GTH 2021 State of the Art—Cardiac Surgery: The Perioperative Management of Heparin-Induced Thrombocytopenia in Cardiac Surgery

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Abstract

Heparin-induced thrombocytopenia (HIT) is a severe, immune-mediated, adverse drug reaction that paradoxically induces a prothrombotic state. Particularly in the setting of cardiac surgery, where full anticoagulation is required during cardiopulmonary bypass, the management of HIT can be highly challenging, and requires a multidisciplinary approach. In this short review, the different perioperative strategies to run cardiopulmonary bypass will be summarized.

Keywords

- Heparin-induced thrombocytopenia
- cardiac surgery
- state of the art

Introduction

Heparin-induced thrombocytopenia (HIT) is a severe, immune-mediated, adverse drug reaction that paradoxically induces a prothrombotic state.[1,2] Particularly in the setting of cardiac surgery, where full anticoagulation is required during cardiopulmonary bypass (CPB), the management of HIT can be highly challenging, and requires a multidisciplinary approach.

In HIT, IgG antibodies (HITabs) bind to heparin-PF4 complexes and the FcγRIIa receptor on platelets, inducing strong platelet activation and aggregation. The resulting expression and release of procoagulant factors induces a state of hypercoagulability that leads to thrombosis.[3] Although a high proportion of patients treated with heparin develop HITabs, platelet activation and thrombotic complications occur only in a small fraction of them.[4] This implies that the mere presence of circulating HIT antibodies is not a diagnostic for the HIT syndrome. The laboratory diagnosis of HIT is based on the detection of HITabs using immunoassays and on the demonstration that these antibodies can induce platelet aggregation in functional tests.[5] In the latter, plasma from the patient containing HITabs is mixed with platelets from a donor and with heparin. Aggregation of the platelets or secretion of serotonin by the platelets confirms the pathogenicity of the antibodies and is diagnostic for HIT. The administration of heparin to a patient with circulating pathogenic HITabs puts the patient at immediate risk of severe thrombotic complications.

The time course of HIT can be divided into four distinct phases.[6] *Acute HIT* is characterized by thrombocytopenia and/or thrombosis, the presence of HITabs, and confirmation of their platelet activating capacity by a functional diagnostic test. In *subacute HIT A*, platelet count has normalized after discontinuation of heparin but platelet activating HITabs are still present and induce platelet aggregation in functional tests. In *subacute HIT B*, HITabs are measurable in the patient's plasma, but they do not induce platelet activation in functional tests. And finally, in *remote HIT*, HITabs are no longer detectable after an acute HIT episode. This can usually be expected 3 months or later after an acute HIT. This categorization is highly relevant for the management of patients who need to undergo cardiac surgery. Elective surgery should be postponed until HITabs are no longer detected to minimize the risk on intraoperative thrombosis and to reduce the need for the transfusion of platelets, contraindicated in acute HIT. If surgery cannot be postponed for at least 3 months, or if antibodies are still detected in spite of a 3-month delay since the diagnosis of HIT, alternative anticoagulation strategies must

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be adopted in the pre-, intra-, and postoperative period, respectively.[7]

According to the guidelines of the American Society of Hematology, alternative anticoagulation strategies must be used for patients in the *acute* and *subacute A* phases. Heparin may be safely used during CPB in patients who are in the phases of subacute HIT B and remote HIT.[7] They do, however, state that the level of evidence supporting this recommendation is very weak. The American College of Chest Physicians recommends using standard heparin-based anticoagulation during CPB only for remote HIT patients. For all patients in higher categories, the ACCP recommends alternative anticoagulation strategies.[6] Regardless of the HITabs status of patients with a history of HIT, alternative anticoagulants, such as argatroban or danaparoid, must be used if pre- or postoperative anticoagulation is indicated.[8]

Alternative Anticoagulation Strategies during Cardiac Surgery

For anticoagulation during CPB, two possible alternatives to standard high-dose heparin are proposed,[7] the choice of which should be based on a thorough evaluation of the patient and a multidisciplinary consensus between the surgeon, anesthesiologist, hematologist, and perfusionist.

In the first strategy, an alternative anticoagulant to heparin is used during CPB. Today the direct thrombin inhibitor bivalirudin is the most used and probably the best studied agent. Bivalirudin is a direct thrombin inhibitor with a relative short half-life of 25 minutes. It is for 80% cleared by plasmatic enzymatic proteolysis and for 20% through renal excretion.[9] Interestingly, the molecule binds with high affinity to thrombin's fibrin-binding site and to its catalytic site. Bivalirudin is cleaved by thrombin at the catalytic site, rendering active thrombin to the circulation. The enzymatic degradation of bivalirudin is responsible for the gradual clearance of the drug in stagnant blood, which can lead to clot formation in parts of the CPB machine or nonperfused cardiac cavities and vessels during bypass. The authors of one study on 50 patients, with acute HIT or with subacute HIT, concluded that bivalirudin can safely be used during CPB instead of heparin.[10] However, the results show that some patients required transfusion of very large quantities of blood products. Several case reports confirm the risk of bleeding when bivalirudin is used during CPB,[11–13] particularly in situations where the team lacks experience with this drug. The peculiar pharmacokinetic properties of bivalirudin require adaptations to the CPB circuit and surgical techniques. According to available literature, activated clotting time (ACT) monitoring should be used with a target ACT of 2.5× baseline[9,11,14] or the conventional 400 seconds target ACT.[14,15] To reduce the risk on severe hemorrhage and thrombosis (in case of venous stasis), bivalirudin should only be used if the staff is familiar with the drug and has experience in its use.[16]

Other nonheparin intravenous anticoagulants are argatroban and danaparoid. Although these drugs are well suited for pre- and postoperative anticoagulation, their pharmacokinetic profiles, the lack of antidotes, and ineffective monitoring make them less suitable for intraoperative use. Argatroban is an L-arginine analog that reversibly binds to thrombin and inhibits thrombin-mediated platelet aggregation, fibrinogen cleavage, and the activation of factors V, VIII, XIII, and protein C. It is eliminated through hepatic hydroxylation and has a terminal half-life of 40 to 50 minutes.[17] Hillebrand et al[18] reported on a series of seven patients benefiting from left ventricular assist device implantation under CPB using argatroban anticoagulation. The initial target aPTT was 50 to 60 seconds and, due to massive intracardiac thrombus formation in one patient, the target was increased to 70 to 80 seconds in subsequent patients. Four patients suffered bleeding complications leading to postoperative reexploration. Other authors also reported on severe bleeding complications, accentuating the inappropriateness of argatroban for intraoperative anticoagulation.[19,20] Danaparoid is a mixture of heparan, dermatan, and chondroitin sulfates from animal origin and inhibits Factor Xa indirectly via antithrombin III[21] and can destroy the antigenic complex of heparin and PF4.[22] It is primarily excreted by the kidneys and is characterized by a long elimination half-life of 24.5 hours, making its usefulness for intraoperative use highly questionable. The few cases reported were complicated by severe hemorrhage and the need for reintervention.[23]

The second strategy aims to prevent HIT-mediated platelet aggregation by combining a potent antiplatelet agent with standard heparin-based anticoagulation.[7]

This strategy offers the advantages and safety of heparin anticoagulation management, namely, the ease of monitoring and titrating anticoagulation level using ACT and its complete reversibility with protamine sulfate, while the antiaggregant agent protects the platelets against activation by circulating HITabs–PF4/heparin complexes. Several studies using the prostacyclin analog iloprost or the GP IIb/IIIa inhibitor tirofiban in this context suggest the ease and safety of this strategy.[24–27]

Tirofiban depends largely on renal clearance for its elimination and evidence for the safe use of tirofiban in this setting in patients with renal failure is limited to a few case series.[24,25,28]

Due to its long half-life (1.4–1.8 hours) relative to the duration of bypass during surgery, the tirofiban perfusion must be interrupted 1 hour prior to the end of CPB to allow at least partial recovery of platelet function and reduce the risk of major hemorrhage.

Iloprost has a very short half-life and is primarily eliminated by hepatic oxidation. Its antiaggregant effect is highly concentration dependent and shows important interindividual variation. Preoperative dose finding studies, intraoperative monitoring of platelet reactivity by a heparin-induced platelet aggregation test (PAT) using light transmission aggregometry, and continuous intraoperative titration of the infusion are necessary to assure sufficient inhibition.[26,29] The potent vasodilator effect of iloprost can lead to profound hypotension and increased need of vasopressor drugs.[30]

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The newer, ultra–short-acting P2Y12 receptor antagonist cangrelor has been proposed as an alternative to tirofiban, but, to date, its use has been reported only in four case reports on HIT patients undergoing cardiac surgery.[31–34] Although no major bleeding requiring reoperation[31] and even possibly decreased postoperative bleeding[34] were reported, no conclusion on its efficacy can be drawn from these reports.[33] One patient with persistent HITabs 8 years following HIT was treated with this strategy during coronary artery bypass surgery and exhibited a huge rise in HITabs with a positive functional assay in the postoperative period, putting her at risk of developing recurrent HIT.[33] Moreover, a recent in vitro study questions the consistency of cangrelor-mediated inhibition of platelet aggregation induced by HITabs-PF4/heparin complexes.[35] The authors found a large variability in its efficacy to suppress heparin-induced platelet aggregation in plasma containing HITabs and propose the use of cangrelor only if its ability to suppress platelet aggregation has been demonstrated in a functional test using the patient's plasma before surgery.

Antibody Activity Mitigation Strategies

Temporary reduction of the titer of antibodies could reduce the risk of perioperative HIT reactions if heparin is used for intraoperative anticoagulation, but data on these techniques are very scarce.

Welsby et al[36] reported on a series of 11 patients with HIT undergoing major cardiac surgery managed with a standard heparin-based protocol combined with pre- or intraoperative plasmapheresis. In this series of highly complex, urgent cardiac surgery, no HIT-related complications occurred. Warkentin et al[37] pointed out that IgG HITabs are not cleared as effectively as IgM antibodies during plasmapheresis and demonstrates that HIT antibody titers, measured by immune assays, decline after each episode of plasmapheresis but increase in the next hours. Nevertheless, the serotonin release assay rapidly becomes and remains negative after the first sessions of plasmapheresis, suggesting that heparin administration could be considered for the short period of CPB. Although they report no HIT-related complications, it is known that brief heparin exposure in the presence of circulating HITabs can lead to a postoperative surge in circulating antibodies putting the patient at risk of delayed HIT.[33] Therefore, postoperative heparin exposure has to be strictly avoided and alternative anticoagulation is needed in these patients after surgery at least for thrombosis prophylaxis.

Intravenous administration of polyvalent immunoglobulins (IVIG) is a strategy that gains popularity for treatment in HIT cases showing persistent thrombocytopenia and/or thrombotic complications after heparin treatment has been stopped and sufficient alternative anticoagulation is performed. It is thought that the immunoglobulins attach to the platelet FcγRIIa receptor with high affinity, thus preventing aggregation induced by HITabs-PF4/heparin complexes through competitive inhibition. Although, due to concerns about the inherent prothrombotic properties of IVIG, warnings against its use in HIT have been formulated,[38] a growing number of reports suggest its safe use specifically in the setting of autoimmune or heparin-independent HIT.[39] Experience in the perioperative use of IVIG in cardiac surgery is limited to a single case report.[40] This patient had subacute HIT-A with circulating functional antibodies when he underwent cardiac surgery with heparin anticoagulation for CPB. IVIG combined with cangrelor successfully prevented thrombotic complications.

In conclusion, cardiac surgery in patients suffering from HIT represents a challenging, high-risk situation. Optimal management requires a patient-tailored multidisciplinary approach and a thorough knowledge of the pathogenic features and the various management strategies. If possible, cardiac surgery should be delayed until HITabs do no longer induce aggregation in functional assays. If surgery cannot be postponed in acute HIT, bivalirudin or heparin combined with platelet inhibition and/or antibody mitigation strategies must be used. In remote and subacute HIT, preoperative screening of antibodies must be performed and their ability to activate platelets tested in functional assays. The intraoperative strategy must be adapted to the results of the latter. Heparin, if selected for the management of the case, should only be used intraoperatively. Alternative anticoagulants must be used in the pre- or postoperative periods in all cases.

Conflict of Interest

The authors declare that they have no conflict of interest.

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