Heparin-associated Thrombocytopenia and Thrombosis

Implications for Perioperative Management

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SINCE its discovery 80 yr ago, heparin has become a valuable component of medical therapeutics.1 Lack of an alternative, rapidly acting, and reversible anticoagulant makes heparin one of the most widely prescribed pharmaceutical agents in hospitalized patients. Unfortunately, a subpopulation of patients exposed to heparin develop antibodies that induce thrombocytopenia and, almost paradoxically in some cases, thrombosis.2 This clinical syndrome of immune complex–mediated thrombocytopenia, thrombosis, or both after heparin therapy comprises the condition of heparin-associated thrombocytopenia (HAT). Lack of standardized diagnostic criteria and limited availability of screening tests contribute to the misconception that HAT rarely occurs in patients having surgery. However, recent evidence suggests that heparin-associated antibodies are more prevalent than previously suspected and may even contribute to perioperative morbidity.

Historical Perspective

Although the anticoagulant activity of heparin was described initially in 1916,1 it was not used clinically until the 1930s.3 In 1941, descriptions of acute thrombocytopenia after heparin administration in laboratory animals4 and humans5 were published. The limited nature of this thrombocytopenic response appeared of little clinical importance. However, in 1958, Weisman and Tobin reported arterial embolism in 10 patients receiving heparin, and they first suggested that these cases represented a complication of “vigorous heparin therapy.”2 In 1964, Roberts et al.6 described 11 patients with unexplained arterial embolization during heparin therapy and suggested that an antigen–antibody mechanism might play a role in these complications. This hypothesis was subsequently confirmed by Rhodes et al.7 in 1973. Using complement fixation and aggregation absorption studies, these authors found a heparin-associated antibody in two patients experiencing HAT complicated by thrombosis.

Clinical Features

Heparin-associated thrombocytopenia typically develops 7–14 days after heparin therapy is initiated. However, in patients with previous exposure to heparin, signs may develop within 1 or 2 days.8,9 Although thrombosis after heparin therapy has been reported in the absence of thrombocytopenia, in most cases these patients experienced a decrease in platelet count before the thrombotic event.10,11 Although severe thrombocytopenia may develop in association with HAT, bleeding rarely occurs in patients who have not had surgery.9

Heparin-associated thrombocytopenia is differentiated into two subtypes based on the severity of the thrombocytopenic response to heparin.12,13 Patients with type I HAT experience a mild and usually asymptomatic thrombocytopenia during heparin therapy. In

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contrast, patients with type II HAT experience a more severe thrombocytopenia and are more likely to experience thrombotic complications. Unlike other drug-induced causes of platelet destruction, type II HAT typically resolves only after heparin is discontinued. Type I HAT often resolves despite continued exposure to heparin and may represent an exaggerated form of the normal acute platelet aggregatory response to heparin.\(^{14,15}\) Whether the two subtypes of HAT represent independent pathophysiological processes or merely variable responses to heparin-associated antibodies is unknown. Given the relatively benign course of type I HAT, the rest of this review will specifically focus on the pathophysiology, diagnosis, and management of type II HAT. Further, because categorization of patients into a particular subtype of HAT occurs only after retrospective examination of the patient’s clinical course and because available diagnostic tests cannot differentiate subtypes of HAT, any patient who becomes thrombocytopenic during heparin therapy should be considered at risk for thrombosis.

In cases of heparin-associated thrombosis, HAT is frequently diagnosed only after the thrombotic event has occurred. These thromboses are most often arterial and involve major vessels of the extremities\(^{6,16}\) and less frequently the cerebral\(^{17,18}\) and mesenteric vasculature.\(^{11}\) Thrombotic complications as a result of HAT have also been implicated in myocardial infarction,\(^{19,20}\) skin necrosis,\(^{21,22}\) and infarction of the kidney\(^{23}\) and adrenal gland.\(^{24,25}\)

The role of HAT in venous thrombosis is less clearly established. Although recurrent venous thromboses and pulmonary emboli have been reported in patients with HAT,\(^{20,21,26}\) whether these complications represent an adverse response to heparin or merely an extension of the preexisting thrombotic disorder for which heparin therapy was instituted is often difficult to discern.

Thromboses in patients with HAT frequently are extensive and involve multiple anatomic sites.\(^{8,25,27}\) The incidence of thrombosis in HAT is unknown, but when it occurs, morbidity and mortality rates approach 80% and 50%, respectively.\(^{8,11,28}\) As many as 20% of patients experiencing thrombosis of an extremity ultimately require amputation of the limb.\(^{29-31}\)

**Incidence**

Although recent evidence suggests the incidence of HAT after full-dose heparin therapy approximates 3%, previously published trials report incidence rates between 1.1% and 50%.\(^{32-36}\) Lack of standard diagnostic criteria and limited sensitivity and specificity of diagnostic tests contribute to these widely varying estimates. Whether the incidence of HAT relates to the heparin dose is unknown, but limited exposure to heparin does not preclude development of this disease. Heparin-associated thrombocytopenia has been reported after low-dose subcutaneous heparin\(^{37-39}\) and after exposure to heparin-containing arterial catheter flush solutions\(^{40}\) and heparin-coated pulmonary artery catheters.\(^{33}\)

The type of heparin administered appears to influence the risk of HAT developing. Pooled estimates, based on recent prospective investigations, demonstrate a 2.9% incidence of HAT in patients exposed to bovine heparin compared with a 1.1% incidence in patients receiving porcine heparin.\(^{36}\) The risk of HAT may be even lower in patients given low molecular weight heparin. In a recent investigation comparing prophylactic anticoagulant regimens for deep venous thrombosis after orthopedic surgery, Warkentin et al.\(^{42}\) reported a 2.7% incidence of HAT in patients receiving prophylactic doses of unfractionated heparin and no cases of HAT in patients receiving low molecular weight heparin. Although isolated cases of HAT have been reported after treatment with low molecular weight heparins, \textit{in vitro} and \textit{in vivo} evidence suggests that low molecular weight heparins are less likely to induce thrombocytopenia and thrombosis.\(^{43,44}\)

**Pathophysiologic Characteristics**

The mechanism by which heparin causes thrombocytopenia is incompletely understood. Heparin-associated thrombocytopenia differs from other drug-induced thrombocytopenias in that platelets are activated before being cleared from the circulation.\(^{45}\) Whether binding of immune complexes to the platelet surface or subsequent platelet activation is primarily responsible for premature clearance from the circulation is unknown. Intravenous gammaglobulin\(^{46}\) and aspirin\(^{12}\) attenuate the thrombocytopenic response to heparin, which suggests that both mechanisms play a contributory role.\(^{47}\)

The appearance of thrombocytopenia 7–14 days after heparin therapy suggests an immune-mediated mechanism for platelet destruction in HAT. Laboratory investigations further support this observation. Heparin-associated platelet aggregating factor appears in the immunoglobulin serum fraction. Both Fc antibody fragments...
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Fig. 1. Proposed mechanisms of thrombosis in HAT. Specific antibodies to the heparin/platelet factor 4 (PF4) complex generate immune complexes that bind to and activate platelets by way of FcγRII receptors. Activated platelets release procoagulant microparticles, which provide a phospholipid surface to accelerate thrombin generation. In addition, heparin/PF4 immune complexes activate the extrinsic pathway of coagulation by binding to the vascular endothelial surface to induce localized expression of tissue factor.

and monoclonal antibodies to the platelet Fc receptor inhibit heparin-associated platelet aggregation, which suggests that heparin, or more likely heparin-immune complexes, activate platelets by binding the platelet Fc receptor (FcγRII). Amiral et al. showed recently that a complex of heparin and platelet factor 4 (PF4) is the antigenic target for heparin-associated antibodies. Platelet factor 4 is a heparin-binding protein found in plasma, stored in platelet alpha-granules, and released during platelet activation. In most patients, heparin/PF4 complexes do not produce adverse sequelae. However, in patients with HAT, antibodies to the heparin/PF4 complex generate immune complexes that bind to platelet FcγRII receptors, resulting in platelet activation.

The mechanism by which HAT is thought to initiate thrombosis is depicted in figure 1. Warkentin et al. found that serum and purified IgG from patients with HAT induce platelet activation and result in generation of procoagulant platelet-derived microparticles. These microparticles, which have been identified in the blood of patients with HAT, provide a phospholipid surface that accelerates formation of thrombin. Thrombin generation, a major regulatory step in coagulation, contributes to further platelet activation and generation of fibrin clot.

Vascular endothelial injury may contribute to the pathogenesis of thrombosis in HAT. Endothelial cell binding sites for heparin have long been recognized. More recently, IgG from the serum of patients with HAT was shown to bind to endothelial cells, promoting vascular endothelial expression of tissue factor, the primary mediator of plasma coagulation in vivo. The vascular endothelial target for heparin-associated antibodies appears to be a complex of heparin, or a heparin-like molecule, and PF4. Platelet factor 4 released during platelet activation and exceeding the binding capacity of plasma heparin presumably binds to heparin-like proteoglycans on the endothelial surface to provide a target for heparin-associated antibodies.

Clinical observations suggest that preexisting vascular endothelial damage may further potentiate thrombosis associated with HAT. Makhoul et al. observed that 19 of 25 patients with HAT and an arterial or venous thrombotic complication experienced the thrombosis in a previously catheterized vessel. Patients having surgery who are subjected to preoperative vascular catheterization and intraoperative trauma may be at particular risk for thrombosis associated with HAT.

Two additional clinical investigations showed an association of adverse postoperative outcome with HAT. In the first, the authors reviewed hospital records for patients with HAT who subsequently underwent vascular procedures requiring repeated exposure to heparin. Three of four patients with HAT who were not receiving antiplatelet medication suffered major vascular thromboses after repeated exposure to heparin, compared with no thrombotic events in nine patients receiving antiplatelet medications before repeated exposure to heparin. In a subsequent investigation, 70 patients with HAT undergoing coronary artery bypass graft surgery in the absence of antiplatelet medication experienced a 44% incidence of thromboembolic complications and a 33% incidence of postoperative death. Preoperative identification of HAT and treatment with antiplatelet medication resulted in no thromboembolic complications or deaths. Limitations of these investigations include their retrospective designs and the limited sensitivity and specificity of the platelet aggregation assay used to detect heparin-associated antibodies. No attempt was made preoperatively to screen patients for heparin-associated antibodies. Reliance on thrombocytopenia, thrombosis, or both to identify patients with HAT may have led the investigators to underestimate the prevalence of heparin-associated antibodies in this patient population. A recent report of a sensitive enzyme-linked immunosorbent assay for antibodies to the
Diagnostic Methods

Clinical investigation of HAT has been hampered by lack of sensitive and specific diagnostic tests. Currently available assays rely on detection of the activation or aggregation of donor platelets incubated with patient serum containing heparin-associated antibodies. The diagnostic “gold standard” has been the [14C]-serotonin release assay described by Sheridan et al. However, this test is performed by incubating washed donor platelets containing [14C]-serotonin in the presence of the test patient’s serum and both therapeutic and high concentrations of heparin. The presence of serotonin release at therapeutic, as opposed to high, concentrations of heparin indicates a positive test, which identifies the presence of heparin-associated antibodies. The serotonin release assay is effective in identifying HAT, with sensitivity and specificity rates of 99%. Unfortunately, specialized skills needed to perform this assay limit its application to research settings.

Platelet aggregation studies that mix normal donor platelets and patient serum in the presence and absence of heparin represent the most widely used diagnostic assay for HAT. Using carefully selected reactive donor platelets, sensitivity and specificity of aggregation studies approach 81% and 100%, respectively. Chemiluminescent detection of adenosine triphosphate release after platelet activation may further increase the diagnostic sensitivity of platelet aggregation studies for heparin-associated antibodies. A recently developed enzyme-linked immunosorbent assay to detect antibodies to the heparin/PF4 complex in plasma may be the most sensitive, specific, and widely applicable diagnostic test for HAT.

Because early diagnosis of HAT provides an opportunity to intervene and reduce the morbidity and mortality associated with this condition, any patient receiving heparin who subsequently develops thrombocytopenia or a thrombotic complication should be evaluated for the presence of heparin-associated antibodies. Some experts recommend that all patients receiving heparin should have platelet counts monitored at least twice each week. Laster et al. demonstrated a 50% reduction in morbidity associated with HAT after introducing daily monitoring for thrombocytopenia during heparin therapy. Because thrombosis may occur early in the course of HAT before the nadir in platelet count, any unexpected decrease in platelet count during heparin therapy should arouse the clinician’s suspicion for the presence of heparin-associated antibodies. However, because diagnosis of HAT requires more than the presence of thrombocytopenia concurrent with heparin therapy, Chong suggests that the diagnosis be based on four criteria: (1) thrombocytopenia during heparin therapy; (2) absence of other causes of thrombocytopenia; (3) resolution of thrombocytopenia after discontinuation of heparin and (4) confirmation of a heparin-dependent platelet antibody by in vitro testing.

Anticoagulation of the Nonsurgical Patient with Heparin-associated Thrombocytopenia

The most essential step in treating any patient with HAT is immediate discontinuation of heparin. Various approaches are at least partially effective in preventing recurrent thrombosis and thrombocytopenia in these patients. Although substitution of warfarin for heparin provides protection, most patients require interim anticoagulation during the 3–5 days needed to achieve an anticoagulant effect from warfarin. Antiplatelet agents such as aspirin and dipyridamole may offer some protection, but they have not proved entirely effective in preventing heparin-associated platelet aggregation.

The most successful approaches to anticoagulation of patients with HAT rely on use of a low molecular weight heparin or a heparinoid. Although 80–90% of low molecular weight heparins cross-react with antibodies responsible for HAT, these drugs have been safely administered to patients after first demonstrating the absence of platelet aggregation during in vitro screening of the patient’s serum. The heparinoid danaparoid sodium (Orgaran TM; Organon Inc., West Orange, NJ) appears to be the most promising treatment for thrombosis in patients with documented HAT. This anticoagulant consists of a mixture of polysulfated glycosaminoglycans—primarily heparan sulfate, dermatan sulfate, and chondroitin sulfate. Because danaparoid cross-reacts with the heparin-associated antibody in only 10–20% of cases, this agent has been widely administered to pro-
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vide anticoagulation in patients at risk for HAT and thrombosis. 

**Perioperative Management of the Patient with Heparin-associated Thrombocytopenia**

The patient with HAT requiring anticoagulation for vascular or cardiac surgery presents a particular challenge for perioperative management. Although other anticoagulants have become available during the past decade, lack of a way to rapidly reverse activity of these drugs limits their application in the perioperative setting. No large-scale trials describe management of intraoperative anticoagulation for the patient with HAT. However, based on case reports and knowledge gained from treating the patient not having surgery who requires anticoagulation, we recommend an approach for perioperative management. Successful methods for providing perioperative anticoagulation in the patient with HAT follow one of three approaches: (1) delay surgery until the patient's plasma no longer induces platelet aggregation in the presence of heparin; (2) administer platelet inhibitors in addition to heparin; and (3) provide an alternative anticoagulant.

Because HAT has an immunologic basis, circulating antibody concentrations in most patients will decrease in time to a value at which an immediate thrombotic response to heparin is unlikely. Several reports describe successful application of this approach to the patient with HAT, with the crucial proviso that the patient receive no additional heparin beyond intraoperative exposure. Anecdotally, additional heparin exposure from arterial catheter flush solutions or heparin-coated pulmonary artery catheters has resulted in recurrent thrombocytopenia and thrombosis. Further, preoperative *in vitro* testing must confirm that heparin-associated platelet aggregation is no longer present. Duration of a positive aggregatory response to a heparin challenge varies. Although the proaggregatory response may resolve in a few weeks, heparin-induced platelet aggregation has been reported months after the initial episode of HAT. Unfortunately, many patients requiring major vascular or cardiac surgery cannot postpone surgery for the period required to clear heparin-associated antibodies from the circulation.

Plasmapheresis may accelerate elimination of heparin-associated antibodies. Several reports in nonsurgical patients describe symptomatic resolution of HAT within several days of initiating plasmapheresis. Although heparin-associated platelet aggregation also resolves, response of these patients to repeated heparin exposure is unknown. Further, plasmapheresis necessitates multiple exchange transfusions of fresh frozen plasma and the attendant risk of transfusion-transmitted diseases.

Several reports describe successful administration of heparin in the patient with HAT after treatment with platelet inhibiting drugs. Aspirin, dipyriddamole, and the prostanooid inhibitor iloprost have each been effective in this setting. Unfortunately, aspirin and dipyriddamole do not inhibit platelet aggregation reliably in the presence of heparin-associated antibodies. Aspirin inhibited *in vitro* heparin-associated platelet aggregation in only 50% of patients with HAT. Before reexposing these patients to heparin, efficacy of aspirin or dipyriddamole at inhibition of heparin-associated platelet aggregation should be confirmed *in vitro*. Iloprost also has partial efficacy inhibiting platelet aggregation in HAT. Patients receiving a continuous infusion of iloprost have received normal doses of heparin for cardiac or vascular surgery without complication. However, vasoconstrictors frequently are necessary to counteract the vasodilating effects of iloprost.

Selecting an alternative anticoagulant to heparin appears to provide the safest approach to perioperative management of patients with HAT (table 1). The heparinoid danaparoid has been particularly successful in this setting. Although low molecular weight heparins may be considered, these drugs cross-react with heparin-associated antibodies in 80-90% of cases, thus limiting their applicability. Because there is a small but definite risk of cross-reactivity between danaparoid and heparin-associated antibodies, preoperative *in vitro* testing must be performed to ensure compatibility in an individual patient. Use of either a low molecular weight heparin or heparinoid complicates perioperative management of anticoagulation. Anticoagulant activity of these drugs is prolonged, and antagonists are currently unavailable. Further, because the major anticoagulant activity of these drugs occurs by inhibiting coagulation factor Xa, thrombin-based measures of anticoagulation such as the activated coagulation time and activated partial thromboplastin time are not useful for titrating the administration of these drugs. Although several reports describe the use of danaparoid for cardiopulmonary bypass in the patient with HAT, lack of an effective neutralizing agent resulted in increased transfusion requirements in these patients. Clinical experience with anticoagulants other than the low molecular weight heparins and danaparoid in

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Table 1. Alternative Anticoagulants for the Patient with Heparin-associated Antibodies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>Chemical Structure</th>
<th>Mechanisms of Action</th>
<th>Cross-reactivity with Heparin Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low molecular weight heparins</td>
<td>Porcine and bovine mucosa extract; synthetic</td>
<td>Glycosaminoglycans; mean MW 4–6.5 kDa</td>
<td>Inhibits factor Xa &gt; thrombin</td>
<td>Yes; 90%</td>
</tr>
<tr>
<td>Heparinoid</td>
<td>Porcine mucosa extract</td>
<td>Mixture of heparan, dermatan, and chondroitin sulfates</td>
<td>Inhibits factor Xa &gt; thrombin</td>
<td>Yes; 10%</td>
</tr>
<tr>
<td>Ancrod</td>
<td>Malayan pit viper venom extract</td>
<td>&quot;Thrombin-like&quot; enzyme, Arginine analog</td>
<td>Proteolysis of fibrinogen, Thrombin active site inhibitor</td>
<td>No</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Synthetic</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Hirudin</td>
<td>Leech salivary gland extract</td>
<td>66 amino acid polypeptide</td>
<td>Thrombin active site inhibitor</td>
<td>No</td>
</tr>
<tr>
<td>Hirulog</td>
<td>Synthetic</td>
<td>Hirudin-derived peptide Prostacyclin analog</td>
<td>Thrombin active site inhibitor</td>
<td>No</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Synthetic</td>
<td></td>
<td>Adenyl cyclase activator, Cyclooxygenase inhibitor</td>
<td>No; limited anticoagulant efficacy</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Synthetic</td>
<td>Acetylsalicylic acid</td>
<td></td>
<td>No; limited anticoagulant efficacy</td>
</tr>
</tbody>
</table>

patients with HAT requiring surgery is limited. Ancrod, a fibrinogen-depleting enzyme derived from venom of the Malayan pit viper, has been administered successfully as an anticoagulant in nonsurgical patients who have HAT complicated by thrombosis. In addition, cardiopulmonary bypass has been successfully performed using ancrod as an alternative to heparin, and several reports describe use of this agent in patients with HAT requiring cardiopulmonary bypass. Unfortunately, lack of an effective way to reverse anticoagulant activity of this agent results in increased postoperative bleeding. In addition, ancrod must be administered hours before surgery to achieve the desired reduction in fibrinogen concentration. As clinical applications of specific thrombin inhibitors become more widespread, these agents may provide additional alternatives for anticoagulation in the patient with HAT. Both hirudin and argatroban have been administered successfully in this setting. However, as with other currently available alternatives to heparin, intraoperative use of these drugs remains limited by their prolonged duration of action and the absence of effective neutralizing agents.

Despite recent improvements in diagnosis and management of HAT, many patients with this disease are identified only after a thrombotic complication. Until effective alternatives to heparin become more widely available, prevention of thrombotic complications of HAT must rely on minimizing heparin exposure and identifying high-risk patients before thrombosis occurs. Recent evidence suggests that patients having surgery may be at particular risk for thrombotic complications associated with this disorder. Although the incidence of HAT in patients having surgery remains unknown, this condition is undoubtedly more common than currently acknowledged and may represent a risk factor for adverse postoperative outcome. Further investigations are needed to define the incidence of HAT associated with surgery and the optimal approach to peroperative treatment of these patients.

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