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ORIGINAL ARTICLE

The frequency of heparin-induced thrombocytopenia in Taiwanese patients undergoing cardiopulmonary bypass surgery

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KEYWORDS
anti-heparin/platelet factor 4 antibodies;
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flow cytometry assay;
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Background/Purpose: There are few studies on heparin-induced thrombocytopenia (HIT) reported from Taiwan and Asian countries. We conducted a prospective study to investigate the frequency of HIT in patients undergoing cardiopulmonary bypass surgeries.
Methods: A cohort of 54 patients was enrolled from January 01, 2010 to October 31, 2011. Patients' clinical information was obtained for 4T score classification. Plasma (2–4 mL) was also collected before surgery and on Days 5 and 10 following heparin administration during the bypass procedure. This was tested for anti-heparin/PF4 antibodies and functional assay using flow cytometry (FC).
Results: The mean platelet count for this cohort followed the expected pattern in the postoperative setting. Seven of the 54 (13%) patients had positive antibodies assays before bypass surgery. This increased to 32% on Day 5 and was markedly elevated to 63% on Day 10 after surgery. Only one of the 54 patients (1.8%) was found to have both positive antibody assay and platelet activation, but no clinical HIT/thrombosis developed.
Conclusion: Our study is the first report on the rates of HIT in the setting of cardiopulmonary bypass surgery in Taiwan and demonstrated no clinical HIT occurrence, despite the high frequency of HIT antibody in our cohort.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Introduction

Heparin-induced thrombocytopenia (HIT) is an acquired immunologic and thrombotic disorder characterized by thrombocytopenia with/without arterial or venous thrombosis following heparin exposure. Devastating complications such as limb gangrene and even fatality may occur if it is not recognized and treated in a timely fashion.[1] Early identification of HIT is therefore essential for the appropriate clinical management of affected patients. In the typical presentation of HIT, thrombocytopenia with or without vascular thrombosis usually develops on Days 5—12 after heparin exposure.[2] The reported incidence of HIT is 1—5%, depending on the clinical situation and the type of heparin used.[3]

Patients undergoing cardiovascular or orthopedic surgeries have a higher probability of developing HIT antibodies as compared to medical patients exposed to heparin.[4,5] However, many patients with detectable anti-heparin/PF4 antibodies may not develop clinical HIT. In fact, only 5—50% of these patients will develop HIT, depending on the patient population.[6] The relationship between the clinical presentation of HIT, the presence of HIT antibodies, and the type of assay used can be conceptualized as an iceberg model, as proposed by Warkentin.[7]

HIT has been well recognized in Western countries, but there are few studies reported from Taiwan and other Asian countries and the Taiwanese have been considered ethnically as a low-risk population for developing thrombosis.[8] Our colleagues have previously reported a female patient with breast cancer who developed progressive thrombocytopenia and venous thrombosis of axillary vessels with impending digit and limb gangrene after Port-A catheter insertion with minimal heparin exposure.[9] She was diagnosed as having HIT by positive enzyme-linked immunosorbent assay (ELISA), and was successfully treated with heparin cessation and subsequent thrombolytic therapy. Systematic studies of the frequency of HIT in various subsets of patients in Taiwan have so far been lacking. Therefore, we consider HIT to be a disease needing further exploration in the Taiwanese population to better understand the epidemiologic and clinical spectrum.

In this study, we focus on patients undergoing cardiopulmonary bypass surgery with unfractionated heparin (UFH) exposure, because these patients have been identified as having a high risk of developing HIT antibodies. The aims of this study were: (1) to determine the frequency of anti-heparin/platelet factor 4 antibody formation in Taiwanese patients undergoing cardiopulmonary bypass surgeries; (2) to estimate how many of these patients have a positive functional assay for HIT antibodies; and (3) to determine the overall frequency of clinical HITT in this cohort of patients.

Patients and methods

Patients

We conducted a prospective study involving a cohort of patients who had undergone cardiac surgeries with UFH use for cardiopulmonary bypass at our institution from January 01, 2010 to October 31, 2011. This study was approved by our institutional review board and signed informed consent was obtained from each patient before their enrollment. Each patient's medical history including age, sex, disease and type of operation were recorded. Additionally, a series of platelet counts before surgery and Days 0, 2, 5, 8, and 10 after surgery were collected for analysis.

None of the 54 patients in this cohort was given either UFH or low molecular weight heparin for deep venous thrombosis (DVT)/pulmonary embolism (PE) prophylaxis in the intensive care unit after surgery.

Inclusion criteria

Patients who were given UFH for extracorporeal anticoagulation while undergoing cardiopulmonary bypass surgery were included.

Exclusion criteria

Patients with known thrombocytopenia (platelet count $< 100 \times 10^3/mm^3$) from causes such as infection, sepsis, liver disease, or acute disseminated intravascular coagulopathy before cardiac surgery were excluded.

Heparin use

UFH (Agglutex, China Chemical and Pharmaceutical Corporation, Taipei, Taiwan), a porcine heparin sodium, was given by intravenous bolus of 300 units/kg with additional dosing to get activated clotting time >400 seconds before cardiopulmonary bypass surgery, followed by repeated UFH boluses as needed to keep the activated clotting time >400 seconds continually during cardiopulmonary bypass.

Platelet transfusion

One unit of platelet pheresis product was transfused for each patient after surgery, which is a standard practice for patients who receive cardiac surgery at our institution.

Patient's plasma

Each patient's plasma (2—4 mL) was collected in a vacuum tube containing 3.2% sodium citrate as an anticoagulant before surgery and on Days 5 and 10 after heparin administration. The samples were centrifuged, aliquoted, and stored at −80°C. One stored frozen sample from each patient was thawed to test for anti-heparin/PF4 antibodies by ELISA. If the result of the ELISA was positive, the other one was thawed and subjected to functional assay using the flow cytometry (FC) method.

Methods

ELISA testing for detection of HIT antibodies

ELISA (Asserachrom HPIA, Stago, Asnières, France) was used according to the manufacturer's guidelines. This assay determined the amount of antibodies (IgG, IgM, and IgA) against heparin-PF4 complexes in a patient's plasma. The absorbance value of each tested sample was measured at 450 nm. The HIT ELISA assay was classified as positive if the absorbance value, optical density (OD), of the tested sample was greater than the absorbance value of the reference reagent multiplied by a fraction number (0.27 or