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# Cardiac Surgery in Patients with Heparin-Induced Thrombocytopenia Using Preoperatively Determined Dosages of Iloprost


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## ABSTRACT

**Background:** Patients with preoperatively diagnosed type II heparin-induced thrombocytopenia (HIT) scheduled for cardiopulmonary bypass (CPB) present a challenge in their intraoperative anticoagulation management because re-exposure to heparin may result in profound thrombocytopenia, intravascular thromboses, bleeding, and even death. Iloprost, a prostacyclin analogue that reversibly inhibits platelet aggregation, has been suggested as a management approach in such cases. The purpose of this study was to assess and confirm the efficacy of a perioperative intravenous iloprost infusion in preventing thromboembolic complications in patients with type II HIT undergoing cardiac surgery and requiring the use of heparin and CPB.

**Methods:** During a one-and-a-half-year period, 22 patients with type II HIT presented at the Cardiac Surgery Service of the Onassis Cardiac Center in Athens. In these patients, platelet aggregation test results were found strongly positive at heparin serum concentrations corresponding to those achieved during CPB. Iloprost was used in a preoperatively, in vitro–determined, patient-specific concentration that was assessed and modified perioperatively depending on its in vivo effect on platelet aggregation as opposed to the conventional constant rate.

**Results:** In the 22 patients, the preoperatively determined concentration of iloprost seemed to correlate well with the in vivo interruption of platelet aggregation, as tested by a perioperative heparin-induced platelet aggregation (HIPA) assay, and in only 3 cases (14%) was the rate of iloprost infusion increased. The patients' platelet counts, which were evaluated peri- and postoperatively, were preserved with no statistically significant fluctuations. Postoperative bleeding was within normal limits and no thrombotic episodes or other complications were reported.

**Conclusion:** Although a number of alternative anticoagulation methods, such as the use of another anticoagulant (danaparoid sodium and recombinant hirudin) or the preoperative use of a defibrinogenating agent (ancorod), have been suggested for patients with type II HIT requiring anticoagulation during CPB, the use of heparin associated with a potent platelet inhibitor such as the prostacyclin analog iloprost is, as this study confirmed, the only to-date safe and effective choice.

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## INTRODUCTION

Heparin anticoagulation, discovered in 1916 by McLean, with its predictable effectiveness, rapid action, and reversibility with protamine, has become invaluable in the development of extra corporeal cardiopulmonary bypass (CPB) [Singer 1993, Aouifi 2001].

First described in animals in 1942, heparin-induced thrombocytopenia (HIT) is among the most serious potential complications of heparin use during CPB [Walls 1990]. Two forms of HIT are currently recognized. A transient non–immune-mediated type I HIT, causing moderate thrombocytopenia (platelet count >100,000/μL) and without severe thromboembolic sequelae, was first described in 1962 and occurs in approximately 15% of patients exposed to heparin [Walls 1990, Aouifi 2001]. It develops early (day 1 to day 5) after the initiation of heparin therapy and is thought to be due to heparin's direct platelet aggregation effect [Singer 1993].

Type II HIT has a more critical presentation and was first described in literature in 1973 [Singer 1993]. The pathogenetic mechanism is immune mediated, with the principal antigen being a multimolecular platelet factor 4 (PF4) and heparin complex, composed of approximately 8 PF4 molecules per heparin molecule [Visentin 1996, Greinacher 1994, Aouifi 2001]. With antigen exposure, IgG and IgM HIT immunoglobulins are produced and can bind on the Fc receptor on the platelet surface (FcgRII, CD32) and cause intravascular platelet activation. Furthermore, the HIT antibodies are not heparin-specific and also bind and activate endothelial cells. This concurrent activation of platelets and endothelial cells is probably a major factor in the development of severe thoromboembolic complication in patients

with type II HIT [Greinacher 1994]. The incidence of reporting type II HIT in literature ranges from 0.2% to 31%. It occurs 4 to 14 days after initiation of heparin therapy but can occur more rapidly if there has been previous exposure and antibody formation [Singer 1993, Greinacher 1994, Munver 1994, Antoniou 2000, Aouifi 2001]. The overall incidence of thromboembolic complication in patients with type II HIT has been quoted at 28% and ranges from saphenous vein graft occlusion and subsequent myocardial infarction to limb amputation (overall rate, 20%), pulmonary embolus, and stroke (overall rate, 7%) [Walls 1990, Singer 1993, Wilhelm 1995, Antoniou 2000]. Postsurgical bleeding has been reported in 48% of patients with type II HIT, and the overall mortality rate can be up to 30% [Walls 1990, Antoniou 2000].

Due to its severity, there must be a high index of suspicion for type II HIT in patients who present with a rapidly falling platelet count of >50% or >30% with concomitant recurrence of, or de novo, arterial or venous thromboembolisms. Restoration of the platelet count after heparin withdrawal further strengthens the diagnosis [Kappers-Klunne 1997]. Platelet aggregation studies in the presence of heparin must be performed to establish the diagnosis of HIT, and an alternative form of postoperative anticoagulation should be given if indicated [Munver 1994].

Unfortunately, the majority of cardiac surgery patients have been previously admitted under the care of other services (eg, cardiology, internal medicine) where they have been exposed to heparin for diagnostic or therapeutic purposes from a variety of sources, including heparin flushes, subcutaneous heparin, heparin-coated pulmonary artery catheters, and cardiac catheterization [Singer 1993]. HIT antibody formation in patients who have received low doses of heparin preoperatively ranges from 22% to 82% [Walls 1992, Greinacher 1994, Visentin 1996]. The development of antibodies is independent of the amount of heparin given, the route of administration, or of the type of heparin used [Walls 1990].

Prevention of heparin-induced platelet activation during CPB by using prostacyclin was first proposed during the 1980s [Aouifi 2001]. Iloprost, a stable and potent prostacyclin analogue that, due to its short half-life (15-30 minutes), reversibly inhibits platelet aggregation, is now being used to permit safe heparin administration during cardiac operations requiring CPB [Kappa 1990, Walls 1990, Marrott 1995].

The objective of this study, performed at the Onassis Cardiac Surgery Center in Athens, was to assess and confirm the efficacy of perioperative intravenous iloprost administration in patients with type II HIT undergoing cardiac surgery and requiring the use of heparin for CPB. Furthermore, in this study we introduced a new parameter: we used a preoperatively, in vitro–determined, patient-specific dosage of iloprost, which was assessed and modified perioperatively depending on its in vivo effect on platelet aggregation. It is thought that such customization of iloprost administration results in better patient response with a more specific and complete inhibition of platelet aggregation and lower rates of postoperative thromboembolic and bleeding complications.

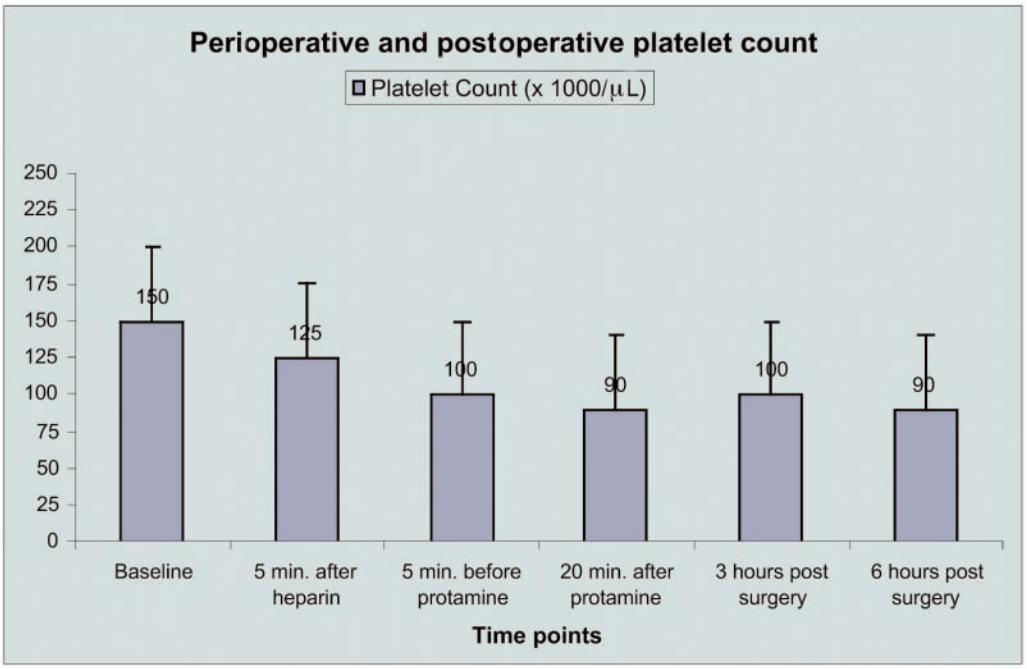
## MATERIALS AND METHODS

Between January 2000 and September 2001, among 946 adult cardiac surgical patients of the Onassis Cardiac Surgery Center, 22 with documented preoperative type II HIT had to undergo cardiac surgery with the use of CPB. The patients' average age was 66.43 years (range, 53-76) and the male-to-female ratio was 16:6. Of those, 12 underwent coronary artery bypass grafting (CABG), 4 underwent aortic valve replacement (AVR), 3 underwent AVR with CABG and 3 underwent mitral valve replacement (MVR) and CABG.

Type II HIT was initially suspected preoperatively from a history of thrombotic or thromboembolic events following heparin exposure, from a low platelet count (≤100,000/μL), or from a reduction in the platelet count greater than 50%. Clinical suspicion was confirmed using a platelet factor 4/heparin enzyme linked immunosorbent assay (PF4-Hep. Elisa) test, for the detection of HIT specific antibodies [Amiral 1992].

If the PF4-Hep. Elisa was positive, then a HIPA assay was performed using increasing micromolar concentrations of iloprost to investigate the effect of each concentration on in vitro platelet aggregation [Greinacher 1991, Marrott 1995]. The results from the HIPA test were used to calculate each patient's specific in vivo concentration of iloprost needed to prevent platelet aggregation.

Induction of anesthesia was performed using etomidate 20 mg, fentanyl 20 μg/kgr, pancuronium 0.1 mg/kgr, midazolam 2mg; maintenance of anesthesia was achieved with isoflurane 1% to 2%. For monitoring of pulmonary arterial pressures, non–heparin-coated Swan-Ganz catheters were used. Following the induction of anesthesia and before the administration of heparin, a continuous intravenous iloprost infusion was started under constant hemodynamic monitoring, at the rate specific for each patient, which ranged from 6 to 12 ng/kgr per minute. Due to iloprost's strong vasodilating properties, a noradrenaline infusion had to be titrated accordingly to prevent excessive fluctuations in blood pressure. Before the initiation of CPB, a HIPA test was repeated to see if the in vitro concentration of iloprost that had been administered was able to stop the patient's in vivo platelet aggregation. Patients in whom the HIPA test results were negative received a 100 to 300 U/kgr intravenous bolus dose of heparin and, with the use of clear pump primer, extracorporeal cardiopulmonary bypass with moderate systemic hypothermia was initiated. If platelet aggregation persisted, the dose of iloprost was increased by an increment of 6 ng/krg per minute, in a stepwise fashion every 10 minutes until the HIPA test result was negative. Iloprost was then continued at that infusion rate. The iloprost infusion was maintained throughout surgery and was discontinued 20 minutes after the reversal of heparin with protamine. Platelet counts corrected for hematocrit were measured at the following time-points: baseline, 5 minutes after heparin administration, 5 minutes before protamine administration, 20 minutes after protamine administration, and 3 and 6 hours postoperative. Time-based changes in the platelet count were evaluated by ANOVA for repeated measures with $P < .05$ accepted as statistically significant.




Perioperative and postoperative platelet levels in patients with type II HIT, who underwent CPB using a preoperatively determined, patient-specific infusion of iloprost.

## RESULTS

With the use of a preoperatively, in vitro–determined, patient-specific dosage of iloprost, which was assessed and modified perioperatively depending on its in vivo effect, a more specific and complete inhibition of platelet aggregation was achieved. In the 22 patients studied, the preoperatively determined concentration of iloprost that was infused seemed to correlate well with the in vivo interruption of platelet aggregation, as per the perioperative HIPA testing, and in only 3 cases (14 %) was the rate of iloprost infusion increased. The average range of iloprost infusion used in this study was 6 to 12 ng/kgr per minute and the maximum dose, which was reached in only 1 patient, was 24 ng/kgr per minute.

The effect of iloprost on the average platelet count at the different time-points is shown in the Figure ◎. It can be seen that the mean postheparin platelet count was not significantly different from baseline and that in general the platelet count was preserved with no statistically significant fluctuations.

Postoperative bleeding was within normal levels, with chest drainage averaging 510 ± 175 mL. Three study patients required postoperative reexploration for bleeding, but in all 3 patients a surgical cause for the hemorrhage was detected, so it was not attributed to iloprost causing hemorrhagic diathesis.

There were no reported thromboembolic or thrombotic episodes or any other adverse events.

## DISCUSSION

HIT in its more severe form is an unusual immune-mediated complication of heparin administration that can have catastrophic results. It produces a systemic intravascular coagulopathy, thrombosis, and thromboembolic events, which can include stroke, saphenous vein graft occlusion, and subsequent myocardial infarction, pulmonary embolism, peripheral arterial ischemia with potential limb loss, excessive postoperative hemorrhage, and even death.

Due to the seriousness of type II HIT, it is important for the clinician to maintain a high index of suspicion for any patient group that has been previously exposed to heparin and has the potential for antibody formation. Cardiac surgery patients make up such a group of patients; often they get exposed to heparin during diagnostic procedures or while hospitalized under the care of other services. Because HIT antibody formation is rapid and can occur within 4 to 14 days after exposure and because antibody formation is independent of the amount of heparin given, the route of administration, or the type of heparin used, then the potential of cardiac surgery patients having developed HIT antibodies at the time of scheduled open-heart operation is quite high [Walls 1990, Singer 1993]. These patients pose a particular problem because of the need for anticoagulation during CPB. Therefore one must first identify such patients among the general cardiac patient group. A fall in the platelet count of >50%, a fall of >30% with associated thromboembolic episodes, or a fall in the platelet count below 100,000/μL should be considered causes to suspect HIT, and further testing in the form of HIPA or PF4-Hep. Elisa should be used for confirmation.

Controversy remains as to the management of cardiac surgery patients who require CPB. Since HIT antibodies have been noted to persist for up to 28 months after diagnosis, delaying open-heart surgery is not a feasible option

[Walls 1990]. Therefore, a variety of options for anticoagulation during CPB have been suggested.

Ancorod, a rapid-acting defibrinogenating agent that is derived from the Malayan pit viper (*Agkistrodon rhodostoma*) and is immunologically distinct from heparin, has been suggested as an alternative anticoagulant during CPB in HIT patients. Findings have shown that this agent does not cause immune thrombocytopenia and that it is safe and effective [Munver 1994]. It has been used in only a limited number of patients because of the lack of an effective neutralizing agent. Moreover, because a patient's plasma fibrinogen level must be decreased to 0.5 g/L before initiation of CPB, preparation which requires more than 12 hours, ancorod's use in emergencies is excluded [Aouifi 2001].

Danaparoid sodium is a heparinoid, developed in the last decade, that is composed of a mixture of polysulfated glycosaminoglycans (heparan sulfate 84%, dermatan sulfate 12%, and chondroitin sulfate 4%) [Aouifi 2001]. It is a potent thrombin inhibitor and has been used successfully in a number of patients who underwent CPB [Wilhelm 1996, Aouifi 2001]. Unfortunately, there are a number of drawbacks associated with its use. Activated clotting time (ACT) measurements are not reliable, making direct monitoring of anti-Xa activity necessary [Wilhelm 1996]. Anti-Xa activity is also prolonged (approximately 25 hours), with the consequence of excessive postoperative bleeding risk and the need for transfusion of blood products. Finally, there is a reported 10% cross-reaction with heparin that limits its use in type II HIT patients.

Recombinant hirudin is a specific direct thrombin inhibitor that is immunologically distinct from heparin and does not cause thrombocytopenia. There has been limited use of hirudin in patients with HIT undergoing CPB, but initial results are promising [Aouifi 2001]. Nevertheless, despite its short half-life (2 hours), the use of this drug remains difficult because of the lack of a specific neutralizing agent and the lack of an easy and standardized way to monitor its anticoagulant activity during CPB [Aouifi 2001].

Iloprost, a potent and reversible prostacyclin analogue, has been used safely and effectively during CPB in patients with HIT by several other authors. In 1990 Kappa and associates [1990] reported the successful use of iloprost in a number of their cardiac surgery patients without severe postoperative complications and bleeding. A number of other authors have reported that patients with HIT who were pretreated with platelet-function inhibiting agents such as iloprost and were not given heparin after surgery had reduced morbidity and mortality [Walls 1990, Marrott 1995].

In this study we were able to confirm the efficacy of iloprost in patients with HIT needing CPB. The perioperative iloprost infusion significantly reduced the incidence of thrombotic and thromboembolic events. Platelet count was preserved peri- and postoperatively and there was no excessive bleeding reported. By determining the concentration of iloprost needed to prevent platelet aggregation preoperatively in vitro, and by modifying the rate perioperatively depending on the in vivo response, we were able to provide our patients with a more complete and precise coverage, customized to their specific requirements. Because the number of patients with HIT who require CPB and who present in a busy cardiac surgery service such as ours is not excessive (22/946 over a period of a year and a half ), such customization of treatment is not difficult to produce, particularly since the data suggest an improved response rate. Further studies are necessary to confirm and further explore this treatment strategy, but we believe that results so far are promising.

## REFERENCES


Amiral J, Bridey E, Dreyfus M, et al. 1992. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thrombosis and Haemostasis 68:95-6.

Antoniou T, Stavridis G, Daganou M, et al. 2000. Heparin induced thrombocytopenia thrombosis after cardiac surgery. A case report. Acta Anesthesiol Scand 44:991-3.

Aouifi A, Blanc P, Piriou V, et al. 2001. Cardiac surgery with cardiopulmonary bypass in patients with type II heparin induced thrombocytopenia. Ann Thorac Surg 71:678-83.

Greinacher A. 1994. Heparin induced thrombocytopenia. Thrombosis and Haemostasis 71:247-51.

Greinacher A, Michels I, Kiefel V, et al. 1991. A rapid and sensitive test for diagnosing heparin associated thrombocytopenia. Thrombosis and Haemostasis 66:734-6.

Kappa J, Fisher C, Todd B, et al. 1990. Intraoperative management of patients with heparin induced thrombocytopenia. Ann Thorac Surg 49(5):714-22.

Kappers-Klunne M, Boon D, Hop W, et al. 1997. Heparin induced thrombocytopenia and thrombosis: a prospective analysis of the incidence in patients with heart and cerebrovascular disease. Br J Haematol 96:442-6.

Marrott P. 1995. Intraoperative management of heparin associated thrombocytopenia with iloprost. In: Norgren L, ed. 1995. Therapeutic applications of iloprost. London: Cambridge Medical Publications.

Munver R, Ira B, Schulman C, et al. 1994. Heparin induced thrombocytopenia and thrombosis: presentation after cardiopulmonary bypass. Ann Thorac Surg 58:1764-6.

Singer R, Mannion J, Bauer T, et al. 1993. Complications from heparin-induced thrombocytopenia in patients undergoing cardiopulmonary bypass. Chest 104(5):1436-40.

Visentin G, Malik M, Cyganiak K. 1996. Patients treated with unfractionated heparin during open-heart surgery are at high risk to form antibodies reactive with heparin:platelet factor 4 complexes. J Lab Clin Med 128(4):376-83.

Walls J, Curtis J, Silver D, et al. 1990. Heparin induced thrombocytopenia in patients who undergo open-heart surgery. Surgery 108(4):686-93.

Walls J, Curtis J, Silver D, et al. 1992. Heparin induced thrombocytopenia in open-heart surgical patients: sequelae of late recognition. Ann Thorac Surg 53:787-91.

Wilheim M, Schmid C, Kececioglu D, et al. 1996. Cardiopulmonary bypass in patients with heparin-induced thrombocytopenia using org 10172. Ann Thorac Surg 61:920-4.