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Heparin Induced Thrombocytopenia in Patients Undergoing Cardiac Surgery in North Indian Population

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Abstract

Heparin-Induced Thrombocytopenia (HIT) is an immune-mediated disorder that follows exposure to heparin which is used commonly during cardiopulmonary bypass. HIT requires prompt recognition and management to avoid life threatening thromboembolic complications. The study was planned to determine the prevalence of H-PF4 antibodies in adult cardiac surgery patient's population and to assess the associated risk of postoperative adverse outcomes. Platelet counts were monitored in 100 consecutive patients at baseline level and post operative day 1 to day 14 on alternate days or at discharge whichever was earlier. Patients having definite thrombocytopenia were further tested using antibody assay. Out of 100 consecutive patients, a total of 42 patients met the criteria for significant thrombocytopenia who were further investigated using antigen assays (ELISA). 18 patients were found positive for H/PF4 antibodies by ELISA in postoperative period and were associated with prolonged hospital stay and higher thrombotic complications than patients without H/PF4 antibodies.

Keywords: Heparin induced thrombocytopenia; Low molecular weight heparin; Cardiac surgery; Unfractionated heparin; Postoperative heparin

Introduction

As a large number of patients are undergoing cardiac operations annually, it is important to identify populations at high risk for adverse outcomes. Thrombocytopenia is commonly encountered in patients undergoing cardiac surgery, often requiring transfusion support. Heparin-Induced Thrombocytopenia (HIT) is an immune-mediated disorder that follows exposure to Unfractionated Heparin (UFH) or (less commonly) low molecular weight heparin (LMWH) an anticoagulant used during cardiopulmonary bypass [1]. Patients classically present with a low platelet count (<150,000/mm^3) or a relative decrease of 50 percent or more from baseline [2,3]. The time to the onset of thrombocytopenia after the initiation of heparin varies according to the history of exposure. The occurrence of HIT after open heart surgery is associated with a high incidence of arterial and venous thromboembolic events and high perioperative mortality. The reported incidence postoperative H-PF4 antibody seroconversion in cardiac surgery patients ranges from 25% to 50% in various studies [4-8]. This incidence should be viewed in light of the high volume of cardiac surgery performed today and the devastating outcomes associated with HIT. There is paucity of data on HIT seroprevalence from India. This study was conducted to determine the prevalence of H-PF4 antibodies in cardiac surgery patient population and to assess the associated risk of postoperative adverse outcomes.

Material and Methods

The study was conducted in patients undergoing cardiac surgery at our institution during a 1 year period November, 2007 to October, 2008. Men and non-pregnant women over the age of 18, who were scheduled to cardiac surgery, were included in the study. 1-3 mg/kg unfractionated heparin was administered to all cardiac patients during cardiopulmonary bypass surgery and postoperatively in some patients. Surgery consisted of single Coronary Artery Bypass Graft (CABG), valve replacement, or valve repair or combined procedures (valve replacement or repair plus CABG). The first day of UFH administration was day 1. Platelet counts were monitored in all patients included in the study at baseline level i.e. preoperatively within 24 hours prior to surgery, and postoperative day 1 to day 14 on alternate days or at discharge whichever was earlier.

All patients with or without clinical suspicion of HIT were further tested for heparin PF4 antibody using commercially available ELISA Asserachrom HPIA [Stago (Asnieres, France)]. Sera were separated from all samples and were kept frozen at -40°C until tested. Clinical HIT was defined as patients with significant thrombocytopenia (>50% fall from baseline or count <100,000/µl), positive antibody assay (ELISA). Various preoperative, operative, and postoperative variables were recorded and compared between Clinical HIT patients and non HIT patients.

Results

A total 100 patients presenting for cardiac surgery were enrolled in the study. The platelet counts in all the patients fell significantly from their preoperative baseline. And a total of 42 patients had significant thrombocytopenia (26 patients had fall of more than 50% from baseline and 41 had nadir platelet counts <100×10^3/mm^3).

On testing the sera of patients with clinical suspicion, only one sample was positive for H/PF4 antibodies before surgery. Post-op day 7, a total of 18 patients were positive for H/PF4 antibodies. There was a significant increase in incidence of H-PF4 positive antibodies after CPB (p<0.0001). No significant difference in incidence of HIT is found between off-pump and on-pump surgeries (p=0.889). When compared to single valve surgeries, double valve surgeries and

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combined surgeries had higher incidence of HIT but this was not found statistically significant (p=0.178). Operative variables were not different statistically (p>0.05). However, patients with HIT antibodies required significantly longer time for weaning from the mechanical ventilation postoperatively (p=0.038). There is no significant difference in ICU stay between Clinical HIT and non HIT patients, however, the hospital stay was significantly higher in patients with HIT antibodies (p=0.003). The mean hospital stay was 12.5 and 10.2 days for patients with and without clinical HIT respectively. The rate of thrombosis in patients with and without clinical HIT was 4 (22%) vs. 6 (7.3%) which is statistically significant. We also evaluated transfusion support to patients with and without clinical HIT; and observed no significant differences in transfusion of PRBCs, FFP, and RDPs (p>0.05) between these two groups.

Discussion

More than 60,000 adult cardiac operations are performed in the India annually [9]. Although mortality rates are relatively low, perioperative complications remain common. Many complications in cardiac surgical patients may result from inflammatory or prothrombotic responses to tissue trauma such as the development of serum antibodies directed against platelet factor 4 (PF4)/heparin complexes. All adult cardiac surgical patients are exposed to heparin at the time or cardiac catheterization or during the subsequent surgical procedure itself. A substantial fraction of these patients have antibodies directed against PF4/heparin complexes, and a small subset progress to having Heparin-Induced Thrombocytopenia (HIT) [10].

In our study, a total of 42 patients met the criteria for clinical thrombocytopenia (defined as platelet count less than 100 $\times 10^3/\mu l$ or fall from preoperative platelet count of >50%). Everett et al. reported clinical thrombocytopenia in 17% of their patients [11]. Platelet counts in HIT seldom drop below 10,000 per cubic millimeter, are rarely associated with bleeding, and typically recover within 4 to 14 days after heparin is discontinued, although recovery may take longer in some patients. Singer et al. has reported a mean decrease in platelet counts of 26% compared to baseline following CPB and has recommended routine monitoring of platelet counts in these patients and prompt investigation for the heparin dependent antibody whenever there is a thromboembolic complication [12]. We have observed a statistically significant (p=0.000) low post operative mean platelet counts in patients undergoing CPB in the presence of antibodies to H/PF4.

Characteristic	Clinical HIT		P value
	Positive (n=18)	Negative (n=82)	
Sex: M:F	10:8	52: 30	0.408
Age (in yrs) Median (Range)	34 (18-70)	43 (18-79)	0.154
Diabetes, n (%)	1 (5.5%)	09 (10.9%)	0.447
Hypertension, n (%)	2 (11.1%)	13 (15.8%)	0.546
Pre-op Heparin, n (%)	14 (73.7%)	36 (44.4%)	**0.022**
Post op heparin, n (%)	04 (21.1%)	08 (9.9%)	0.179
Fall of platelet counts % (Mean ± SD)	56.4 ± 13.15	35.35 ± 15.48	**0.000**
Nadir platelet count (Mean ± SD)	73 ± 22	128 ± 45	**0.000**
Ventilation time (hrs)	9.75 ± 5.7	7.6 ± 4.9	**0.038**
Hosp stay, Mean ± SD	12.5 ± 3.2	10.1 ± 5.6	0.003
Infection n (%)	4 (22.2%)	14 (17.0 %)	0.702
Thrombosis n (%)	04 (22.2%)	06 (7.3%)	**0.002**
Mortality n (%)	1(5.5%)	2 (2.4%)	0.523
Transfused n (%)	15 (83.3 %)	67 (81.7%)	0.702
PRBC units/patient (Mean ± SD)	2.6 ± 2.4	2.3 ± 2.0	0.567
FFP units/patient (Mean ± SD)	3.9 ± 4.0	3.3 ± 3.9	0.534
RDP Transfusion N (%)	8 (42.1)%	33 (40.2%)	0.914

Table 1: Comparison of various parameters between patients with and without Clinical HIT.

We evaluated the prevalence of heparin/PF4 antibodies in the patients presenting for cardiac surgery at our institute and found that the prevalence of the heparin/PF4 antibody increased from 2.5% to 45% (18/42). The incidence of HIT varies with the type of heparin used (UFH or LMWH]), duration of heparin therapy, and the patient-population (e.g., in the case of orthopedic patients, the incidence is between 1% and 3%). The difference in prevalence of these antibodies in various parts of the world may be due to the genetic makeup and the quality of heparins used. The increase in prevalence of H-PF4 antibodies in India may be due to the quality of heparin used.

There are reports of occurrence of HIT after exposure to small quantities of heparin such as catheter flush. Majority of our patients with clinical HIT (73.7%) had history of previous exposure to heparin. This is in accordance with Gettings et al. who reported previous heparin exposure in 68% of his HIT patients [13]. It has been widely accepted that rapid onset HIT occurs in patients who have previous exposure to heparin. This may be the reason for early onset of thrombocytopenia in our patient population as 73.7% of patients had previous exposure to heparin.

Other reports have also suggested a higher prevalence of the antibody in cardiac surgery patients. In a study of 111 patients undergoing cardiac surgery, Bauer et al. [5] reported the prevalence of the antibody to be 19% prior to cardiopulmonary bypass and 51% on the fifth postoperative day. Rates of thrombosis were low (only two of 111 patients). In smaller studies, each of 51 patients, Trossaert et al. [6] and Visentin et al. [4] found a postoperative heparin/PF4 antibody prevalence of 27% and 61%, respectively.

Kerendi et al. observed prolonged ventilation time (>24 hrs) in 64% of HIT patients compared to 50% of patients without HIT [14]. There is no specific explanation for prolonged ventilation in HIT patients; however, it could be related to poor respiratory function secondary to endothelial damage induced by H-PF4 antibodies and platelet activation. Bennett- Guerrero et al. has reported association of H-PF4 antibodies with indirect measures of morbidity i.e. death and prolonged hospitalization (>10 days) [15]. This increased ICU and hospital stay in patients with HIT will significantly increase the management costs more than the patient without HIT. As far as the mortality is concerned, though, there was an increased rate of mortality in HIT compared to non HIT patients (5.5% vs 3.6%) in our study, the difference was not significant. This may be because of small sample size and moreover heparin exposure was limited to pre operative and per operative phase only. However, other authors have reported significantly higher rate of mortality in patients with HIT [13,16].

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