IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2021 Vol.:21, Issue:3
© All rights are reserved by Polam. Rajasekhar Reddy et al.

A Review on Heparin-Induced Thrombocytopenia (HIT)

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Polam. Rajasekhar Reddy*[1], Goli Prassana Lakshmi[1]

[1]Department of pharmacy practice, A.M. Reddy memorial college of pharmacy, Narasaraopet- 522601, Guntur district, Andhra Pradesh, India.

Submitted: 25 May 2021
Accepted: 02 June 2021
Published: 30 June 2021

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Heparin-induced thrombocytopenia, platelet count, immune-mediated, heparin therapy, Danaparoid

ABSTRACT

Heparin-induced thrombocytopenia (HIT), is the most important and most frequent drug-induced and immune-mediated type of thrombocytopenia which typically occurs in the second week of heparin therapy associated with thrombotic risk. HIT is characterized by a decline in platelet count which is due to the production of antibodies against the heparin that combines with platelet factor 4 (Pf4) and forms as heparin- Pf4 complex. The incidence of HIT ranges from 1 to 5% of patients receiving heparin and 20% of secondary thrombotic complications seen in some patients. About one-third of patients suffering from venous and arterial thrombosis in HIT patients. Clinical features include platelet count fall >50% from the highest value after day 4 of heparin therapy. Thrombosis is the most serious complication of HIT and combines with disease morbidity and mortality. Checking platelet count regularly at least twice a week, 4Ts clinical scoring system, platelet activation assays, Immunoassays, are the most frequently used diagnostic tests to detect HIT. Low molecular weight heparinoid, Danaparoid, Lepirudin, Argatroban, Fondaparinux are strongly recommended anticoagulation therapy to treat HIT. In this article, we provide information regarding the history, epidemiology, pathophysiology, clinical presentation, Diagnosis, and Treatment of Heparin-induced thrombocytopenia.

INTRODUCTION:

Heparin:

Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharide called glycosaminoglycans is a sterile, non-pyrogenic derived from the porcine intestinal mucosa. Heparin has anticoagulant properties used to help prevent clot formation i.e venous thrombosis, pulmonary embolism, coagulopathies, and coronary artery clots. Heparin is used in the treatment of cardiovascular surgery, venous thromboembolism, atrial fibrillation, acute coronary syndromes, peripheral occlusive disease, dialysis, and extracorporeal circulation. Heparin is available in both generic and under brand names. Heparin is available as heparin sodium injection (USP), contains 1,0000, 1, 2500, 2, 0000, and 2,5000 USP heparin units to which 40 or 80 mg of sodium chloride need to be added to maintain Isotonicity. The common side effects of heparin include pain at the injection site, rashes, redness, warmth, irritation or skin changes at the site of injection, easy bleeding, itching, bluish-colored skin. Serious effects of heparin are thrombocytopenia, heparin-induced thrombocytopenia, and thrombosis (HITT), Heparin-induced thrombocytopenia (HIT).

Heparin-induced thrombocytopenia:

Heparin-induced thrombocytopenia is an Immunologic adverse effect of heparin therapy characterized by low blood platelet count which is caused by the body by forming antibodies to heparin where it is bound to platelet factor 4 (Pf4) a protein present in the blood. These antibodies bind to the complex of heparin and Pf4 and activate the platelets which in turn clump together and cause small clots in the bloodstream leads to a fall in platelet count. If major clots form and blocks the blood vessels lead to thrombosis, the condition is even more serious called Heparin-induced thrombocytopenia thrombosis (HITT) Although HIT is relatively rare means one of the highest numbers of patients exposed to heparin may develop HIT.

Two different types of HIT are recognized. The first one is HIT type 1 also called as Heparin-associated thrombocytopenia which is a benign form and is associated with the increased risk of thrombosis. This form of HIT affects up to 10% of patients under the treatment of heparin which is characterized by the mild effect and transient asymptomatic thrombocytopenia (less than 1,00,000 platelets/ml) that develops after the first two days of heparin therapy and disappears quickly after the heparin therapy is stopped. The mechanism of HIT type 1 is still

unknown but likely to be non-immune resulting in a platelet aggregating effect. The second type of HIT is HIT type 2 which is probably immune-mediated and associated with the risk of formation of thrombosis. This mainly occurs after 4- 10 days after the heparin therapy which may lead to life-threatening thrombotic complications. In general medical practice, HIT refers to HIT type 2. In this review, we give a brief on History, Epidemiology, Pathophysiology, Clinical manifestations, diagnosis, and treatment of Heparin-induced thrombocytopenia.

HISTORY:

Acute thrombocytopenia occurring within minutes of heparin therapy. It was first described in animals in 1942 and later observed in humans as a non- immune-mediated complication of heparin therapy which is referred to as HIT type 1 caused by agglutinating effects of heparin on platelets. The more serious immune-mediated complication of heparin therapy is HIT type 2 which was first discovered by two surgeons named Weismann and Tobin in 1958 in nearly 10 patients in their institution. Similar findings were noted by Robert et al in nearly about 11 patients and discovered that reaction was due to antigen and antibody reaction a few years later.

EPIDEMIOLOGY:

Heparin-induced thrombocytopenia is the most important of the immune-mediated, drug-induced thrombocytopenia. The true incidence of HIT type 2 depends on the Type of heparin administered, characteristics of patients considered, rate of administration, dosage, duration of therapy, the definition of thrombocytopenia, and laboratory tests concerning the prospective studies in which the diagnosis is clinically based. The incidence of HIT was about 1% for the therapeutic dosage of porcine heparin and 5% for the therapeutic dosage of bovine heparin. The incidence of secondary thrombotic complications is about 20% for the therapeutic dosage of heparin. In the recent prospective studies, about 8% of heparinized patients will develop the antibody associated with HIT and about 1- 5% of patients on heparin therapy has the chance to develop HIT. About one-third of cases are suffering from venous or arterial thrombosis. The incidence of HIT is less in patients treating with low dosages of subcutaneous heparin compared to patients on high dosages of intravenous heparin. Recent studies stated that antibodies occur against heparin more frequently in patients undergoing cardiovascular surgery than those undergoing orthopedic surgery, and in post-surgical patients than normal medical patients. Some studies have shown that the

development of heparin-dependent antibodies and thrombotic events were more in patients treated with unfractionated heparin than in patients who are treated with low molecular weight heparin.

PATHOPHYSIOLOGY:

The mechanism involved in Heparin-induced thrombocytopenia is an Immune-mediated response. Antibodies are produced against the heparin due to immunological response which combines with the principal antigen i.e complex of antigen and platelet factor 4. Platelet factor 4 is present in the alpha granular of platelets which is a small positively charged molecule of uncertain biological function. The Pf4 is released into the bloodstream after the activation of platelets and some of them binds to the platelet surface. After the initiation of heparin therapy, in some patients, the heparin and other glycosaminoglycans bind to the Pf4 molecules due to opposite charges leads to exposure of neoepitopes that act as immunogens leads to antibody production. The produced IgG antibody binds to heparin- Pf4 complex on platelet surface on Fab region where the Fc region of the antibody produced by heparin-induced thrombocytopenia (HIT) binds to the platelet Fc receptor and this interaction triggers activation and aggregation of platelets. Again, the platelets get activated and release vPf4 and continue the cycle of Heparin-induced platelet activation. Finally, the platelet activation leads to the generation of prothrombotic platelet microparticles which promotes coagulation. The activation of coagulation cascade and thrombin generation after the presence of heparin and heparin- Pf4 complex on the surface of endothelial cells.

Antibodies are produced due to Heparin-induced

immunological response

↓

Heparin + platelet factor 4 (Pf4)

↓

Formed as Heparin- Pf4complex

↓

Results in production of IgG antibody against heparin- Pf4 complex

↓

The IgG antibody combines with the heparin- Pf4 complex

↓

Forms as IgG antibody- heparin- Pf4 immunocomplex

↓

The formed Immunocomplex binds to the platelet surface

↓

This leads to platelet activation and aggregation and releases Pf4

↓

Cyclic reoccurrence of platelet activation

↓

Generation of prothrombotic platelets microparticles

↓

Promotes the activation of coagulation

CLINICAL PRESENTATION:

Heparin-induced thrombocytopenia usually causes a decline in platelet count >50% from the highest value after day 4 of heparin therapy. Chance of occurring new thrombosis typically after 5- 14 days of the prophylactic or therapeutic dose of heparin. Thromboembolic complications mainly affect the venous blood flow and other rare complications mainly affect the venous blood flow and other rare complications include skin necrosis, adrenal hemorrhage necrosis. The cardinal manifestation of HIT is the occurrence of thrombocytopenia, which occurs in 95% of patients in temporal association with heparin therapy. Thrombocytopenia may result either as an absolute drop in platelet count ($<150*10^9$/L) or a relative decline of 50% from baseline platelet count. In HIT the absolute drop in platelet count is moderate and typically not associated with bleeding complications. Thrombosis is the most severe complication of HIT and contributes to disease morbidity and

mortality. Venous thrombosis occurs at the site of injury due to catheters. Rare presentations such as bilateral adrenal hemorrhage, venous limb gangrene, and skin necrosis may be seen in fewer cases. Some patients remain asymptomatic until they progress to severe conditions.

DIAGNOSIS:

During the heparin therapy, the patient should be checked for platelet count regularly, at least weekly twice, especially in patients receiving treatment for more than 4 days, those who have resistance to heparin, or in patients having heparin related skin manifestations. In reparative individuals Pf4- heparin antibodies become detectable at a median of 4 days from the start of heparin therapy. In patients with recent heparin exposure (<100 days), the thrombocytopenia occurs within 24 hours of re-exposure to heparin because of circulating anti- Pf4 heparin antibodies.

Clinical scoring tools have been developed to aid clinicians to diagnose the disease. The 4Ts clinical scoring system which is developed by Warkentin is the simplest and most widely used risk assessment tool to detect HIT. The 4Ts clinical scoring system mainly used to categorize disease likelihood based on cumulative score i.e low risk: 0-3, intermediate risk: 4-5, high risk: 6-8 and incorporates essential features of disease described previously i.e timing of heparin therapy, complications of thrombocytopenia and thrombosis and exclusion of other causes. The HIT expert probability score is another clinical scoring system developed by Cuker and Colleagues utilizing 8 clinical features to diagnose HIT.

A diagnosis of HIT cannot be made without laboratory evidence of anti Pf4- heparin antibodies. Laboratory assays are also used to detect the presence of HIT antibodies using platelet activation assays, such as Immunoassays. Platelet activation assays such as the C-SRA, platelet aggregation are the most recent flow-based platelet activation assays used to detect antibodies capable of binding Pf4 heparin platelets. Immunoassays are also used to measure the presence of anti- Pf4 heparin antibodies using an enzyme-linked immunosorbent assay. Particle gel. Immunoturbidimetric methods.

For most patients who are suspected of HIT i.e high or intermediate 4Ts combining clinical scoring data with Immunoassays, results offers greater diagnostic utility than the approach alone.

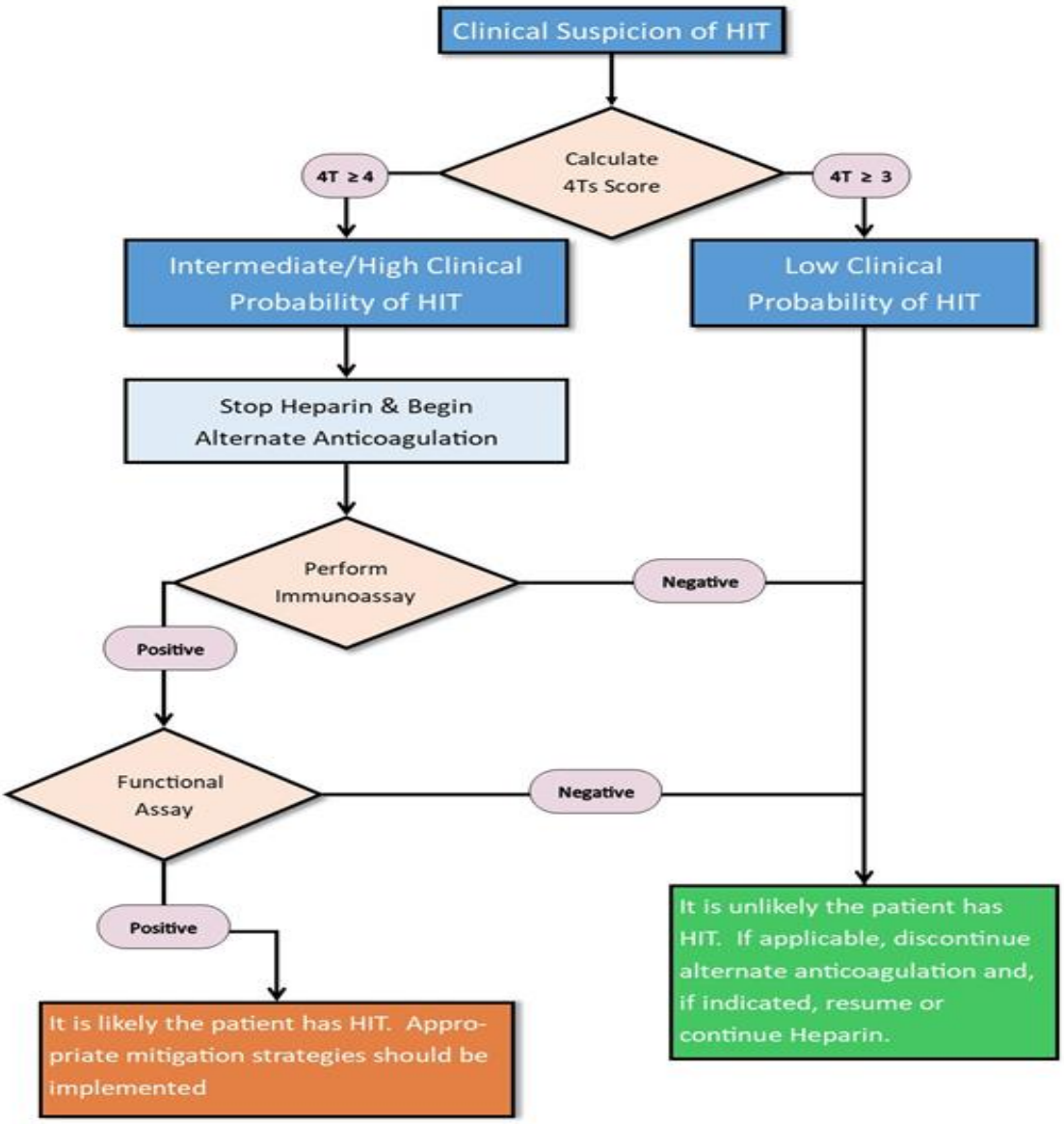

Figure No. 1: Diagnostic algorithm for Heparin-induced thrombocytopenia

TREATMENT:

The management of HIT begins at the time of disease suspicion which includes discontinuation of all sources of heparin and by administration of one of the parenteral alternative agents described subsequently. The selection of another parenteral alternative agent is largely based on the drug availability and patient co-morbidities like renal and hepatic failure. Intravenous direct thrombin inhibitors are preferable agents in critically ill patients who often require multiple procedures and may be at higher bleeding risk. Vitamin K antagonist should give us a combined therapy only after platelet count recovers to normal baseline or greater than 150* 10^9/L.

The duration of anticoagulation therapy for HIT is based on the formation of thrombosis. Currently, three direct thrombin inhibitors like danaparoid, lepirudin, and argatroban are available for an alternative anticoagulant that does not cross-react with the HIT antibodies in HIT. These drugs show immediate action by either inhibit thrombin generation or inhibiting the thrombin directly. LMWH cannot be used in patients with HIT because of the strong-cross-reactivity of the HIT antibody with the LMW heparin- complex. The duration of treatment for patients with HIT will depend on the severity of disease, type of heparin used, formation of thrombosis. To prevent the reoccurrence of thrombosis, anticoagulation therapy is required for at least 2 to 3 months in HIT patients. Oral anticoagulation with warfarin is recommended after the platelet count reaches the baseline.

Danaparoid is the first alternative agent for the replacement of heparin in patients with HIT. This anticoagulation is composed of a mixture of three glycosaminoglycans i.e heparin sulfate, dermatan sulfate, and chondroitin sulfate via antithrombin inhibits anti- Fxa activity. Lepirudin or recombinant hirudin is another anticoagulant protein originally produced by the medicinal leech that inhibits thrombin activity directly. Argatroban, an arginine-based synthetic anticoagulant a direct inhibitor of thrombin that reversibly binds the catalytic site of thrombin. Bivalirudin a synthetic thrombin inhibitor that prolongs the prothrombin time which is cleared by plasma proteases and partially by renal excretion. Fondaparinux, a synthetic pentasaccharide LMWH is another anticoagulant that is being increasingly used for the management of HIT.

SUMMARY:

Heparin-induced thrombocytopenia will continue to be a significant problem for years to come because heparin is likely to continue to be used widely because of its ease, short half-life, low cost, and ease of availability among other attributes. HIT is not only a common but also a serious complication of heparin with a high rate of morbidity and mortality. Early recognition of clinical and laboratory findings helps to stop the heparin use immediately and administration of other alternative agents. Danaparoid, Lepirudin, Argatroban, Fondaparinux, low molecular weight heparinoid have shown to be effective in Heparin-induced thrombocytopenia.

REFERENCES:

1. John G. Kelton, Theodor E Warkentin. Heparin-induced thrombocytopenia: a historical perspective. Blood; October 2008; 112(7):2607- 2616.
2. Gowthami M. Arepally. Heparin-induced thrombocytopenia. Blood, 25 May 2017;129(21):2864- 2872.
3. Heeger P.S, Backstrom J.T. Heparin flushes and thrombocytopenia. Ann. Intern. Med. 105: 143.
4. Fidlar E, Jaques LB. The effect of unfractionated heparin on the platelet count. J Lab Cin Med. 1948; 33(11): 1410- 1423.
5. Chong BH, Ismail F. The mechanism of heparin induced platelet aggregation. E U J Haematol. 1989;43(3): 245- 251'
6. Chong BH, Berndt MC. Heparin induced thrombocytopenia. Blut.1989; 58(2):53- 57.
7. Fabrizio Fabris, Walter Jeske. heparin-induced thrombocytopenia: pathophysiology, clinical and diagnostic implications- A review. Arch pathol Lab Med. November 2000;124:1657- 1666.
8. Massimo Franchini. Heparin- induced thrombocytopenia: an update. Thrombosis Journal. 2005;3(14):1- 5.
9. Warkentin TE. An review of the heparin- induced thrombocytopenia syndrome. Semin ThromHemost. 2004;30:273- 283.
10. Jang I- K, Hursting HJ. When heparins promote thrombosis. Review of heparin- induced thrombocytopenia. Circulation, 2005, 111:2671- 2683.
11. Chong BH. Heparin- induced thrombocytopenia. J Thromb Haemost. 2003; 1: 1471- 1478.
12. A. Greinacher, K. Aithaus, K. Krauel, S. Selleng. Heparin- induced thrombocytopenia. Hamostaseoligic. 2010; 30: 17- 28.
13. Aster RH, Curtis BR, Mcfarland JG, Bougie DW. Drug induced- immune thrombocytopenia: pathogenesis, diagnosis, management. J Thromb Haemost. 2009;7:911- 918.
14. Salma M. Aldallal. Heparin in HIT: Effectiveness as an anticoagulant. IJPSR. 2017; 8(8): 3261- 3264.
15. Baglin JP: Heparin- induced thrombocytopenia/ thrombosis syndrome(HIT): diagnosis and treatment. Platelets.1997; 8: 72- 82.
16. Warkentin T, Greinacher A. Heparin- induced thrombocytopenia. Marcel Dekker INC, New York. 2004: 25- 52.
17. Lewis BE, Hursting MJ. Argatroban an therapy in heparin- induced thrombocytopenia. Heparin induced thrombocytopenia. Informa healthcare. 2007; 379- 408.
18. Bell WR. Heparin associated thrombocytopenia and thrombosis. J Lab Clin Med 1988, 111:600- 605.
19. Warkentin TE, Kelton JG. Delayed onset heparin induced thrombocytopenia and thrombosis. Ann intern Med 2001; 135:502-506.
20. Chong BH. Diagnosis, treatment and pathophysiology of Immune mediated thrombocytopenia. Crit Rev OncalHematol. 1995; 20: 271- 296.
21. Ortel TL, Chong BH. New treatment options for heparin- induced thrombocytopenia. Sem Hematol. 1998; 35(5): 26- 34.
22. Hrish J, Heddle N, Kelton JG. Treatment of heparin induced thrombocytopenia: a critical review. Arch Intern Med 2004; 91: 361- 369.
23. Arepally G M, Ortel JL. Clinical practice: Heparin- induced thrombocytopenia. N Engl J Med. 2006;355:809- 817.
24. Theodore E. Warkentin, John G. Kelton. Heparin- induced thrombocytopenia. Ann. Rev. Med. 1989. 40:31- 44.
25. Schwartz K.A, Royer G. Kelton. Complications of heparin administration in normal individuals. Am. J. Hematol. 19: 355- 363.
26. John G. Kelton, David Sheridan, James Smith. Heparin- induced thrombocytopenia: Laboratory studies. Blood. 1998; 72(3): 925- 930.
27. Hrushesky W.J. Subcutaneous heparin- induced thrombocytopenia. 1978. Arch. Intern. Med. 138: 1489- 91.