Complications From Heparin-induced Thrombocytopenia in Patients Undergoing Cardiopulmonary Bypass

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The purpose of this study was to evaluate retrospectively the incidence and severity of heparin-induced thrombocytopenia (HIT)-related complications in patients undergoing cardiopulmonary bypass. We reviewed the records of 1,500 consecutive patients who underwent cardiopulmonary bypass between August 1987 and December 1991 at Thomas Jefferson University Hospital. During this period of time, there were 1,155 coronary artery bypass graft operations (77 percent); 225 valve replacements and repairs, or both (15 percent); 60 combination coronary artery bypass graft or valve operations, or both (4 percent); and 60 miscellaneous procedures (4 percent). Although not all patients with postoperative complications were tested for the HIT antibody, 11 patients (0.75 percent) were diagnosed with HIT. There were 17 complications in these 5 men and 6 women including 6 cases of ischemic limbs which required amputation, 4 strokes, 2 instances of saphenous vein graft occlusion with resulting myocardial infarction, 2 cases of pulmonary emboli, 1 case of phlegmasia cerulea dolens, and 2 deaths. The complications occurred an average of 3.6 days postoperatively, with a range of occurrence of 1 to 11 days postoperatively. The mean nadir platelet count at the time of recognition was 123,000/mm³ (range 32,000 to 193,000/mm³) with 9 of 11 patients (81.8 percent) having counts greater than 100,000/mm³. There was, however, a mean percent decrease in the platelet count of 50 percent (range, 31 to 75 percent) from the time of first exposure to heparin to the time of recognition of HIT. In our patients, HIT was not related to the type, duration of treatment with or amount of heparin, or to pretreatment with aspirin.

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**HIT** = heparin-induced thrombocytopenia

Since its discovery in 1916 by McLean,¹ heparin has had extensive clinical applications, including the prevention and treatment of venous thrombosis and pulmonary embolism, stroke, myocardial infarction, preventing thrombosis after coronary artery thrombolyis or angioplasty, atrial fibrillation with embolization, peripheral arterial embolization, disseminated intravascular coagulation, fetal growth retardation, and so on.² Heparin also has been invaluable in the development and use of extracorporeal devices such as the heart-lung machine, cell-saver devices, hemodialysis, as well as for an expansive list of clinical and experimental laboratory uses.

Heparin-induced thrombocytopenia (HIT) occurs when specific heparin-dependent antibodies attach to platelet membranes, causing platelet activation. The aggregation and degranulation of platelets during this process result in a variety of clinical scenarios ranging from asymptomatic thrombocytopenia to devastating intravascular coagulation.

The purpose of our study was to evaluate the incidence and severity of HIT-related complications in patients undergoing cardiopulmonary bypass. A further review of the literature will be discussed with particular emphasis on early recognition and treat-
terization, was with porcine mucosal heparin. Postopera-
tive heparin exposure, such as in heparin flushes,
was also with porcine mucosal heparin.

Eleven of 1,500 patients (0.75 percent) were diag-
nosed as having HIT, including 5 men (45 percent)
and 6 (55 percent) women. All 11 patients had exposure
to heparin while on another service prior to cardio-
pulmonary bypass from a variety of sources, including
heparin flushes, subcutaneous heparin, heparin-coated
pulmonary artery catheters, and cardiac catheteriza-
tion. The mean time from initial exposure to heparin
to time of cardiopulmonary bypass was 4.5 days, with
a range of 3 to 10 days. No patients were suspected of
having HIT preoperatively, since there was no signifi-
cant change in their platelet counts during this time
nor were there any thromboembolic events prior to
surgery. Six of 11 patients (55 percent) were receiving
aspirin immediately prior to surgery and 5 of 11
patients (45 percent) had no recent exposure to aspirin.
All 6 patients taking aspirin received a daily dose of
325 mg of aspirin for a minimum of 1 week prior to
surgery.

There were 17 complications in these 11 patients,
including 6 cases of limb amputation (patients 3, 5,
and 6), 4 instances of stroke, 2 cases of saphenous vein
graft occlusion with resulting myocardial infarction
(patients 3 and 10), 2 instances of pulmonary emboli
(patients 2 and 4), 1 case of phlegmasia cerulea dolens
(patient 7), and 2 deaths (patients 3 and 6).

In those patients who underwent amputation of an
extremity, all had prior intravascular devices present
at those sites. Specifically, patients 3 and 6 had an
infra-aortic balloon pump in place postoperatively in
the affected legs, leading to amputation. Patient 5 had
a history of claudication and therefore the infra-aortic
balloon pump was placed in a transthoracic position;
however, a left femoral arterial line and right femoral
venous line were in place postoperatively. Both pa-
tients 5 and 6 had radial arterial lines in place in the
affected arms, leading to amputation.

The complications occurred at a mean of 3.6 days
postoperatively, with a range of 1 to 11 days. Combined
with their preoperative exposure to heparin, compli-
cations occurred an average of 7.4 days from time of
initial exposure to heparin, with a range of 4 to 14
days. The mean nadir platelet count at the time of
recognition was 123,000/mm$^3$ (range, 32,000 to
183,000/mm$^3$) with 9 of 11 patients (81.8 percent) with
platelet counts greater than 100,000/mm$^3$. There was,
however, a mean percent decrease in the platelet
count of 50 percent (range, 31 to 75 percent) from the
time of first exposure to heparin preoperatively to the
time of the first postoperative complications and
suspicion of type 2 HIT.

The mean nadir platelet count in 100 consecutive
normal patients with no evidence of HIT was 207,000/

| Table 1—What Are "Normal" Platelet Counts After Cardiopulmonary Bypass? |
|---------|------------------|
| 100 consecutive control subjects | Mean platelet count, mm$^3$ |
| Preoperative | 281,000 |
| 2nd day postoperative | 207,000 (decrease of 26%) |
| 5th day postoperative | (range, 0-79%) |
| 7th day postoperative | 279,000 |
| 11 patients with HIT | 380,000 |
| Nadir platelet count | Mean platelet count, mm$^3$ |
| | 123,000 (decrease of 50%) |
| | (range, 31-79%) |

mm$^3$ (range, 66,000 to 332,000/mm$^3$), with a mean
percent decrease in the platelet count of 26 percent
(range, 0 to 70 percent) from the time of first exposure
to heparin preoperatively to the time of the nadir
postoperative platelet count (Table 1).

**Comment**

As with virtually all drugs, heparin also is associated
with adverse reactions, the most common being hem-
orrhage. Other reported complications include local
irritation from subcutaneous use, skin necrosis after
systemic administration, osteoporosis following long-
term administration of high doses of heparin, delayed
transient alopecia, priapism, rebound hyperlipide-
nia on discontinuation of heparin therapy, elevations
of aminotransferase (serum glutamic oxaloacetic trans-
aminase and serum glutamic pyruvic transaminase)
levels, hypoaaldosteronism, and hypersensitivity re-
actions.

One particularly well-studied complication of hepa-
rin therapy is thrombocytopenia, with or without
thrombosis or thromboembolism. Historically, it was
known as early as 1942 that heparin caused a decrease
in platelet count in vitro. In 1958, Weismann and
Tobin described arterial embolism occurring during
systemic heparin therapy. Roberts et al reviewed 11
patients who suffered unexplained arterial emboli-
ozation while being treated with heparin. They
wrote: "We have no explanation for the underlying
mechanism but feel that the hypothesis of antigen-
 antibody reaction, with production of antiheparin
factors or platelet agglutinates, warrants attention." In
1973, Rhodes et al confirmed that a heparin-depen-
tent antiplatelet antibody was responsible for the
heparin-associated thrombocytopenia and thrombo-
embolism.

The clinical features of HIT generally have been
described to occur in two forms, type 1 and 2. In type
1 HIT, platelet counts fall between 1 and 5 days after
the initiation of therapy and often return to normal
values in spite of the continued use of heparin therapy.
This form of HIT is not associated with thrombosis or
thromboembolic sequelae. The pathogenesis is be-
lieved to be due to a direct aggregating effect of
heparin and not to any immune-mediated reaction.
Unfortunately, often it is difficult to determine exactly when heparin exposure was initiated, since HIT is known to occur with even minute amounts of heparin such as in heparin flushes and with heparin-coated intravenous catheters. Further, heparin is available from many other sources, such as subcutaneous heparin, intravenous heparin therapy, cardiac catheterization, and cardiopulmonary bypass.

In type 2 HIT, platelet counts fall between 4 and 14 days after initiation of therapy, and the fall is not uncommonly associated with thrombosis and thromboembolic complications. The pathogenesis is believed to be immune mediated, whereby specific heparin-dependent antibodies attach to platelet membranes causing platelet activation. The aggregation and degranulation of platelets during this process result in a variety of clinical scenarios ranging from asymptomatic thrombocytopenia to devastating intravascular coagulation. The thrombotic phase of this syndrome can lead to saphenous vein graft occlusion, myocardial infarction, pulmonary embolus, stroke, limb loss, and even death. The incidence of type 2 HIT has been reported to be from 0.4 to 31 percent. Since mass screening is impractical, clinical suspicion of HIT is needed so that diagnostic confirmation with the antibody test can be performed while prompt withdrawal of all heparin therapy and institution of appropriate therapy are carried out. If further heparin therapy cannot be avoided, as in cases in which the patient requires cardiopulmonary bypass, alternative therapy is available and will be discussed later.

The incidence of detection of type 2 HIT in this series was 0.75 percent of patients undergoing cardiopulmonary bypass. Although this is consistent with reports in the literature ranging from 0.4 to 31 percent, we believe that the prevalence of the syndrome may be much greater than is routinely suspected.

One of the problems with recognizing HIT lies in the very definition of the syndrome; i.e., "heparin-induced thrombocytopenia." In this series, 9 of 11 patients (81.8 percent) had platelet counts greater than 100,000 cu/mm at the time of recognition of the syndrome, although on closer inspection there was a mean percent decrease in the platelet count of 50 percent, with a range of 31 to 75 percent. Kappa et al described 3 of 16 patients (19 percent) with thrombotic complications but no thrombocytopenia. As a result of their findings, they suggest the syndrome be referred to as "heparin-induced platelet activation," since thrombocytopenia need not be present.

Another problem in securing a diagnosis of HIT lies in the availability of the appropriate assay for the heparin-dependent platelet antibody. A widely available and often used test is platelet aggregometry. While this test may be highly specific (>92 percent), the sensitivity of the test may vary from about 40 to 80 percent. In 1986, Sheridan et al described a test based on platelet 14C-serotonin release. This test is both highly sensitive and specific (>99 percent). Unfortunately, the test may not be readily available at most institutions which may further delay the confirmation and allow for more chance of laboratory error.

An additional consideration is the timing of cardiac surgery in relation to the initial exposure to heparin. Many patients are admitted to the cardiology service where they are exposed to heparin from multiple sources, eg, heparin flushes, subcutaneous heparin, intravenous heparin, heparin-coated pulmonary artery catheters, and cardiac catheterization. Depending on the urgency to perform surgery as well as outside pressures to limit hospital stays, the time between the initial exposure to heparin and cardiopulmonary bypass may be less than 24 h, leaving little opportunity to observe changes in platelet counts or to allow for adequate clinical and laboratory evaluation.

It is important for the clinician to have a high index of suspicion for HIT in any patient receiving heparin therapy. In our study of 100 control patients, the mean decrease in platelet counts following cardiopulmonary bypass was 26 percent. We recommend routine monitoring of the platelet counts in patients being exposed to heparin and prompt investigation for the heparin-dependent antibody whenever there is a thromboembolic complication. A 30 percent decrease in the platelet count may be significant.

The variety of thromboembolic events is striking and includes strokes, saphenous vein graft occlusions, peripheral arterial ischemia, emboli, deep venous thrombosis, and pulmonary embolus. Indeed, Stead et al described five patients with pulmonary embolism after coronary artery bypass surgery, all documented to have the platelet-dependent antibody. We are currently studying all patients with perioperative thromboembolic complications, regardless of the platelet count.

Controversy remains concerning the type of heparin used and its relative risk for causing HIT. The literature is conflicting, some series showing a higher incidence of HIT with bovine lung versus porcine mucosal heparin, while others suggest the incidence is equally low in both types of preparations. In this series, patients were exposed to porcine mucosal heparin preoperatively and bovine lung heparin during cardiopulmonary bypass. This switching of heparin preparations did not appear to lower the incidence of HIT or lessen the severity of complications, thus suggesting crossover of antigenicity between different preparations of heparin. Furthermore, the literature is varied on the suggestion that low molecular weight heparin or heparinoids decrease the risk of HIT.

Aspirin has been described both for the prevention
and treatment of patients with HIT. In this series, 6 of 11 patients (55 percent) were taking aspirin immediately prior to surgery and 5 of 11 patients (45 percent) had no recent exposure to aspirin. No difference was noted in the incidence of HIT or severity of complications in those patients receiving aspirin. This correlates with Kappa et al. who found, in 40 percent of patients tested, that aspirin failed to prevent heparin-induced platelet aggregation and release in vitro.

Unfortunately, the cure for complications from HIT is as elusive as the diagnosis. The mainstay of therapy in the care of these patients is to suspect the syndrome as early as possible and to eliminate all sources of possible exposure to heparin. As mentioned above, the success of antiplatelet drugs, such as aspirin, dipyridamole, or dextran, has been mixed at best. Other therapy has included thrombolytic therapy, plasmapheresis, and administration of immunoglobulin. If continued anticoagulation is required, warfarin should be administered.

What if the diagnosis of HIT is made preoperatively? One approach is to wait 4 to 8 weeks, or more, until the antiplatelet reaction has vanished and then perform the surgery. This approach is limited by the variable length of time for the antibody reaction to dissipate and is not practical in most patients requiring urgent cardiac surgery. Furthermore, the heparin antibody may be present for years; therefore, it is imperative that a negative antibody test be noted prior to performing the procedure.

Ancrod, a defibrinogenating agent derived from Malayan pit viper venom, has been described as an alternative to heparin for cardiopulmonary bypass in cases of known HIT. Although successfully used, it appears to be associated with increased bleeding.

Iloprost, a prostacyclin analogue, has been used in conjunction with heparin in patients with HIT requiring cardiopulmonary bypass. Iloprost is a strong inhibitor of platelet function, and yet, because of its short half-life of 15 to 30 min, platelet reactivity returns quickly and is associated with less bleeding. Because of its vasodilating activity, iloprost can be associated with severe hypotension resistant to large doses of phenylephrine.

Recombinant hirudin is a homogeneous preparation which directly inhibits thrombin without the need of a cofactor and appears to have minimal interaction with platelets and no immunogenicity problems in early studies. In the future, this may provide an alternative to heparin in patients undergoing cardiopulmonary bypass.

References