Use of Plasma Exchange and Heparin During Cardiopulmonary Bypass for a Patient with Heparin Induced Thrombocytopenia: A Case Report

Michio Kajitani, M.D., Ph.D.,* Miguel Aguinaga, M.D.,* Charles E. Johnson, C.C.P.,* Margie A. Scott, M.D.,† and Tamim Antakli, M.D.*

**Division of Cardiothoracic Surgery, University of Arkansas for Medical Sciences, Little Rock, Arkansas and †Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas*

ASTRACT Patients with documented history of heparin-induced thrombocytopenia (HIT) pose a difficult problem during surgery using cardiopulmonary bypass (CPB). Several alternatives to heparin exist, but these products either are not approved for use in the United States or have more side effects than heparin. We report on a patient with documented heparin-induced antibody and left main coronary artery disease who underwent uneventful coronary artery bypass surgery and recovery by using preoperative plasmaphresis and limited use of porcine intestinal heparin during CPB. *(J Card Surg 2001;16:313-318)*

Patients with documented history of heparin-induced thrombocytopenia (HIT) who need surgery using cardiopulmonary bypass (CPB) pose a difficult problem for anticoagulation. Several alternatives to heparin exist, such as low molecular weight heparin (LMWH), danaparoid, argatroban, dermatan sulfate, Ancrod, Iloprost, and recombinant hirudin. These products either are not approved for use in the United States or have more side effects than standard heparin.[1,2] Due to the lack of an antidote and the difficulty in monitoring at the high range level of anticoagulation intraoperatively, we have avoided the use of recombinant hirudin. We report on a patient with documented HIT and unstable angina who underwent uneventful coronary artery bypass surgery and recovery by using preoperative plasma exchange and limited use of porcine intestinal heparin during CPB.

Address for correspondence: Dr. Tamim Antakli, Division of Cardiothoracic Surgery, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot #713, Little Rock, AR 72205-7199. Fax: (501) 686-8503; e-mail: antaklitamim@exchange.uams.edu

CASE

A 57-year-old male with a known history of coronary artery disease was admitted with an acute coronary syndrome. Electrocardiogram (ECG) showed inferior wall ischemia; in addition, his myocardial enzymes were elevated. He was admitted to the coronary care unit and was started on heparin intravenously. His initial platelet count on admission was 243,000/mm^3 but decreased to 20,000/mm^3 within 12 hours. Heparin was discontinued, and recombinant hirudin was given intravenously to provide anticoagulation, maintaining an activated partial thromboplastin time (aPTT) level of 1.5 to 2.5 times normal. The platelet count returned to 152,000/mm^3 in 2 days. Heparin-induced platelet antibody (HIPA) studies using an

enzyme-linked immunosorbent assay (ELISA) method were strongly positive (Diagnostica Stago ASSERACHROM ® HPIA).[38,39] The patient subsequently underwent coronary angiography, which revealed > 95% proximal stenosis of the left anterior descending artery and a similar lesion in the midcircumflex coronary with left ventricular ejection fraction of 40%. The patient had a history of rotator cuff repair 3 years before, at which time he had an exposure to heparin. After reviewing the case in detail, he was scheduled for elective coronary artery bypass grafting. The issue of optimal anticoagulation method during CPB was discussed. Consideration was given for use of recombinant hirudin (Lepirudin, Hoechst Marion Roussel); however, due to the lack of Food and Drug Administration (FDA) approval for ecarin clotting time (ECT, Pharmanetics, Raleigh, NC USA) at the time of surgery and the absence of an antidote, we do not use this product for CPB at our institution. ECT is the only test to have linear correlation with hirudin levels at high levels of anticoagulation.

Because the patient's preprocedure positive ELISA optical density reading far exceeded the known positive control level, we anticipated that multiple plasma exchanges might be needed. The number of plasma exchanges required was determined by following the optical density readings of the ELISA test as compared with positive and negative plasma controls, with a goal to closely approach the negative plasma control levels prior to CPB surgery (Fig. 1). Since plasma exchange removes intravascular IgG but does not affect tissue-distributed IgG, multiple-timed postpheresis ELISA optical density readings were reviewed to determine the potential rebound effect of IgG antibodies in the immediate postpheresis period. A total of three plasmapheresis procedures were performed over 4 days using the following fluid replacements: Exchange #1: 100% albumin; Exchange #2: 50% albumin and 50% fresh frozen plasma; Exchange #3: 100% fresh frozen plasma. A final ELISA assay was performed following plasmapheresis #3 to ensure that no HIPA-positive units of fresh frozen plasma were inadvertently transfused during the final exchange procedure. After the third plasma exchange procedure, the ELISA optical density reading closely approached the negative plasma control level (Fig. 1) and the patient was taken for CPB surgery.

Unfractionated heparin of porcine intestinal ori-

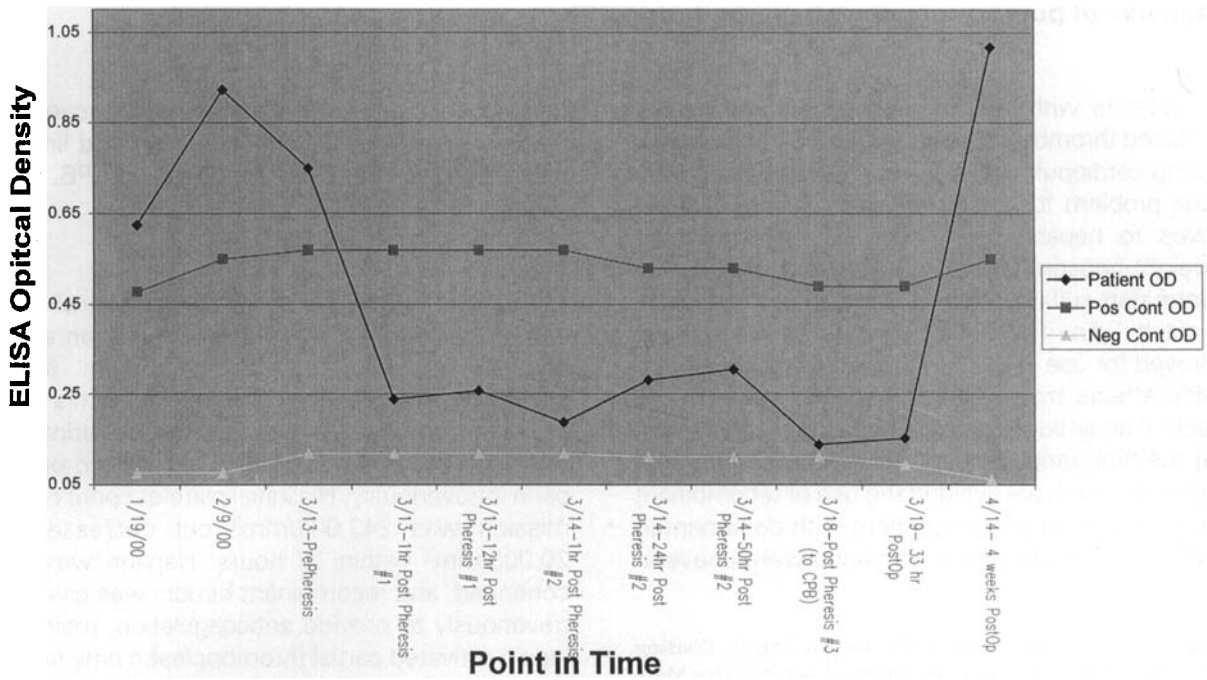

Figure 1. *Heparin induced platelet antibody testing. Patient OD = patient optical density; Pos Cont OD = positive control optical density; Neg Cont OD = negative control optical density.*

gin, rather than bovine lung origin, was selected. The patient was kept on aspirin and received preoperatively two doses of clopidogrel (Plavix) 75 mg orally and two doses of methylprednisolone 250 mg intravenously. Ten thousand units of porcine intestinal heparin were used to prime the CPB machine and 30,000 units were given intravenously prior to CPB, as indicated by the Hepcon method (Medtronic, Minneapolis, MN USA). No heparin-coated circuits or intravenous access lines were used. Heparin flush through intravenous or arterial lines was strictly avoided. Three coronary artery bypass grafts were performed using reversed saphenous vein grafts from aorta to the left anterior descending, the diagonal, and the first obtuse marginal branches. The use of internal mammary graft was avoided to shorten the patient's heparin exposure. After the patient was weaned off from CPB, heparin was reversed with 350 mg of protamine sulfate intravenously, after which the activated coagulation time (ACT) returned to 107 seconds. Aortic cross-clamp time was 48 minutes and cardiopulmonary bypass time was 63 minutes. The patient was weaned off CPB without inotropic support. Platelet count was 205,000/mm^3 before surgery and 76,000/mm^3 immediately after surgery. Two apheresis units of platelets were given. Total chest tube drainage was 1200 cc and hematocrit remained above 34%. No other blood products were needed. Patient's postoperative recovery was uncomplicated without any clinical evidence of HIT. Platelet count remained stable throughout the postoperative course (Table 1). ELISA testing performed on postoperative day 1 remained negative, very near the negative control readings. The patient was discharged home in stable condition on postoperative day 5. He was seen 4 weeks after surgery in the clinic, at which time he was doing well, without chest pain or any clinical signs or symptoms of HIT. His platelet count was 470,000/mm^3, and ELISA testing was again strongly positive, with optical density readings greater than twice the level of a known strong positive control (Fig. 1).

DISCUSSION

HIT occurs in 5-10% of heparin-treated patients. HIT-I presents with mild thrombocytopenia of 100,000-130,000/mm^3, and is usually of little clinical impact and resolves once heparin is stopped.[3-6] HIT-I is caused by direct interaction between heparin and platelets rather than an antibody-mediated effect.[1,7] Heparin-induced thrombocytopenia and thrombosis (HITT), or HIT-II compose 10%-20% of HIT. It has mortality of up to 30% and permanent morbidity of 20%-30%.[1,8] It presents thrombocytopenia of less than 100,000/mm^3 caused by antibody-mediated effect on platelets, and has increased predilection for venous and arterial thrombotic events.[1,7]

Our patient had marked thrombocytopenia within 12 hours of intravenous heparin therapy, which strongly suggests presence of HIT-II due to previous exposure to heparin and acquired antibody. ELISA testing confirmed the presence of HIPA, and discontinuation of heparin and use of recombinant hirudin reversed thrombocytopenia. Subjecting this patient to heparin reexposure seemed very dangerous because of the high possibility of developing HITT.[9]

Alternatives to heparin were considered and are summarized in Table 2. LMWH has 80% chance of cross-reactivity with unfractionated heparin (UFH)[1,10,11] Danaparoid has been used outside the United States,[12] but it cross-reacts with UFH in 20% of cases. It could be monitored by aPTT and ACT,[13] but it lacks an effective antidote. Argatroban is a direct thrombin inhibitor and has been shown to be safe in the setting of HIT.[14,15,16] Major studies of its use in HIT patients undergoing CPB are nearing completion. Dermatan sulfate (DS) is a heparin-like compound. It catalyzes the inhibition of thrombin through heparin cofac-

TABLE 1
Platelet Count and Platelet Antibody

Date	Jan 18	Jan 19	Jan 21	Feb 9	Mar 13	Mar 14	Mar 17	Mar 18	Mar 19	Mar 20	Mar 21	Mar 22	Apr 12
PLT	205	76	152	306	237		76	156	107	114	145	185	470
HIPA		Pos			Pos	Neg		Neg	Neg				Pos

PLT = platelet count × 1,000/mm3; HIPA = heparin-induced platelet antibody (ELISA).
Date: Jan 18: first admission; Mar 13, 14, 16: plasma exchange; Mar 18: surgery; Apr 12: clinic.

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TABLE 2
Alternatives to Heparin

	Cross-reaction with UFH	Monitor	Antidote	CPB Use in US
LMWH	80%	activated factor X	partially with protamine	Yes
Danaparoid	20%	ACT	No	No
Argatroban			No	pending
Dermatan Sulfate				No data
Ancrod		fibrinogen		No
Iloprost				No
r-Hirudin		ECT, aPTT	No	Yes

LMWH = low molecular weight heparin; DS = dermatan sulfate; UFH = unfractionated heparin; ECT = ecarin clotting time.

tor II.[17,18] It inhibits clot-bound thrombin through heparin cofactor II. It has been used safely in hemodialysis,[19,20] but no data are available for its use in CPB.[2] Ancrod is a defibrinating snake venom used in Canada for treatment of HIT.[21] It is not approved for use in the United States.[1,22] Iloprost (ZK 36374) is a prostacyclin analogue and is a potent endogenous inhibitor of platelet function. It is not available for use in HIT in the United States.[22,23]

Recombinant hirudin (r-hirudin, Lepirudin, and Refludan) has been shown to be a good alternative for antithrombotic therapy in patients with HIT,[24,25] has received FDA approval, and is a potential alternative in CPB for patients with HIT.[26,27,28] Linear correlation between whole blood ECT and serum recombinant hirudin levels has been shown.[29] However, ECT reagents and methods were not approved by the FDA at the time of our surgery. Hirudin also lacks any antidote.

Plasma exchange has been reported for managing thrombocytopenia and thrombotic complications of HIT. It works on the principle of removing heparin-associated IgG antibodies. When performed repeatedly with the adjunctive use of antiplatelet agents, reversal of HIT has been reported.[30-32]

Aspirin and dipyridamole, along with intraoperative heparin, have been used to prevent thromboembolic complications for HIT patients.[33] Because thromboxane-independent pathways exist,[34] a 40% failure rate in preventing heparin-induced platelet aggregation and release in vitro have been reported.[23] Clopidogrel (Plavix) is an inhibitor of adenosine diphophate (ADP)-induced platelet aggregation that directly inhibits ADP binding to its receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Since it uses a different pathway than aspirin, it supplements the inhibition of platelet aggregation and release.

King[4] and Kelton and Bell[35] and Royall reported higher frequency of thrombocytopenia with bovine heparin (35%) than porcine heparin (7%-9%).[4,35] Accordingly, we elected to use heparin of porcine intestinal mucosa origin (Elkins-Sinn, Cherry Hill, NJ, USA).

By using plasma exchange combined with aspirin, clopidogrel, and methylprednisolone, we were able to use heparin of porcine intestinal mucosa origin using ACT for monitoring, and reversing its effect with protamine safely. Clearance of HIPA was confirmed following multiple plasma exchanges before surgery. Paradoxically, two studies using ELISA for testing heparin-induced antibodies before and after surgery showed no correlation between antibody positivity, thrombocytopenia, and adverse thrombotic events.[36,37] A possible explanation for this could be rapid discontinuation and reversal of heparin after CPB.[1] As long as the use of heparin is limited only to the CPB run, it seems safe to use heparin, as in our case, after clearing the antibody from the serum by using plasma exchange. This patient had an uneventful recovery without thromboembolic complications and was discharged in 5 days. Follow-up 1 month after surgery showed normal ECG, platelet count, and no evidence of thromboembolism. As expected, ELISA became strongly positive at 1-month follow-up.

CONCLUSION

Patients with documented HIT who need CPB pose a difficult problem to anticoagulation. This case suggests that limited use of heparin to the CPB run can still be safe, as long as clearance of antibody was confirmed after plasma exchange.

Supplemental doses of antiplatelet agents and steroids can be useful without major side effects.

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