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Acute Intraoperative Onset of Heparin-Induced Thrombocytopenia (HIT) During Off-pump Coronary Artery Bypass Grafting: A Case Report and Literature Review

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Abstract

This case report presents a unique case of intraoperative Heparin-Induced Thrombocytopenia (HIT) during cardiac surgery. Without any preoperative warning signs of HIT, intraoperative complications emerged, including occlusion of the aortocoronary arteries and rapid deterioration of ventricular function. This case illustrates the need for 1) raised awareness of intraoperative HIT and 2) for interdisciplinary contingency plans for suspected intraoperative HIT.

Keywords: HIT • Cardiopulmonary bypass • Cardiac surgery

Introduction

Heparin-Induced Thrombocytopenia (HIT) is a seldom yet serious immune-mediated adverse reaction generally triggered by heparin administration. This condition occurs due to the formation of antibodies against a compound of heparin and Platelet Factor 4 (PF4) found on the surface of platelets. The result is platelet activation, the production of thrombin, and thrombotic events [1]. Without treatment, some 50% of patients with HIT will suffer thromboembolic complications, most frequently pulmonary embolism and venous thrombosis of lower limbs with a high mortality rate (6.1%/day) [2].

Heparin is arguably the most important medication in cardiac anesthesia. Full anticoagulation is essential for Cardiopulmonary Bypass (CPB) and even Off-Pump Coronary Artery Bypass grafting (OPCAB) requires a substantial degree of anticoagulation. A clinical suspicion of HIT is generally first assessed by the 4T score and then by antibody testing against the PF4/heparin complex and functional assays [3]. Literature and guidelines for the management of preoperatively known HIT exist [4], but are severely lacking for intraoperative suspicion of HIT.

Case Presentation

A 77-year-old patient with intermittent angina pectoris was referred to our institution for revascularization of a coronary 3-vessel disease. Prior to referral, the patient received acetylsalicylic acid 400 mg and heparin (5000 units). Upon arrival, continuous heparin was initiated, and the patient was both stable and comfortable. Laboratory tests the day before surgery revealed anemia (Hb 86 g/l) and a platelet count of 330 10^9/l. There were no signs of thromboembolic events.

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Induction of anesthesia was uneventful. Other than an ejection fraction of 45%, the intraoperative transoesophageal echocardiography was normal. After sternotomy and graft harvesting, 25'000 units of unfractionated heparin were and the Activated Clotting Time (ACT) was 196 seconds. Subsequently, another 10'000 units of heparin and 1000 units antithrombin III were given, yielding an adequate off-pump ACT of 345s. ACT was repeatedly measured above 300s during the quadruple OPCAB: Left Internal Mammary Artery (LIMA) - Left Anterior Descending (LAD), Right Internal Mammary Artery (RIMA) - diagonal branch (RD1), vein - Right Circumflex Artery (RCx), and vein - Right Coronary Artery (RCA). Although initially with satisfactory flows, the final measurements showed a significant decrease of the LIMA-LAD flow and anteroapical akinesia in TEE was observed. The bypass was revised after additional heparin as a beating heart procedure, flow measurements were again satisfactory, and the wall motion abnormalities regressed. After weaning from CPB, decannulation, and protamine administration, apical akinesia was again seen for the entire left ventricle and poor flow was measured on all bypasses, particularly the LIMA-LAD. Heparin was given and CPB was again initiated. The LIMA-graft itself showed pulsatile flow, but no backflow from the LAD was observed. A thrombus was aspirated and then again satisfactory flows on the LIMA-LAD bypass was observed. An intra-aortic balloon pump was put in place and separation from CPB commenced with 0.08 mcg kg^{-1} min^{-1} norepinephrine and 0.04 mcg kg^{-1} min^{-1} epinephrine. However, with worsening contractility, increasing ST-elevation, and increasing epinephrine doses, the patient was taken to the catheter laboratory for visualization of graft patency and possible stenting.

In the catheter lab, all four bypasses were visualized and shown to be occluded. The main stem was recanalized and stenting of the left main stem and LAD was performed. During the procedure the patient was briefly resuscitated and an Impella heart pump inserted. Upon admission to the intensive care unit right heart function deteriorated. A VA-ECMO was placed, and the patient was stabilized. Postoperative workup showed a thrombocytopenia with a nadir of 47 10^9/l on the first Postoperative Day (POD) and a positive antibody screening test (anti-PF4/heparin antibodies). Thereafter, anticoagulation was changed to bivalirudin. The Impella-purge solution with heparin was altered to glucose and bicarbonate. Prior to surgery the patient had stated that extended resuscitation and life support measures were not desired. Following intense exchange with the patient's family therapy was de-escalated and the patient died on the second postoperative day. Eight days after surgery, the confirmatory C-serotonin release assay for functional platelet activation activity was also positive for HIT [5].

Results and Discussion

Most literature pertaining to HIT in cardiac surgery addresses patients with preoperatively known subacute or remote HIT. First time manifestation of HIT during cardiac surgery is exceedingly rare.

HIT is generally divided into 5 phases: Suspected (clinical suspicion, but no definitive laboratory tests), acute (thrombocytopenia, antibodies against PF4/heparin complex, and functional platelet activating capacity), subacute A (platelet count normalized, antibodies against PF4/heparin complex, and functional platelet activating capacity), subacute B (presence of antibodies against PF4/heparin, but no platelet activating capacity), and remote HIT (antibodies no longer detectable). In acute and subacute A phases, it is recommended that surgery be postponed. However, if surgery is urgent, alternative intraoperative anticoagulation protocols are recommended. Alternative intraoperative anticoagulation protocols generally include either a non-heparin anticoagulant (e.g. bivalirudin or argatraban) or heparin and an antiplatelet agent (e.g. prostacyclin receptor agonists such as epoprostenol or iloprost, GP IIb/IIIa antagonists such as tirofiban, or $P2Y_{12}$ receptor agonists such as cangrelor). As an adjunct, IVIG may be useful for eliminating antibodies. For all stages, preoperative and postoperative anticoagulation should be a non-heparin [6].

To the best of our knowledge only one case report of two patients suffering from intraoperative HIT exists [7]. In both patients, the venous reservoir of the cardiopulmonary bypass circuit clotted. The first patient was treated intraoperatively with additional heparin and HIT was only diagnosed postoperatively (postoperative treatment with hirudin) and the second was treated with a bolus of hirudin into the cardiopulmonary bypass circuit. Our circuit did not clot, so we had no initial suspicion of HIT. Preoperatively, our patient did not exhibit thromboses or thrombocytopenia and the 4T score was 0. As testing for antibodies against PF4/heparin complex is only recommended with a higher pre-test probability (4 points or more) due to a high false positive rate, this would not have been sensible. Perioperatively, the first reasonable suspicion was visualization in the catheter lab that all bypasses had clotted after cardiopulmonary bypass. Retrospectively, the serial clotting in the LAD with no backflow could potentially have served as an early warning sign, although other factors are much more common for poor bypass flow. Furthermore, acting on a mere suspicion intraoperatively has serious potential consequences, and no protocols or recommendations exist on this topic.

What are future possible intraoperative rescue strategies?

One option is to discontinue heparin and switch to bivalirudine. Bivalirudine has been shown to be safe and efficient when used for cardiac surgery with CPB for CABG and/or valve replacement, albeit with significantly higher early postoperative bleeding [8]. This is also our experience, particularly when bivalirudin is not routinely used, but rather only in HIT-cases. Specifically, for OPCAB, the CHOOSE-OFF trial [9] demonstrated that in a population known to be carrying HIT antibodies undergoing cardiac surgery bivalidrudin is safe and effective. But what about the intraoperative change from heparin to bivalirudin on a suspected HIT? How do we monitor it in the presence of heparin? What do we do with the heparin? Do we antagonize? If so when and how much? Should we bypass the reservoir, stop the cell salvage stop all other stagnant blood? A change in anticoagulation seems difficult and is something very few people have experience with. Additionally, our patient was hemodynamically compromised which bound resources.

Another option is to add something "on top" of heparin to inhibit platelet function. First, the synthetic prostacyclin analogon iloprost has been described as an alternative. However, its effect on platelet inhibition in the context of HIT and CPB is about ~50% [10] and may be insufficient for acute intraoperative HIT. Second, cangrelor - a $P2Y_{12}$ -antagonist - has been propagated as an "on top" agent for HIT. However, in most cases it has been used in subacute or remote HIT. Its capacity in the presence of functional HIT antibodies is unknown *in vivo* beyond individual case reports. Although *in vitro* studies have shown a median reduction in platelet aggregation by 91%, only 45% reached the suggested 95% reduction, and in 14% cangrelor did not inhibit *in vitro* heparin-induced aggregation at all. Revelly E, et al. [5] recommend cangrelor only be used after assessing its individual efficacy in laboratory testing prior to surgery, unless a pretreatment with IVIG can be applied. Third, tirofiban - a GP IIb/IIIa antagonist - is also an option as an "on top" agent for HIT. Again, however, data is very scarce. A study in nearly 50 patients with HIT showed this approach to be feasible and safe [11]. In this protocol, a bolus of 10 ug/kg followed by a perfusion of 0.15 ug kg^{-1} min^{-1} are applied before CPB. This perfusion rate is continued until 1h prior to CPB separation. Laboratory testing for individual efficacy seems not to be required, but the half-life is significantly longer than cangrelor (1-2 hours vs. 3-6 minutes).

Regardless of the "on top" agent used, pretreatment (or concomitant treatment) with IVIG is probably a central point to avoid thrombosis and increase platelet count and a repetition dose should be considered. [12].

Conclusion

In summary, an intraoperative manifestation of HIT should be a differential diagnosis in patients receiving heparin prior to cardiac surgery who unexpectedly require repeated revision of bypasses. Postoperatively, caution must be used as some as some 33.4% of patients may be positive for anti-PF4/H antibodies at the time of discharge, and 62% by day 30. Institutions should develop an interdisciplinary back-up plan for suspected intraoperative HIT. It is our suggestion that this plan be safe, quick to implement, and require as few changes as possible to the standard operating procedure, particularly in smaller institutions. Therefore, the addition of a reliable platelet inhibiting agent on top of heparin and treatment with IVIG seems to be a decent rescue strategy for intraoperative suspicion of HIT.

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Contribution of Authors

F.H.: Study conception, analysis and interpretation; drafted & critically revised manuscript, final approval, agreement to be accountable for all aspects related to accuracy and integrity of work.

S.M.: Study conception, analysis and interpretation; drafted & critically revised manuscript, final approval, agreement to be accountable for all aspects related to accuracy and integrity of work.

N.H.: Study conception, analysis and interpretation; drafted & critically revised manuscript, final approval, agreement to be accountable for all aspects related to accuracy and integrity of work.

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E.M.: Study conception, analysis and interpretation; drafted & critically revised manuscript, final approval, agreement to be accountable for all aspects related to accuracy and integrity of work.

Conflict of Interest

None.

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