Incidence of Heparin-Induced Thrombocytopenia and Therapeutic Strategies in Pediatric Cardiac Surgery

Andreas Böning, MD, Torsten Morschheuser, MD, Udo Bläse, ECCP, Jens Scheewe, MD, Michael von der Brelie, MD, Ralf Grabitz, MD, PhD, and Jochen T. Cremer, MD, PhD

Departments of Cardiovascular Surgery and Pediatric Cardiology, University Hospital Kiel, and Department of Cardiology, Albertinen-Hospital, Hamburg, Germany

Background. **We identified the incidence of heparin-induced thrombocytopenia and the antiheparin-platelet factor 4 (PF4) antibody in pediatric patients undergoing cardiac surgery and documented the differences in the anticoagulation management for the extracorporeal circulation.**

Methods. **Between January 2001 and September 2003, 559 cardiac procedures with extracorporeal circulation in 415 patients with congenital heart defects were performed in our institution. Because the development of heparin-induced thrombocytopenia requires previous exposition to heparin, only the 144 patients undergoing a scheduled second procedure on extracorporeal circulation were screened preoperatively. Of these 144 patients, 41 underwent also a third procedure and were screened before each procedure for presence of antiheparin-PF4 antibodies and for clinical signs of heparin-induced thrombocytopenia.**

Results. **The incidence of antiheparin-PF4 antibodies during the study period was 1.4% (2 of 144 patients). Patients with clinically significant heparin-induced thrombocytopenia could not be identified. Outside the study protocol, 2 more patients with antiheparin-PF4 antibodies were found. In these 4 patients, surgery was performed using lepirudin (Schering, Berlin, Germany) instead of the usual heparin management for extracorporeal circulation. Three of these 4 patients had an uneventful procedure and postoperative course. In 1 patient after total cavopulmonary connection, a reoperation was necessary on the seventh postoperative day owing to partial thrombosis of the lateral tunnel.**

Conclusions. **The incidence of heparin-induced thrombocytopenia and of antiheparin-PF4 antibodies in patients undergoing repeated cardiac surgery is low. In antiheparin-PF4 antibody positive patients, the complete avoidance of heparin can be achieved and may account for an uneventful perioperative course.**

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Heparin-induced thrombocytopenia type II (HIT II) is an immune-mediated coagulation disorder resulting when preexisting antibodies against heparin are exposed to complexes of platelet factor 4 (PF4) and heparin [1, 2]. Platelet activation is then caused by complexes of heparin, PF4, and immunoglobulin G on the platelets' surfaces, which leads to subsequent activation of coagulation and to a decrease in platelet counts in blood samples. In approximately 40% to 75% of HIT II patients, venous or even arterial thromboses develop [3, 4].

Heparin-induced thrombocytopenia type II is a rare (1% to 2.4%) but severe complication after adult cardiac surgery [4, 5] with the use of heparin for the anticoagulation management during extracorporeal circulation (ECC). Data regarding the frequency of HIT after pediatric cardiac surgery are not available. After the first publications about an alternative anticoagulation method in adult cardiac surgery [6, 7], there are few anecdotal reports about the treatment of HIT-positive children [8–10]. Publications about the anticoagulation management of the ECC in pediatric cardiac surgery are even more rare [11].

We sought to identify the incidence of HIT II and antiheparin-PF4-antibody positivity in pediatric patients undergoing cardiac surgery and documented the differences in the intraoperative and postoperative anticoagulation management.

Patients and Methods

Between January 2001 and September 2003, 559 cardiac procedures with ECC in 415 patients with congenital heart defects were performed in our institution. Because the development of HIT II requires previous contact with heparin, only the 144 patients undergoing a scheduled second procedure, 207 ± 180 days (range, 15 to 2,156) after the first procedure, on ECC were screened for antiheparin-PF4-antibodies before each surgery and for clinical signs of HIT II in their intermediate course up to the second or third approach. Of these 144 patients, 41 underwent also a third procedure, 372 ± 273 days (range, 10 to 861) after second procedure and were screened again.

Patients with second procedures less than 10 days after

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Address reprint requests to Dr Böning, Department of Cardiovascular Surgery, University Hospital, Arnold-Heller-Str 7, 24105 Kiel, Germany; e-mail: aboening@kielheart.uni-kiel.de.

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Abbreviations and Acronyms

BW = body weight
CoA = coarctation
DILV = double inlet left ventricle
DORV = double outlet right ventricle
ECC = extracorporeal circulation
ECT = ecarin clotting time
HIT II = heparin induced thrombocytopenia type II
HPIA = heparin-induced platelet activation assay
HTX = heart transplantation
IAA = interrupted aortic arch
PF4 = platelet factor IV
PTT = plasma thrombin time
RVOT/PA = right ventricular outflow tract/Pulmonary artery
TAPVD = total anomalous pulmonary venous drainage
TCPC = total cavopulmonary connection
TGA = transposition of the great arteries
TOF = tetralogy of Fallot
TV = tricuspid valve
VSD = ventricular septal defect

their first surgery (n = 10) and patients who died shortly after their first surgery (n = 6) were excluded from the study.

The congenital pathologies of the study patients were as follows: hypoplastic left heart syndrome (n = 70); transposition of the great arteries ([TGA] simple, with ventricular septal defect [VSD], double inlet left ventricle or double outlet right ventricle, n = 20); tetralogy of Fallot (also with pulmonary atresia, n = 16); coarctation (also with VSD, n = 13); truncus arteriosus communis (n = 5); total anomalous pulmonary venous drainage (n = 5); tricuspid atresia (n = 5); VSD/pulmonary stenosis (n = 2); miscellaneous (n = 8). The surgical procedures are displayed in Table 1. Heparin-induced thrombocytopenia type II was suspected if a positive value (cutoff point, 28.5%) of the antiheparin-PF4-antibody was detected by a heparin-induced platelet activation assay (Asserachrom HPIA; Roche Diagnostics, Mannheim, Germany).

Table 1. Surgical Procedures in Patients Screened for Antiheparin PF4 Antibodies Before Repeat Cardiac Surgery With Extracorporeal Circulation

Procedure	First	Second	Third
Norwood 1	63 (43.5%)	0	0
Hemifontan/Glenn	15 (10.6%)	68 (47.1%)	3 (8.3%)
RVOT-PA repair	2 (1.2%)	15 (10.3%)	7 (16.7%)
Shunt	17 (11.8%)	8 (5.7%)	0
CoA (+VSD), IAA	14 (9.4%)	3 (2.3%)	0
Fallot-Correction	3 (2.4%)	3 (2.3%)	0
Total cavopulmonary connection	0	10 (6.9%)	16 (38.9%)
Tricuspid valve reconstruction	0	10 (6.9%)	5 (11.1%)
Unifocalization + shunt	3 (2.4%)	0	0
Truncus arteriosus correction	5 (3.5%)	0	0
TAPVD correction	5 (3.5%)	0	0
Arterial switch (+VSD)	5 (3.5%)	0	0
Heart transplant	0	3 (2.3%)	0
Re-VSD	0	7 (4.6%)	0
Miscellaneous	12 (8.2%)	17 (11.5%)	10 (25%)

CoA = coarctation; IAA = interrupted aortic arch; PA = pulmonary artery; RVOT = right ventricular outflow tract; TAPVD = total anomalous pulmonary venous drainage; VSD = ventricular septal defect.

Patients who tested positive for antiheparin-PF4-antibody were treated specifically, as if they were HIT II positive: heparin contact before, during, and after ECC was avoided. During ECC, lepirudin (Refludan; Aventis, Bad Soden, Germany), a recombinant hirudine acting as a direct thrombin inhibitor, was used. Because the plasma thrombin time (PTT) is invalid in higher lepirudin dosages, the lepirudin concentration during ECC was monitored by the Ecarin clotting time (ECT, Pentapharm, Basel, Switzerland). The advantage of the ECT monitoring is the proportionality of the ECT to lepirudin concentrations of greater than 2 μg/mL [12]. Before surgery, an individual calibration graph was obtained using the patient's blood: after adding lepirudin in concentrations of 1 μg/mL, 2 μg/mL, 3 μg/mL, and 4 μg/mL to the patient's blood, the ECT values for these samples were determined.

Lepirudin was added to the ECC priming (0.2 mg/kg body weight) and given intravenously (0.25 mg/kg body weight) before ECC start after having obtained the first ECT. During ECC, a lepirudin infusion was adjusted according to the relevant ECT, which was measured every 10 minutes. Target values were a minimum of 3.5 μg/mL and a maximum of 5 μg/mL patient blood. Thirty minutes before termination of the ECC, the lepirudin infusion was stopped, and the lepirudin was removed from the patient by ultrafiltration and stimulation of the diuresis.

If bleeding continued, a cell-saving device primed with lepirudin (1 mg/L rinsing fluid) was used, further renal elimination of lepirudin was intensified, and increased efforts for subtle surgical hemostasis were made.

Results

The incidence of antiheparin-PF4-antibody positivity (266 $\pm$ 168 days after last surgery) during the screening period was 1.4% (2 of 144 patients). In these 2 patients, as well as in all other screened patients, no sign for previous HIT II could be found: neither a thrombopenia of less than 50% of the preoperative value 5 to 10 days after previous surgery, nor the generation of thrombosis or embolization combined with a positive antiheparin-PF4-antibody could be proved. In the 2 patients positive for antiheparin-PF4-antibody, in whom heparin exposition was totally avoided, surgery was performed using lepirudin instead of heparin on ECC. Additionally, the cell-saving device suction was also primed with lepirudin.