Thrombocytopenia Associated With Heparin-Coated Catheters in Patients With Heparin-Associated Antiplatelet Antibodies

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- Thrombocytopenia was associated with the presence of heparin-coated pulmonary artery catheters in 12 patients with heparin-associated antiplatelet antibodies. The thrombocytopenia persisted so long as the heparin-coated catheters were in place, even when all other sources of heparin were discontinued. The high morbidity and mortality associated with heparin-induced thrombocytopenia mandates that heparin administration cease and that all heparin-coated catheters be removed from patients with heparin-associated antiplatelet antibodies.

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Pulmonary artery catheters have an important role in the care of critically ill patients. Since the introduction of the catheters in 1971, many serious complications including premature atrial or ventricular contraction, catheter sepsis, subclavian vein and/or superior vena cava thrombosis, pulmonic valve perforation, pulmonary infarction, transient consumptive thrombocytopenia, pneumothorax, skin infection, pulmonary artery rupture, and knotting of the catheter within the right ventricle have been associated with their use. Heparin-coated pulmonary artery catheters were introduced clinically in 1981 to reduce the risk of catheter-associated thrombosis.

We report a case of thrombocytopenia associated with a heparin-coated pulmonary artery catheter in a patient with known heparin-associated antiplatelet antibodies, and review 11 other similar cases. The thrombocytopenia persisted so long as the heparin-coated pulmonary artery catheters remained in place, even when other sources of heparin had been eliminated.

REPORT OF A CASE

A 66-year-old man was admitted to the vascular surgery service with an abdominal aortic aneurysm. The patient was first exposed to heparin in 1980 by the infusion of saline solution containing heparin to maintain the patency of an arterial pressure catheter, when he had an anterior cerebral artery aneurysm "clipped." Later in 1980, the patient required a sigmoid colectomy for diverticulitis and received subcutaneous heparin for venous thromboembolism prophylaxis. The patient experienced no thrombocytopenia or thromboembolic episodes during these exposures.

The patient was referred for management of the aortic aneurysm in September 1987. At the time of admission, his platelet count was $253 \times 10^9$/L (Figure). On the day of admission, he received 1500 U of heparin intravenously during an aortogram. Three days later, a heparin-coated pulmonary artery catheter was placed and the aneurysm was replaced with a Dacron graft. During surgery, the patient received a bolus of 7000 U of heparin intravenously and a heparin infusion (500 U/h) was continued postoperatively. The patient received six units of packed red blood cells during the operation and the next 24 hours.

The platelet count was $98 \times 10^9$/L immediately after surgery and was $43 \times 10^9$/L on the morning of the first postoperative day, at which time the patient's left leg was noted to be cool, pulseless, pale, and paresthetic. A left thrombectomy was performed and a "white clot" was removed from the left limb of the graft. The next day, a four-compartment fasciectomy of the left leg was done; the platelet count was $50 \times 10^9$/L. All heparin therapy was discontinued and the heparin-coated pulmonary artery catheter was removed. The patient received a transfusion of six platelet packs on the next day in response to bleeding from the lower leg incisions, while the platelet count was $45 \times 10^9$/L. The platelet count rose to $75 \times 10^9$/L after infusion of the platelets; the patient was not receiving heparin at this time.

The platelet count increased to $165 \times 10^9$/L on the morning of the second day after the cessation of heparin therapy. At this time, the patient's cardiovascular function was deteriorating. A heparin-coated pulmonary artery catheter was placed and the platelet count fell to $102 \times 10^9$/L within 24 hours. Results of platelet aggregation studies were positive, indicating the presence of heparin-associated antiplatelet antibodies. The heparin-coated pulmonary artery catheter was removed and a non-heparin-coated pulmonary artery catheter was inserted. The platelet count rose to $125 \times 10^9$/L by the next day and to $207 \times 10^9$/L in 2 days after the insertion of the non-heparin-coated catheter.

At the time of heparin-coated catheter placement, the patient was receiving aspirin (325 mg/d), dipyridamole (25 mg three times a day), and dopamine (3 to 15 µg/kg per minute). The thrombocytopenia was the only abnormality of the hematologic profile that was noted.
Blood for platelet counts was collected in ethylenediaminetetraacetic acid tubes. The counts were made with a Coulter counter (Coulter Electronics Inc, Hialeah, Fla).

The heparin-associated antiplatelet antibodies were demonstrated by a previously described method using platelet aggregometry. Samples of the patient's plasma (experimental) and fresh plasma obtained from volunteer donors (control) known to have no prior heparin exposure were simultaneously tested for their ability to aggregate platelets when heparin was added to the test system.

A summary of 12 cases of thrombocytopenia associated with heparin-coated pulmonary catheters appears in the Table.

**COMMENT**

Flow-directed pulmonary artery catheters were introduced clinically in 1970 and have a well-defined role in the care of critically ill patients. Early catheters were thrombogenic and instances of major and sometimes fatal thromboembolic complications were reported. In 1971 described applying a heparin—benzalkonium chloride complex to the exterior of angiography catheters to prevent fibrin deposition and thrombosis. This remains the most commonly used coating for pulmonary artery catheters.

In 1981, Hoar and associates described 20 patients having open-heart procedures who had pulmonary artery catheters placed preoperatively. Ten of them received heparin-coated catheters and 10 received non—heparin-coated catheters. At operation, all 10 non—heparin-coated catheters exhibited thrombus formation, while the 10 heparin-coated catheters were thrombus free. Heparin-coated pulmonary artery catheters were introduced for clinical use in 1981 and are now the most common pulmonary artery catheters used.

It has been suggested that the thromboresistance of heparin-coated catheters is related to the elution of heparin from the catheters. Idezuki and associates have noted that an elution rate of heparin greater than $4.0 \times 10^4$ g/cm² per minute is required for catheter antithrombogenicity. However, Basmadjian and Sefton, while noting the elution of heparin from catheters, have speculated that the antithrombogenicity of heparin-coated catheters “must be attributed to the action of the bound heparin.” While the reason for the decreased thrombogenicity of heparin-coated catheters remains unclear, it appears that all heparin-coated catheters release heparin into the solutions with which they are in contact.

The heparin—benzalkonium chloride complex used to coat catheters is relatively insoluble in water. However, when exposed to plasma, the heparin is exchanged with plasma proteins that are deposited on the catheter surface. Kramer et al demonstrated that tritiated heparin-Silastic beads incubated in normal saline lost 28% of their radioactivity in the first hour, while similar beads incubated in plasma lost 48% of their radioactivity in the first hour. Tritiated heparin-coated Silastic beads incubated for 21 days in normal saline retained 33% of their heparin activity, while similar beads incubated in plasma for 21 days only retained 12% of their activity, indicating that heparin eluted from heparin-coated Silastic beads into the plasma.

We have demonstrated similar heparin elution in the laboratory. One-centimeter segments of heparin-coated pulmonary artery catheters, incubated in the plasma of patients with known heparin-associated antiplatelet antibodies and normal platelets, induced platelet aggregation. However, incubation of non—heparin-coated catheter segments in the serum of patients with heparin-associated antiplatelet antibodies and normal platelets failed to induce platelet aggregation.

The heparin-induced thrombocytopenia syndrome is recognized complication of heparin administration, occurring in 0.6% to 30% (average, 5% to 6%) of all patients receiving heparin. There are no known risk factors for the occurrence of this syndrome, i.e., the syndrome occurs in patients of all ages and both sexes and is independent of dose, route of administration, and type of heparin administered. The occurrence rate may be slightly increased in patients receiving bovine heparin compared with patients receiving porcine heparin. The usual time for presentation in patients receiving

![Diagram showing relationship between platelet count and development of "white clot" in patient with heparin-associated antibodies who received heparin therapy and heparin-coated catheters. In 1980, the patient received heparin during cerebral aneurysm clipping; in 1987, he received heparin after sigmoid colectomy.]

<table>
<thead>
<tr>
<th>Patient Profiles</th>
<th>Platelet Count With Catheter In Place, x 10^11</th>
<th>Platelet Count With Catheter Removed, x 10^11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No./Age, y/Sex</td>
<td>Diagnosis/Procedure</td>
<td></td>
</tr>
<tr>
<td>1/45/M</td>
<td>Multiple trauma/long bone fracture</td>
<td>50</td>
</tr>
<tr>
<td>2/62/M</td>
<td>Abdominal aortic aneurysm/aortobifemoral bypass</td>
<td>71</td>
</tr>
<tr>
<td>3/57/M</td>
<td>Perforated cecal carcinoma/exploratory laparotomy with ileostomy</td>
<td>17</td>
</tr>
<tr>
<td>4/71/M</td>
<td>Abdominal aortic aneurysm/aortobifemoral bypass</td>
<td>68</td>
</tr>
<tr>
<td>5/47/M</td>
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<tr>
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<td>49</td>
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<tr>
<td>7/66/M</td>
<td>Abdominal aortic aneurysm/aortobifemoral bypass</td>
<td>109</td>
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<tr>
<td>8/57/F</td>
<td>Thoracoabdominal aneurysm/aortobifemoral bypass</td>
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<tr>
<td>9/81/F</td>
<td>Abdominal aortic aneurysm/aortobifemoral bypass</td>
<td>41</td>
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<td>10/79/F</td>
<td>Thoracoabdominal aneurysm/no operation</td>
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<td>Infected aortic graft/axillobifemoral bypass</td>
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</tr>
<tr>
<td>12/66/M</td>
<td>Abdominal aortic aneurysm/aortobifemoral bypass</td>
<td>43</td>
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</tbody>
</table>

*Numbers in parentheses indicate number of days after catheter removal.
heparin for the first time is the eighth day of heparin administration, while those patients who have received heparin previously may experience the onset of heparin thrombocytopenia as early as the first or second day of the reexposure to heparin. We have demonstrated that even miniscule amounts of heparin, on the order of 3 U/h, can result in significant thrombocytopenia. The heparin-induced thrombocytopenia syndrome has been associated with a 22.5% morbidity rate and a 12% mortality rate. The mortality rate in patients developing complications as a result of the heparin-induced thrombocytopenia syndrome may be as high as 55%.

Daily platelet count monitoring of all patients receiving heparin, with cessation of heparin administration when an unexplained platelet count decrease occurs, significantly reduces the morbidity and mortality associated with the heparin-induced thrombocytopenia syndrome. Our criteria for performing platelet aggregation studies are increasing heparin resistance, a rapidly falling platelet count, or an absolute platelet count of less than 100 × 10^9/L while the patient is receiving heparin.

We advocate inhibition of platelet function with aspirin in all patients who develop heparin-associated platelet antibodies. Our experience indicates that platelet function inhibition in these patients reduces the risk of thromboembolic complications.

Twelve patients (Table 1) with heparin-associated antiplatelet antibodies who developed thrombocytopenia while having hemodynamic monitoring with heparin-coated pulmonary artery catheters have been identified in our institution. All demonstrated marked thrombocytopenia while the heparin-coated catheters were in place, even when all other sources of heparin had been discontinued. When the heparin-coated catheters were removed, the platelet counts returned to more normal levels in all patients. All of the patients had had prior heparin exposure or were receiving heparin at the time of insertion of the heparin-coated pulmonary artery catheters. We believe that the slow release of the heparin from the catheters contributed to the development of heparin-associated antiplatelet antibodies in some of the patients.

Most patients in whom pulmonary artery catheters are placed are receiving, or will receive, heparin. Most pulmonary artery catheters in use today are heparin-coated. Approximately 0.4% of our patients with heparin-coated pulmonary catheters developed thrombocytopenia that was related to the catheter. The widespread use of these heparin-coated catheters, especially in unstable and/or critically ill patients, makes it mandatory that these patients' platelet counts be monitored. If a patient has a falling platelet count or a platelet count below 100 × 10^9/L, the administration of heparin should be stopped and the heparin-coated catheter should be removed or replaced with a non-heparin-coated catheter. It is advisable that testing be done to determine whether heparin-associated antibodies are present. If the catheter remains in place or if heparin administration continues, the patient with heparin-associated antiplatelet antibodies is at risk for developing thromboembolic complications.

CONCLUSIONS

We found 12 patients to have heparin-induced thrombocytopenia that was related to the presence of heparin-coated pulmonary artery catheters. The thrombocytopenia persisted when all other sources of heparin were discontinued, until the heparin-coated catheters were removed.

Patients with heparin-associated antiplatelet antibodies should not receive heparin or heparin-coated pulmonary artery catheters. If these patients require a pulmonary artery catheter, a non-heparin-coated catheter should be used.

References