Case Report

A Heparin-Induced Thrombocytopenia with Thrombosis in Coronary Artery Bypass Grafts Can Be Fatal: A Case Report.

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ABSTRACT

Heparin is the preferred anticoagulant for cardiac surgery because of its easy availability, monitoring and reversibility. A few set of patients who are exposed to heparin in the past have a risk of developing heparin-induced thrombocytopenia which can be dreadful while undergoing any cardiac interventions.

Key Words: Cardiac surgery, heparin, HIT, thrombosis.

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INTRODUCTION

A rare but possibly fatal side effect of heparin therapy is thrombocytopenia caused by heparin (HIT)[1]. HIT puts the patient at higher risk for thrombotic problems, both arterial and venous. Amputation, stroke or other irreversible disabilities affect an equal proportion of patients as a result of thrombosis in HIT, which is linked to a death rate of 20 % to 30 %[2–5]. This report's major goal is to draw attention to the possibility that heparin resistance could show as an HIT symptom before the commonly used 4 *T* probability score system.

CASE REPORT

A 53-year-old woman who had been using statins, nitrates and beta blockers was diagnosed with unstable angina and was treated with a loading dose of *T*. Ecospirin (325 mg), *T*. Clopidogrel (300 mg) and Inj. Heparin 5000 U (Intravenous) three times per day on the day of diagnosis. Her echocardiogram revealed mild left ventricular dysfunction with a 50 % ejection fraction and septal and inferior wall hypokinesia. The results of her coronary angiography had shown triple vessel disease. Two weeks after optimising, an off pump Coronary Artery Bypass Graft (CABG) was scheduled. Her preoperative tests revealed that she had normal renal and hepatic function, a haemoglobin level of 11.3 g/dl, a platelet count of 2,98,000 cells/cu.mm, a PT of 13.6 s, an INR of 1 and an aPTT of 28.3 s. Seven days before the CABG procedure, *T*. Ecospirin and *T*. Clopidogrel were stopped and they were replaced with Inj. Clexane 0.4 ml SC O.D. Inj. Heparin 5000 units SC 8th hourly were used in place of Inj. Clexane 24 h before surgery. Eight hours before the operation, the last heparin dose was administered. Subcutaneous heparin was given after stopping the Low molecular weight heparin(LMWH) as an institutional protocol 24 h before the surgery.

A median sternotomy was carried out following the onset of general anaesthesia, and OPCAB was carried out following the administration of 2 mg/kg of heparin and an ACT of 252 s. Aorta-saphenous venous grafts (SVG) were anastomosed to the obtuse marginal (OM1) and (OM2) and a left internal mammary artery (LIMA) graft was anastomosed to the left anterior descending (LAD). Then, a 1 : 1 ratio of Inj.Protamine was used to reverse the anticoagulant effects of heparin. Initially there was hypotension in reaction to protamine followed by ECG showing sustained ST elevation in all leads (greater in II, III and avF.(5.4 mm)) despite revascularization. The continued low blood pressure necessitated strong inotropic support. Cardiopulmonary bypass support was given to the heart since the right ventricular contractions were obviously weak. 3 min after systemic heparinization with 3 mg/kg UFH, the ACT value was 452 s. The ACT did not cross 480 s despite a 6 mg/kg heparin dosage, leading to the suspicion that there was heparin resistance. With an ACT of 478 s, cardiopulmonary bypass was started after two units of fresh frozen plasma. At the distal anastomosis, it was discovered that LIMA was thrombosed. It was modified to graft LIMA to LAD. In addition, the diagonal artery and distal right coronary artery were grafted. The measured serial ACT values were 469 and 462 s. The patient was moved to the ICU with mechanical ventilation. Repeated blood tests showed a haemoglobin level of 10.7 and a platelet count of 43 000. The patient suddenly suffered an acute hypotension, and the ECG subsequently showed ST elevation and ventricular fibrillation. After then, the patient experienced cardiopulmonary arrest, which could not be revived. A significant thrombus was found in the left anterior descending artery when the sternum was opened after the arrest. The clinical diagnosis of HIT was strongly supported by the abrupt decline in platelet count

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(> 50 %fall- 2 points), a new arterial thrombosis(2 points) and exposure to heparin within 30 days (2 points) and no other cause of thrombocytopenia (2 points and hence a *T* score of 8/8 (Tables 1 and 2). There was no history of thrombosis in the preceding weeks before the surgery. The first instance of thrombosis was noted during the surgery.

Table 1 : The 4TS scoring system:

4Ts category	2 points	1 point	0 point
Thrombocytopenia	Platelet count >50% and platelet nadir >or equal to 20	Platelet count 30% to 50% or platelet nadir 10-19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset days 5-10 or platelet fall 1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (e.g., missing platelet counts); onset after day 10; or fall 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall <or equal to 4 days without recent exposure
Thrombosis or other Sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of Thrombocytopenia	None apparent	Possible	Definite

Table 2 : Risk Stratification of *T* score in HIT:

T Score	Probability of HIT
0–3	Low
4–6	Intermediate
6–8	High

DISCUSSION

Unfractionated heparin is the anticoagulant of choice in cardiac surgeries as it is effective, easily available, has a rapid onset of action and is efficiently reversed by protamine. The continued use of unfractionated heparin in clinical practice places patients at risk for developing heparin-induced thrombocytopenia (HIT), a potentially devastating immune disorder associated with catastrophic thrombosis[6]. Heparin-induced thrombocytopenia is the most significant adverse effect of heparin after bleeding complications[7]. In general, the antibodies occur more frequently in patients undergoing cardiovascular surgery and in postsurgical patients than in medical patients[8]. HIT antibodies are also more frequent in patients receiving unfractionated heparin (UFH) compared to low molecular weight heparin[9,10] although antibodies developing in patients receiving UFH frequently cross-react with LMWH[7].

HIT is classified into 2 distinct subtypes. Type I HIT is characterised by mild decrease in platelet count and typically occurs within 1 to 2 days of heparin administration. It is non-immune-mediated and appears to be due to a direct activation of the platelets by heparin, leading to platelet aggregation and hence thrombocytopenia. It is not considered pathologic and usually resolves spontaneously[1].

Type II HIT is the more severe form and is associated with thromboembolic complications. It is immune-mediated and is caused by IgG antibody formation against the circulating Heparin-Platelet factor 4 complexes. Platelet factor 4 is normally present in the alpha granules of platelets and is released into circulation on platelet activation. The Fab region of the antibody then binds to heparin- P4 complex. The Fc portion of the antibody then binds to the platelet Fc receptor and this interaction triggers activation and aggregation of the platelets. Activated platelets release PF4, thus the cycle perpetuates[7]. Activation of platelets leads to thrombocytopenia and aggregation of platelets produces thrombosis (white clot syndrome)[7]. The activated platelets further release prothrombotic platelet microparticles which promote coagulation and hence there is paradoxical thrombosis inspite of thrombocytopenia.

HIT is known to be one of the causes for heparin resistance, which is defined as the inability of an adequate heparin dose to increase the activated clotting time (ACT) to the desired level[11]. Heparin resistance was the first manifestation of HIT in our patient. The proposed mechanism for heparin resistance in HIT is heparin neutralization by platelet factor IV, which is released by platelet aggregation in the presence of heparin-dependent platelet membrane antibodies[12]. The cause of heparin resistance could have been due to both antithrombin (AT III deficiency) and non-antithrombin mediated mechanisms (neutralisation by platelet factor 4). Measurement of AT III and whole blood heparin levels would have been a more coherent approach[13]. In our case AT III assay couldn't be done because of the non-availability in the lab. Since AT III concentrate is not available, FFP was transfused in an effort to the reverse the ATIII deficiency but that did not elevate the ACT timings.

HIT is essentially diagnosed clinically and laboratory assays usually play a supportive role[1,8,14,15]. To aid in the clinical diagnosis of HIT, a 4 *T* scoring system (Table 1) was developed by Lo *et al.*[16].

The *T* score in our patient was 7/8 indicating a high probability of HIT. (2 points for platelet count fall from 2,98,000 to 43,000, 2 points for timing of the fall i.e. recent heparin exposure, 2 points for new thrombosis and 1 point for possible other causes of thrombocytopenia like post-surgery, post CPB).

Functional and immunological tests for HIT involve the platelet aggregation test (PAT), serotonin release assay (SRA), heparin-induced platelet aggregation (HIPA) test, the anti-H-PF4 complex antibody enzyme-linked immunosorbent assays (ELISA), and flow cytometry studies[1,17]. The H-PF4 ELISA test is sensitive (90%) but less specific(~71%) and is often used as a screening test. The SRA with a sensitivity of 100% and specificity of 97% can be performed as a confirmatory test, but is not universally available and utilised[18].

CONCLUSION

Delays in the availability of diagnostic assay results warrants the identification and management of HIT on the basis of clinical evaluation and since heparin resistance can serve as an earlier red flag for HIT[13], a chance encounter with heparin resistance should raise a high index of suspicion for HIT especially in the setting of new onset thrombosis and thrombocytopenia.

Heparin-induced thrombocytopenia can present as heparin resistance in initial stage which can be effectively managed peroperatively by transfusing fresh frozen plasma to increase the levels of antithrombin III. Preoperative or intraoperative plasmapheresis can be done to eliminate the anti-heparin antibodies. A potent antiplatelet like tirofiban or direct thrombin inhibitors such as bivalirudin can be tried for cardiac surgeries. HIT can be catastrophic if not diagnosed earlier. Alternatives are available to heparin for cardiac surgeries if the operation is not delayed.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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