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Diagnosis and treatment of heparin-induced thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a major side effect secondary to the administration of heparin. This syndrome is serious and potentially life threatening. This response is the result of antibodies formed against the platelet factor 4 (PF4)/heparin complex. The incidence of this immune-mediated syndrome has been estimated to be 1–3% of all patients receiving heparin therapy. The occurrence of HIT in patients requiring full anticoagulation for cardiopulmonary bypass (CPB), therefore, presents a serious challenge to the cardiac surgery team. The diagnosis of HIT should be based on both clinical and laboratory evidence. While functional assays, platelet aggregation tests, and the serotonin release assay can be used to support the diagnosis, the negative predictive value of these tests is generally less than 50%. In contrast, although non-functional antibody detection assays are more sensitive, they have a low specificity. HIT can be treated in several ways, including cessation of all heparin and giving an alternative thrombin inhibitor, platelet inhibition followed by heparin infusion, and the use of low molecular weight heparins. In this presentation, the pathology and current diagnostic tests, as well as the successful management of patients with HIT undergoing CPB at New York Presbyterian Hospital, are reviewed. - *Perfusion* (2003) **18,** 47–53.

Introduction

Heparin-induced thrombocytopenia (HIT) is defined as a decrease in platelet count induced by the administration of heparin for therapeutic purposes.[1] Mild thrombocytopenia, which occurs within four days of starting heparin, is the result of a direct agglutination effect of heparin on platelets. It is not associated with thrombosis and resolves within a couple of days.[1] The immune form of HIT, which is associated with both arterial and venous thrombosis, is serious and life threatening.[2] The incidence of immune-mediated HIT in cardiac surgical patients can be as high as 1.9%, and late recognition with continued exposure to heparin can result in bleeding, thromboembolic complications, and death.[3] Early diagnosis, treatment, and proper management of patients with HIT during cardiac surgery present a formidable challenge for the surgical team. The purpose of this paper is to provide an in-depth review of the pathology, diagnosis, and treatment of HIT, as well as the anticoagulation management of patients with a history of HIT during cardiac surgery.

Pathology

The first symptoms of the immune-mediated HIT generally occur between four and 14 days after exposure to heparin, but they may be seen within hours in patients with previous exposure to heparin.[4] Recent evidence suggests that this syndrome is initiated by a heparin-platelet-antibody interaction.[3]

It has been shown that the platelet aggregating factor in HIT sera is immunoglobulin G (IgG).[5] Current evidence supports a mechanism by which heparin binds to platelet factor 4 (PF4), a protein normally found in the alpha granule of platelets, to form a strongly antigenic hapten on the platelet surface,[5,6] which induces the production of specific IgG antibodies. On re-exposure to heparin, these specific IgG antibodies react with heparin/PF4 complexes and bind to the carboxy terminal receptor (Fc receptor)[6] of circulating platelets.[7] This antibody-receptor interaction initiates signal transduction and cell activation. Platelet activation caused by HIT antibodies results in the translocation of

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anionic phospholipids from the internal to the external leaflet of the platelet membrane.[1]

Activation of platelets results in their lysis and agglutination. PF4 can also bind to heparin-like molecules on the endothelial surface to provide targets for antibody binding and local injury.[3]

Patients who produce such antibodies are at risk of developing venous or arterial thrombotic complications.[8] The risk for these new thrombotic events is enhanced by the interaction of the antigen/antibody complexes with platelets[5] and endothelial cells,[9] which result in the release of platelet microparticles, thromboxane, and massive thrombin generation.[7] The thrombosis is typically characterized by the presence of white clots rich in platelets.[10]

The clinical manifestations of HIT include local skin lesions, venous thrombosis, arterial thrombosis, and end organ failure.[11] Erythematous plaque and localized skin necrosis are two well known but relatively uncommon early manifestations of HIT that may precede the development of hematological abnormalities.[12] The incidence of venous thrombosis exceeds arterial thrombosis fourfold in HIT and most often involves the proximal deep vein of the lower extremities. Arterial occlusion of small and medium-sized vessels is a classic complication of HIT.[11]

The morbidity and mortality of HIT have been reported as high as 23–61% in early studies.[13] Early diagnosis and prompt treatment have reduced mortality to 1.1–7.4%.[14]

Diagnosis

The diagnosis of immune HIT should be considered in any patient who develops a 50% reduction of platelet count while on heparin treatment. It is recommended that the platelet count is measured twice weekly in the first week or two of heparin treatment to detect the development of HIT early, and thus prevent thrombosis.[15]

The laboratory diagnosis of HIT is made functionally and serologically.[16] Functional assays (Table 1) include the ^{14}C-serotonin release and platelet aggregation assays.[17] In the platelet aggregation test, platelet-poor plasma from the patient is mixed with normal donor platelets and heparin. Plasma with HIT causes activation and aggregation of platelets. In the ^{14}C-serotonin release test, healthy donor platelets are incubated with ^{14}C-serotonin, which is taken up by the platelet membrane. After washing, the platelets are mixed with the serum to be tested and with heparin. In the presence of HIT, the release of serotonin is increased.[3,16] Optimal sensitivity and specificity with either assay are obtained by using washed platelets rather than platelet-rich plasma.[17] Functional assays give a high rate of false negative results, since these assays require fresh donor platelets and not all platelets are reactive to HIT sera.[18] The test should be performed at high and low heparin concentrations to optimize specificity.[17]

Table 1 Summary of diagnostic procedures for patients with HIT

Functional assays	*Immunologic assays*
C-serotonin release Platelet aggregation	Negative ELISA

In contrast to the functional assays, the immunologic assays detect the binding of antibodies to immobilized heparin/PF4 complexes.[19] These assays are much more sensitive but have low specificity. Negative enzyme-linked immunosorbent assay (ELISA) results have been obtained in patients with clinically apparent HIT and a positive serotonin release test result.[20] However, ELISA appears to detect antibody development in some patients who do not develop thrombocytopenia or other manifestations of the syndrome.[22] At least 50% of patients exposed to heparin develop detectable antibodies by ELISA without the development of HIT.[21]

Recently, several flow cytometric methods have been described that may approach the level of sensitivity obtained with the ^{14}C-serotonin release assay.[23] A potential advantage of this development is the ability to distinguish antibodies capable of causing immune HIT from non-immune HIT.[24]

Treatment

If there is a strong suspicion of immune HIT, therapeutic management should be started immediately, which consists of two steps: (1) removal of the immune stimulus by discontinuing heparin therapy, including heparin line flush; (2) inhibition of thrombin, either directly or by blocking the generation of new thrombin.[25]

To inhibit the generation of thrombin, an alternative anticoagulation should be started. This anticoagulation (Table 2) could be in the form of nonsensitive low molecular weight heparin (LMWH), heparinoids, direct thrombin inhibitors, and platelet function inhibitors.[1,16,25]

LMWHs, such as enoxaparin and dalteparin, have been used in the treatment of HIT in the past.[16,26] However, it has been found that the cross-reactivity between LMWH and heparin-associated antiplatelet antibodies from patients receiving unfractionated heparin is 34% with enoxaparin[27] and 25.5% with dalteparin. LMWHs should not be used unless antibody cross-reactivity is excluded.[28]

Platelet function inhibitors, such as aspirin and dipyridamole, protect patients with heparin-asso-

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Table 2 Pharmacological alternatives for patients with HIT

Pharmacological agent	*Considerations*
LMWH Enoxaparin Dalteparin	Difficult to monitor effect on coagulation. Cross-reactivity with heparin. No antidote. Potential for increased blood loss postoperatively.
Glycoprotein IIb/IIIa inhibitor	Blocks potential platelet aggregation. Need thrombin inhibition as well, i.e., heparin.
Thrombin inhibitors Recombinant hirudin (lepirudin) Bivalirudin Argatroban	Difficult to monitor effect on coagulation. No antidote. Potential for increased postoperative blood.

ciated antiplatelet antibodies (HAAbs) from thromboembolic complications during brief exposures to heparin, but not from thrombocytopenia.[29] The glycoprotein IIb/IIIa inhibitor abciximab inhibits HAAb-induced platelet aggregation, but the glycoprotein IIb/IIIa inhibitors have not been shown to provide adequate anticoagulation in patients with HAAbs.[30] Therefore, these agents cannot provide adequate therapeutic effects as sole agents in patients with HIT.

Danaparoid is a mixture of heparin sulfate, dermatin sulfate, and chondroitan sulfates.[31] Cross-reactivity with heparin-dependent antibodies from patients with HIT can be demonstrated by *in vitro* assays in 10–40% of patients tested, but this is usually clinically insignificant.[32] Moreover, thrombocytopenia might be resolved during danaparoid treatment even when cross-reactivity is present.[1,31] Platelet counts recover during treatment in approximately 90% of patients.[33] Danaparoid is, therefore, a useful substitute for heparin, particularly in patients with a previous history of HIT who require antithrombotic prophylaxis. Treatment can be monitored by anti-Xa activity. Danaparoid has a long half-life of plasma anti-Xa activity of approximately 24 hours and is renally cleared, so it must be used cautiously in patients with renal insufficiency.[31–33] The activated partial thromboplastin time (aPTT) is not sensitive to the antithrombotic effect of danaparoid. In addition, danaparoid is not neutralized by protamine sulfate.

Thrombin inhibitors chemically unrelated to heparin are now available. Heparin-dependent antibodies have no cross-reactivity with these agents. These agents offer the patient adequate anticoagulation with no risk of cross-reaction with their HAAbs.[34,35]

Recombinant hirudin (lepirudin) is a direct thrombin inhibitor. It received FDA approval in 1998 for patients with HIT.[35] Lepirudin binds to clot-bound thrombin as well as soluble thrombin.[9] It has been reported that the incidence of the combined endpoint death, amputation, or new thromboembolism was significantly reduced in patients treated with lepirudin.[34] The aPTT should be used to monitor treatment, aiming for an aPTT ratio of 2.5.[1] The drug is renally cleared. Lepirudin has a short circulating half-life of 1.3 hours in patients with normal renal function.[9] Dose adjustments need to be made for patients with renal insufficiency. One problem that occurs with lepirudin is that antihirudin antibodies develop in about 40% of patients treated with lepirudin. In some patients, this can result in an increased anticoagulant effect due to delayed renal elimination of active lepirudin/antihirudin complexes.[36]

Bivalirudin is a synthetic hirudin-based 20 amino acid peptide that binds to both the anion-binding exosite and enzyme catalytic site of thrombin. In contrast to lepirudin, bivalirudin is a reversible thrombin inhibitor, which may account for the lower rate of hemorrhage observed with bivalirudin compared with hirudin.[15]

Argatroban is a synthetic L-arginine derivative that exerts its anticoagulant effects by competitively and reversibly inhibiting thrombin. It is a small compound, which binds directly to the catalytic site of thrombin, independently of antithrombin III (AT III).[37] It showed comparable *in vitro* efficacy against both fibrin-bound and soluble thrombin.[38] This property would, theoretically, make argatroban more efficient than unfractionated heparin in managing patients who present in late stages of thrombotic events. Under its investigational name MD-805, it has been used in Japan since the early 1980s and received approval for the treatment of patients with HIT.[39] It was evaluated in a multicenter trial comparing treatment in 160 patients with HIT and 144 with heparin-induced thrombocytopenia and thrombosis with a group of historical controls treated in different ways. Argatroban reduced the number of thromboembolic complications and related deaths, with no increased risk of major bleeding.[1,40] The aPTT is used for monitoring its therapeutic effects. The PT is also prolonged in patients on argatroban, which can complicate the initiation of warfarin in these patients, since warfarin alone prolongs PT. Argatroban is hepatically metabolized and can be used with renal insufficiency. Dose adjustments may be needed in patients with hepatic failure.[16] In patients with normal liver function, the half-life of argatroban has been estimated to range between 39 and 51 minutes.[41]

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Management of patients with HIT requiring a heart operation

Heparin is the principle drug used for anticoagulation during cardiac surgery because it is effective, immediately reversible, inexpensive, and generally well tolerated.[42] Managing patients who require cardiac surgery and have a previous history of HIT is a therapeutic challenge (Table 3).

LMWH has been documented as an alternative of unfractioned heparin on patients with HIT for cardiopulmonary bypass (CPB).[43] In 1983, the first successful use of nadroparin for CPB in a 66-year-old man with HIT undergoing an emergency pulmonary thrombectomy was reported.[44] In another case report, enoxaparin was used for anticoagulation during CPB on a patient with HIT undergoing heart transplantation.[45] In this case report, the patient manifested important blood loss and significant hypotension. A surgical revision was performed for significant blood loss. This result suggested ineffectiveness of activated clotting times (ACT) as a sole measurement in providing a precise monitoring of anticoagulation.

Argatroban has been reported to substitute unfractionated heparin during cardiac procedures on patients with HIT. In one case report by Arnoletti and colleagues, on a 51-year-old man with an ejection fraction (EF) of 15% who presented with an acute myocardial infarction with a history of HIT,[46] argatroban at a rate of 3 μg/kg pre minute replaced unfractioned heparin for anticoagulation. aPTT was maintained between 1.5 and three times baseline. Bypass surgery was scheduled for this patient who was diagnosed with 2-vessel disease. The argatroban infusion was discontinued 30 minutes prior to surgery in anticipation that the anticoagulant effects would last throughout the surgery. Anticoagulant therapy was not administered intraoperatively. Surgery was performed using an 'octopus' tissue-stabilizing device. By the sixth day postsurgery, the patient was discharged home safely without any complications.

Danaparoid has also been used as a heparin alternative during cardiac surgery.[43] Most of these patients survived their operations, although a large portion of them had excessive postoperative bleeding. In a report by Magnani and colleagues, 53 patients received danaparoid for CPB; clots were observed in either the CPB circuit or the operative field in 38% of the patients. Fifty-five percent of these patients required more than eight units of postoperative blood products.[47]

Theodore and coworkers reported the successful use of danaparoid anticoagulation for off-pump coronary artery bypass grafting.[48] In this case, CPB standby was available if required, with sufficient danaparoid.

In 1989, Zulys *et al.* reported the use of ancrod for CPB in a pilot study of 20 patients undergoing elective coronary artery bypass graft operations.[49] Ancrod is a defibrinogenating agent derived from the Malayan pit viper. It produces a rapid decrease in plasma fibrinogen concentration following its thrombin-like action to cleave fibrinopeptide A from fibrinogen.[50] All patients survived their operations and none had neurologic complications or delayed wound healing. However, these patients required significantly more intra- and postoperative blood products. Subsequent successful uses of ancrod for CPB have been documented. For instance, Robitaille *et al.* showed that a successful CPB case was performed on a HIT patient with the use of ancrod as anticoagulant.[50]

Hirudin has been used as an alternative anticoagulant for CPB in patients with HIT by several centers.[46,51,52] No clots were observed in any patient during CPB and no patient had a thromboembolic complication. In a subsequent study performed by Koster and coworkers, 21 patients undergoing different complex cardiovascular procedures using recombinant hirudin as the anticoagulant for CPB were investigated.[52] They concluded that, if recombinant hirudin is used as the anticoagulant for CPB in patients with HIT and impaired renal function, the risk of postoperative bleeding is increased.

Although the above cases have shown that several heparin alternatives can be used as anticoagulants during cardiac surgery, all of these agents have their significant limitations. The cross-reactivity of HIT antibodies with an LMWH may be found in approximately 90% of patients with HIT,[32] making LMWHs a potentially dangerous alternative to unfractioned heparin in these patients. In addition, no current coagulation assay or set of assays has been shown to

Table 3 Recommendations for HIT patients requiring cardiac surgery

Intervention	*Considerations*
Heparin alternatives	All these drugs have potential for significant blood loss due to lack of antidote.
Platelet inhibitors and full heparinization	Data support this technique, however, there is little experience. Minimal blood loss in these case reports.
Full heparinization	This is a good option if there are no antibodies present at time of surgery.
Off-pump procedure	Requires some heparin alternative. Can use aPTT, which is a readily performed coagulation test. Off-pump only good for coronary artery bypass surgery, not valvular surgery.

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indicate whether satisfactory CPB anticoagulation has been achieved with any LMWH. Danaparoid does not affect the ACT or aPTT, requiring antifactor Xa determination. With lepirudin, the aPTT may be used to monitor patients who receive small dose.[53] However, the levels of r-hirudin recommended for anticoagulation during CPB exceed those that can be effectively monitored with either the aPTT or ACT.[54] The ecarin clotting time assay, a clot-based method that uses a prothrombin-activating snake venom derivative and can be measured with a TAS instrument (Cardiovascular Diagnostics, Raleigh, NC), produced adequate dose–response curves with r-hirudin in patients during CPB,[54] but is not widely available. In addition, ecarin clotting time can be substantially prolonged by hemodilution or CPB-related reductions in procoagulant proteins. Moreover, the lack of antidotes for these agents means that severe postoperative bleeding can occur.[55]

Compounds that allow easy monitoring and reversibility are greatly needed. Another approach for CPB on patients with a history with HIT is to use a brief intraoperative exposure heparin. The theory underlying this option is that during secondary immune responses, the concentration of antibody in the serum begins to increase no earlier than three days after the challenge.[56] Moreover, in the absence of heparin, HIT antibodies are not thrombogenic. Thus, it has been postulated that in patients with a history of HIT who are challenged with heparin, the HIT antibody concentrations should start to increase only after the heparin is completely cleared from the circulation.

This theory was tested by Potzsch and Klovekorn.[57] In their investigation, on 10 patients with a history of acute HIT who required CPB, heparin was used. During the acute episode, all patients had detectable HIT antibodies on the heparin-induced platelet-aggregation assay. At the time of surgery, all patients were negative for these antibodies. CPB was performed with the use of heparin without any problems. None of the 10 patients had prolonged thrombocytopenia. They concluded that antibody-negative patients with a history of HIT who undergo CPB should be treated according to established heparin protocols. However, the use of heparin should be restricted to the operative period. Postoperative anticoagulation should be achieved with alternative anticoagulants.[57]

Selleng reported a successful conduction of emergency coronary artery bypass surgery with the use of heparin as anticoagulant on a patient with a history of HIT.[58] This case demonstrates that short-term re-exposure to heparin is possible in patients with a history of HIT. Short-term re-exposure to heparin in patients who do not have circulating HIT antibodies should be safe as long as heparin is strictly avoided before and after heparin administration.

The combination of hirudin, platelet inhibitor, and heparin has been used for anticoagulation during CPB in patients with HIT and renal impairment.[59] In this investigation, the 10 patients enrolled were anticoagulated with r-hirudin to an aPTT of 40–60 seconds preoperatively. Anticoagulation during CPB was achieved with a bolus of 400 μg/kg unfractioned heparins after a bolus of short-acting plate glycoprotein IIb–IIIa antagonist tirofiban 10 μg/kg followed by an infusion of tirofiban at a rate of 0.15 μg/kg per minute until one hour before conclusion of CPB. Coagulation was monitored by an abciximab-modified TEG and the adenosine diphosphate stimulated platelet aggregometry. Postoperative antithrombotic therapy was started immediately with r-hirudin anticoagulation to an activated partial thromboplastin time of 40–60 seconds. No patients needed re-exploration and in no patient was there clinical evidence of thrombosis or embolism in the postoperative period.

In summary, patients with acute HIT who require heart operations have options. One option is to wait for the HIT antibodies to become undetectable and then to operate using a brief intraoperative exposure to heparin. This approach is not suitable for an unstable patient, however, as it might take several months for antibody levels to decline sufficiently. A second option is to perform heart operations using heparin substitutes. The relative appropriate agents should be selected according to patient's specific medical condition, such as renal or liver function, and the availability of the proper monitoring techniques.

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