosis of HIT cannot be established without laboratory detection of anti- PF4/heparin antibodies.[13] Laboratory assays detect the presence of HIT antibodies using

- Platelet activation assays ("functional") or
- By immunoassays.

Platelet activation assays detect antibodies that can bind with and cross-link to platelet FcgRIIA, such as

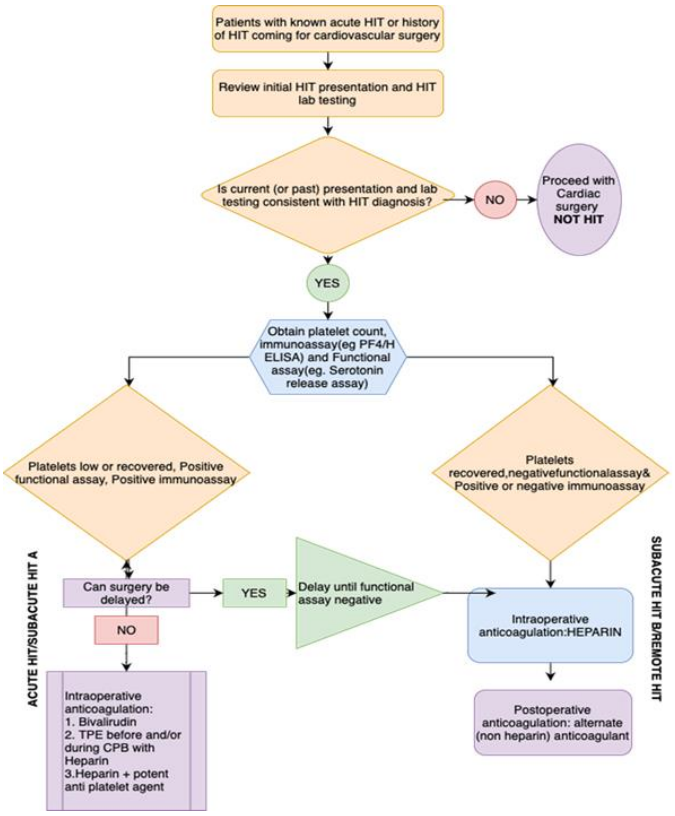
- The 14C-SRA
- Platelet aggregation
- Flow-based platelet activation assays[14]

On the other hand, Immunoassays measure the presence of anti- PF4/heparin antibodies using a number of antibody capture platforms (enzyme-linked immunosorbent assay, particle gel, immunoturbidimetric, etc).[13]

Advantages of immunoassays are technical ease and high sensitivity (99%). However, immunoassays lack with specificity (30% to 70%) for the diagnosis of HIT because of the phenomenon of asymptomatic seroconversions.[15]

Management

Management of HIT begins as soon as there is a disease suspicion, and begins with discontinuation of all sources of heparin and administration of one of the many parenteral alternative agents mentioned subsequently. Selection of a parenteral agent largely depends on the drug availability and patient comorbidities (renal or hepatic disease).[16]



Intravenous direct thrombin inhibitors	Useful in critically ill patients who often need multiple procedures and may be exposed to a higher bleeding risk.
Danaparoid	A Parenteral anticoagulant, used as the first alternative agent for the treatment of HIT.

Argatroban	Synthetic reversible inhibitor of thrombin.
Bivalirudin	Synthetic thrombin inhibitor which is cleared by plasma proteases and partially cleared by renal metabolism.
Fondaparinux	A synthetic pentasaccharide LMWH and is another anticoagulant used off label.
Direct oral anticoagulants(DOACs)	Only a few case reports,

Conclusion

HIT is a real and ever present risk in cardiac surgery patients, maybe in causal relationship to the preference for UFH during surgery. HIT can affect around 1 to 2% of patients who are exposed to CPB followed by postoperative UFH thromboprophylaxis.[1]

Precise and careful clinical judjement and assessment of the main cardinal features of HIT post cardiac surgery can be a crucial determinant in targetting the subset of patients that are appropriate for HIT laboratory testing.

In patients with a past history of HIT who will undergo cardiac surgery, laboratory investigations may be used to demarcate the disease phase and guide management options about intraoperative anticoagulation. UFH is the standard drug of choice in those with remote HIT and subacute HIT B. In patients with acute HIT or subacute HIT A, an alternative non heparin based anticoagulant (e.g., bivalirudin) or pre procedure plasma exchange should be used if surgery cannot be delayed.[1]

Newer anticoagulant therapies are promising not only for the treatment of HIT but also will be beneficial in reducing its incidence.[13]

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