Management of Heparin-Induced Thrombocytopenia During Renal Replacement Therapy

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Awareness is increasing concerning the development of antibodies to heparin–platelet factor 4 complex in both regular hemodialysis patients and those treated with continuous forms of renal replacement therapy. Although the development of antibodies does not result in thrombocytopenia or thrombosis in some patients, most patients present with thrombocytopenia, premature platelet activation, and clotting of the extracorporeal circuit. When systemic anticoagulation is also required to treat venous thrombosis, then synthetic heparinoids or recombinant hirudin will be the agents of choice. However, neither the synthetic heparinoids nor hirudin are without problems. A few patients may have cross-reacting antibodies against the currently available heparinoids. Similarly, antibodies may develop against recombinant hirudin, leading to a potentiation of anticoagulant activity and increased risk of hemorrhage.

In the future, thrombin inhibitors such as recombinant hirudin and the arginine derivative argatroban will probably be the agents most widely used to prevent thromboembolic complications. However, anti-platelet agents used alone or in combination with hirudin or synthetic heparinoids may provide adequate treatment by inhibiting both platelet and clotting cascade activation.

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Key words

Heparin-induced antibodies, hirudin, heparinoids, HIT type II

Introduction

It is well recognized that, when patients reach end-stage renal failure and start chronic hemodialysis, an initial, progressive fall in the peripheral platelet count occurs. This occurrence was first attributed to continual exposure to the extracorporeal circuit and repeated platelet activation by the dialyzer membrane. More recently, Shojania and Turnbull [1] showed that most chronic hemodialysis patients who use standard unfractionated heparin as the extracorporeal anticoagulant develop a pro-aggregator that is heparin-dependent, and that the pro-aggregant (antibody) causes increased platelet destruction and a reduction in the peripheral platelet count.

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Other studies in patients treated with standard unfractionated heparin have also reported that heparin may induce a state of thrombocytopenia, usually in a time- and dose-dependent manner. Although the condition responds to a reduction in dosage and is termed heparin-induced thrombocytopenia (HIT) type I, the platelet count usually recovers without any change in the heparin dose and may even rebound to above the pre-heparin values.

Less commonly, an immune-mediated thrombocytopenia occurs as a consequence of heparin therapy. This syndrome (HIT type II) occurs more commonly with bovine heparin (up to 5%) than with porcine heparin (1% or less) [2,3] and is usually due to the development of an immunoglobulin G (IgG) antibody directed against the multimolecular complex of heparin and platelet factor 4 (PF4). Although the incidence of HIT type II is much less with the low-molecular heparins, it can still occur.

Characteristically in cases of HIT type II, the peripheral platelet count falls precipitously, although, occasionally, the platelet count can be maintained [4]. The diagnosis is usually established by using a platelet aggregation assay, incubating the patient's platelet-rich plasma with heparin. This very specific test can be used to confirm the diagnosis, but its sensitivity is low. A negative test does not exclude the diagnosis. The "gold standard" test is still the serotonin release assay, which measures platelet serotonin release from the patient's platelet-rich plasma when incubated with heparin. This highly specific test is fairly sensitive, but is available only in a few laboratories.

If HIT type II is suspected, but the platelet aggregation test is negative, then an antigen assay, using a solid-phase immunoassay should be carried out, using an ELISA plate coated with bound platelet factor 4 complexed with heparin [4]. However, the plasma from patients with HIT type II does not always contain anti–heparin–PF4 antibodies and antibodies may be present even when the patient doesn't have HIT type II. [5].

Typically, HIT type II develops after 5 – 12 days of heparin exposure. Its incidence varies among various patient subsets. The highest incidence, based on ELISA testing, has been reported in cardiac patients following cardiopulmonary bypass surgery [6]. In those patients it ranged from 20% to 50%, depending on the assay used. That incidence compares with 14% – 34% in patients heparinized following vascular surgery [7], and 3.2% – 7.5% in patients given prophylactic subcutaneous heparin following orthopedic surgery, who were prospectively screened. Several small series, ranging from single case reports to prevalence studies, have been reported

in patients anticoagulated for chronic hemodialysis or for acute renal failure treated by continuous forms of hemofiltration or dialysis, and in those treated by plasma exchange or staphylococcal A protein immunoadsorption [8].

Within the hemodialysis population, up to 6% of patients have been reported to develop HIT type II [9,10]. However, most cross-sectional studies have reported a lower prevalence, ranging from 0% to 4.2% with standard unfractionated heparin, and 0.3% with low molecular weight heparin [10]. Interestingly, most of the patients with heparin-associated antibodies did not have thrombocytopenia or an increased risk of systemic thromboembolic or hemorrhagic events [10]. The prevalence appeared to be greater in patients who had recently started hemodialysis as compared with those who had been on long-term treatment. Heparin-induced antibodies are more commonly reported in patients with pre-existing anticardiolipin antibodies [11].

Paradoxically, although more patients develop HIT type II following cardiovascular and general vascular surgery than following orthopedic surgery, more orthopedic patients have been reported to develop the clinical manifestations of the syndrome [6]. This apparent discrepancy has led to much research into characterizing the antibody. Studies have shown that, although the typical antibody is of the IgG isoform, other isoforms, including IgA and IgM, can be present alone or can co-exist [7]. These antibodies bind to the surface of platelets using the PF4 and Fc receptors. In addition, more than one antibody has been described, some can activate platelets even in the absence of heparin [12,13]. This observation may explain the clinical finding of patients with persistent thrombocytopenia despite withdrawal from heparin. Thus, HIT type II is now thought to be associated with a variety of polyclonal and polyspecific antibodies, which develop in patients repetitively exposed to heparin [13].

When platelets are exposed to the dialyzer tubing and dialyzer membrane in the extracorporeal circuit, they are partially activated, exposing PF4. Heparin can bind to the exposed PF4, and this binding can result in the exposure of platelet neo-epitopes, which are potentially antigenic and could lead to the development of HIT in hemodialysis patients or in patients treated by continuous renal replacement therapy.

The differences in the antibodies generated may explain why the risk of thrombosis varies from patient to patient. Some heparin-induced antibodies specifically bind to the heparin–PF4 complex via the Fab region and then to the platelet surface via the Fc receptor [5]. They can also bind to endothelial cells, thus activating not only platelets, but also the endothelium, increasing the risk of venous and arterial thrombosis [14]. Other authors have reported that thrombosis is more likely in the presence of additional upregulation of cell surface adhesion molecules and inflammatory markers, in combination with endothelial and leukocyte activation. Because the antibodies differ in their specificity according to the novel epitope with which they interact, different antibodies may have varying effects on platelet adhesion and the formation of circulating platelet microparticles, which predispose to thrombosis. Other studies that have investigated PF4 sequences to determine whether genetic polymorphisms are important in determining which patients are susceptible to developing both HIT type II and thrombosis have failed to demonstrate any predisposing PF4 phenotypes [15].

Clinical manifestations of HIT type II

Many patients develop HIT type II antibodies without any obvious clinical sequelae [7]. Between 1% and 5% of patients with HIT develop agglutination of platelets and thrombosis—which can be both arterial and venous—due to accelerated platelet aggregation and activation [16]. Once HIT type II develops, the risk of thrombosis significantly increases, even in the asymptomatic patient. One study estimated that patients presenting with HIT type II and without thrombosis had a 52.8% increased risk of thrombosis within the next 30 days [17]. Excessive platelet activation and consumption may occasionally lead to hemorrhage, because patients require alternative anticoagulation. Increased thrombotic events have been reported in cardiac patients who were not thrombocytopenic and who were followed for up to a year after treatment with heparin [18]. This finding is supported by other studies, which have reported neurologic complications—typically cerebrovascular ischemia and cerebral venous thrombosis—in patients with HIT type II and a normal peripheral platelet count [19]. This wide variation in clinical sequelae reflects the underlying intrinsic heterogeneity of the antibodies.

Most hemodialysis patients who show a pro-aggregator response with heparin do not experience clinical sequelae [1]. Typically, hemodialysis patients and those with acute renal failure treated by continuous renal replacement therapy present with clotting of the extracorporeal circuit. When a new extracorporeal circuit is set up, clotting occurs much earlier, and repeatedly.

Management of HIT type II

Once HIT type II is suspected, heparin should be withdrawn immediately, and another anticoagulant started. Antibody levels fall spontaneously following heparin withdrawal, although the peripheral platelet count does not always improve. Once the antibodies have disappeared, some patients have subsequently been successfully re-exposed to heparin during angioplasty without redeveloping type II HIT [20]; however, extreme caution and careful monitoring are mandatory under such circumstances.

In dialysis patients, the subsequent management depends on the clinical situation—whether the patient has evidence of venous or arterial thrombosis, or hemorrhage. If the patient has HIT type II, but no evidence of thrombosis or hemorrhage, then the extracorporeal circuit should be anticoagulated with a systemic anticoagulant in the acute situation. If the episode of HIT occurred in the past, then a regional anticoagulant could be used. If the patient has evidence of major

venous thrombosis, systemic anticoagulant will be required. In the rare case of hemorrhage, a regional anticoagulant or an anticoagulant-free circuit would be required.

Platelet activation is increased even in those cases of HIT type II with normal total peripheral platelet counts. Maintaining the integrity of anticoagulant-free extracorporeal circuits simply by relying on pre-dilution and saline flushes is therefore difficult. Modification of the circuit by using tubing specially coated with nitric oxide release polymers could potentially prevent platelet activation, and allow anticoagulant-free dialysis to take place in a bleeding patient [21]. Although, at present, no reports describe the use of heparin-coated lines or dialyzers in patients with type II HIT, these devices have only recently become available. Reports from intensive care units have described HIT type II in patients monitored with heparin-bonded pulmonary artery occlusion catheters, and in those given daily heparin flushes to maintain central catheter patency [22]. Thus, heparin-coated lines and dialyzers should not be used in cases of HIT type II.

Anticoagulants that have regional action and that inhibit platelet activation have been successfully used in patients without thrombosis or hemorrhage [2,3]. Citrate and the vasodilator prostanoids (prostacyclin, epoprostenol, and prostaglandins E1 and F1) reduce platelet activation in the extracorporeal circuit. Citrate anticoagulation requires the use of a special calcium-free dialysate and an infusion of calcium, adjusted to maintain a normal serum ionized value. The vasodilatory prostanoids may lead to hypotension. Nafamostat mesilate and aprotinin, serine protease inhibitors that act as regional anticoagulants, have been used, but are not successful in maintaining flow through the extracorporeal circuit in patients with evidence of platelet activation.

The most difficult clinical situation is when systemic anticoagulation is required owing to major venous or arterial thrombosis. With the advent of commercially available low molecular weight heparins, these agents were initially used. Although some early reports were positive, it soon became clear that significant cross-reactivity occurred between IgG antibodies to unfractionated and low molecular weight heparin. Recent studies have shown that in cases of HIT type II, cross-reactivity with the low molecular weight heparins is substantial: dalteparin, 89%; nadroparin, 86%; enoxaparin, 83% [23]. Although *in vitro* testing could be carried out to exclude a cross-reacting antibody before a low molecular weight heparin is used, no currently published reports indicate that a negative result assures clinical safety. Thus, the recommendation is that low molecular weight heparins should not be used in cases of HIT type II.

Further development has led to the introduction of synthetic heparinoids. Several case reports have mentioned successful treatment with the synthetic heparinoid danaparoid [24,25]. Clinical testing has shown that there is little cross-reactivity (<10%) in patients with HIT type II [19]; however, a check for cross-reactivity before use would still be prudent [26]. Some centers have reported increased cross-reactivity (28%) in asymptomatic patients who developed HIT type II following cardiac bypass surgery [27]. Case reports also exist of continued dialyzer circuit clotting [28] with danaparoid. Other synthetic pentasaccharide heparinoids that do not contain the highly sulfated glycosaminoglycans of heparin are currently being developed, and these have been reported not to cross-react with anti–heparin–PF4 antibodies from patients with HIT type II [29]. Similarly, dermatan sulfate, another sulfated proteoglycan, has been reported to have been successful in treating dialysis patients with HIT type II.

Another option is to use one of the commercially available recombinant hirudins, desirudin or lepirudin. Hirudin, which is made by the salivary glands of the leech, is the most active and specific inhibitor of thrombin currently known. Several centers have successfully used recombinant hirudin (r-hirudin) in the management of patients with HIT type II [4], and a recent meta-analysis of two prospective trials using lepirudin in symptomatic patients with HIT type II showed that these thrombin inhibitors were effective in reducing further thromboembolic events [30].

Hirudin accumulates in renal failure, because it is normally degraded in the renal tubules. Lower doses are required in renal failure because the half-life is prolonged. Hirudin dosages must therefore be adjusted according to renal function. More recently, it has been recognized that hirudin (unlike standard and low molecular weight heparins) is removed during dialysis by some of the high-flux synthetic membranes. Fortunately, anticoagulation with hirudin can be monitored using the activated partial thromboplastin time (APTT), although the ecarin clotting time provides a more accurate assessment of anticoagulant effect.

As is the case with heparin exposure, continued exposure to r-hirudin may result in antibodies [31]. These antibodies differ from those associated with heparin in that either they have no effect on anticoagulation, or they may actually increase the potency of hirudin. Antibodies to hirudin do not appear to directly potentiate its anticoagulant activity. They bind to hirudin, markedly reduce its renal clearance, and alter its apparent volume of distribution. Thus, if r-hirudin is used repeatedly to treat patients with HIT type II, both types of antibodies should be sought, and the anticoagulant effect should be monitored on each occasion in case antibodies that enhance the effect of hirudin develop and provoke hemorrhage [31].

Hirudin is not the only thrombin inhibitor available. Argatroban is a synthetic derivative of arginine, which binds to the active site on thrombin [32]. This agent has recently been approved by the U.S. Food and Drug Administration. Argatroban is not renally excreted, and therefore does not require dose modification in patients with renal failure [33].

Because HIT type II is associated with platelet activation, several groups have advocated treatment with anti-platelet agents either alone or in combination with r-hirudin [34]. *In vitro,* ADP receptor antagonists such as ticlopidine and clopidogrel, and inhibitors of the glycoprotein platelet surface receptor GP IIb/IIIa, have been shown to block the ef-

fects of heparin-induced antibodies on platelet activation. However, the use of ADP receptor antagonists or platelet receptor inhibitors, or both, will increase the risk of bleeding, and these agents have effects that persist for some time following withdrawal. Indeed, the effective dose of ticlopidine is somewhat high. A standard dose of clopidogrel, in combination with a reduced dose of recombinant hirudin or synthetic heparinoid, may be efficacious in preventing further HIT type II induced thrombosis, while reducing the risk of hemorrhage [34].

Summary

An increasing number of chronic hemodialysis and acute renal failure patients treated with heparin anticoagulation have been reported to develop the HIT type II syndrome. The incidence appears to be increased in those recently starting hemodialysis. The condition may occur without thrombocytopenia. Similarly, in many reports, no increased risk of systemic thromboembolic or hemorrhagic events has been noted. Thus, most hemodialysis patients with a positive antibody test do not experience systemic clinical sequelae. However, the increased platelet activation leads to accelerated clotting of the extracorporeal circuit, resulting in shortened circuit life.

Management includes withdrawal of heparin or use of low molecular weight heparin. When systemic anticoagulation is not required, several groups have reported success with regional anticoagulants, including citrate and prostacyclin. The latter acts mainly by inhibiting platelet function, and it has not proved particularly successful in our own unit. We and others have used synthetic heparinoids such as danaparoid. However, because a risk of cross-reactivity exists between the heparin-induced antibody and the synthetic heparinoids, testing should ideally be undertaken before heparinoid use. If testing cannot be performed, or if cross-reactivity occurs, then recombinant hirudin is the agent of choice. Hirudin is not without complications. It has a prolonged half-life in renal failure, and later development of antibodies could prolong its anticoagulant action because of decreased clearance. However, it is also lost during dialysis. In the future, combinations of oral anti-platelet agents and either recombinant hirudin or synthetic heparinoids may become the preferred treatment for HIT type II.

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