Factor XII Deficiency and Cardiopulmonary Bypass

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Abstract: Factor XII deficiency is a laboratory finding in patients who normally do not present with bleeding tendencies. This deficiency is important in the patient undergoing cardiopulmonary bypass because activated clotting times are not helpful in determining proper levels of heparin anticoagulation and its reversal. We present a case of a patient with factor XII deficiency that had coronary artery bypass grafting and cardiopulmonary bypass using heparin for anticoagulation. Cardiopulmonary bypass was successfully carried out by monitoring heparin concentration ensuring adequate heparinization during the procedure. Results from activated clotting time, heparin dose–response, and heparin protamine titration are given. Heparin anticoagulation in patients with factor XII deficiency can be safely carried out with heparin concentration monitoring. Keywords: cardiopulmonary bypass, anticoagulation, Factor XII deficiency.

Factor XII is an autosomal-recessive disorder that is not associated with increased risk of bleeding. Factor XII deficiency is typically discovered in individuals with a prolonged activated partial thromboplastin time (aPTT). Homozygous individuals have undetectable factor XII levels. Heterozygous individuals have factor XII levels between 25% and 50% (1).

Coagulation disorders after cardiac surgery can pose considerable challenges in diagnosing and treating the patient as a result of the complexities that exist with the disorder (2). In addition, extracorporeal circulation activates multiple biological systems in response to blood contact with foreign surfaces (3). Anticoagulants like heparin are used to block steps in the coagulation system to prevent gross clotting of blood within the extracorporeal circuit (4). Thus, it is imperative that proper monitoring of anticoagulation is used to ensure the extracorporeal circuit remains intact for cardiopulmonary bypass (CPB).

Screening tests such as aPTT and activated clotting time (ACT) are used to aid clinicians to either maintain hemostasis and/or monitor anticoagulation (2). ACT and aPTT are inadequate for monitoring anticoagulation in patients deficient in factor XII because these tests are routinely used to measure the intrinsic coagulation pathway, which requires factor XII to accurately reflect in vivo anticoagulation. However, heparin concentration monitoring is done by titrating known quantities of protamine with heparinized whole blood. This facilitates anticoagulation monitoring for patients deficient in factor XII undergoing CPB.

DESCRIPTION

In accordance with local research ethics board policy, written consent was obtained from the patient to present this case report.

A 68-year-old, 107.7-kg man with a body surface area of 2.25 m² presented with coronary artery disease. Cardiac catheterization showed an occluded midright coronary artery, 95% occluded left circumflex artery, and 70% occluded left anterior descending artery.

The patient’s preoperative aPTT was found to be 43 seconds (normal 27–39 seconds) with an international normalized ratio of .9 (normal .8–1.2). This prolongation of the aPTT was the first indication of a coagulation abnormality. The patient was found to have factor XII levels of .24 U/mL (normal .50–1.50 U/mL). Factors VIII, IX, and XI were found to be within normal range. There were no other coagulation abnormalities identified with additional testing. The patient’s hemoglobin was 135 g/L (normal 135–180 g/L), hematocrit .403 L/L (normal .405–.546 L/L), and platelets 185 × 10^9/L (normal 150–400 × 10^9/L). We did not perform antithrombin analysis because it is not a common test for our institution.
The extracorporeal circuit consists of a Sorin S5 venous–arterial loop that is phosphorylcholine-coated (Sorin/Dideco, Mirandola, Modena, Italy), a 20-μm arterial filter, a trillium-coated affinity oxygenator, and a trillium-coated open hard-shell venous reservoir (Medtronic, Minneapolis, MN). Cardioplegia was delivered using the Quest MPS (Quest Medical, Allen, TX). Anticoagulation monitoring was done by using the Hepcon Heparin Management System (HMS) Plus and the Activated Coagulation Time Plus System (Medtronic, Minneapolis, MN).

After induction of anesthesia, predicted heparin dose–response (HDR), predicted heparin concentration, and heparin bolus calculations were performed using the Hepcon HMS Plus. The “candy-striped” HDR cartridge, which contains whole blood heparin concentration ranging from 0 to 2.84 U/mL and a kaolin activator, was used. It should be noted that this test is a modified ACT and would be falsely prolonged in a patient with FXII deficiency (Table 1; Figure 1). Results of this test is the projected heparin concentration which gives a loading does of heparin needed to achieve an ACT of 480 seconds. Department protocol is to add an additional 100 IU/kg to the projected heparin concentration to achieve sufficient anticoagulation before CPB with an ACT greater than 480 seconds. An additional 10,000 IU of heparin were added to the priming constituents of the extracorporeal circuit. We decided to administer a larger heparin dose rather than a lower dose in a patient who may be hypercoagulable as a result of the factor deficiency.

The patient was heparinized using results of the Hepcon HMS plus. Projected heparin concentration to achieve an ACT of 480 seconds was 181 IU/kg. Based on our institutional protocol, our projected heparin concentration was set to 300 IU/kg, which equated to a projected heparin bolus of 35,000 IU (Sandoz, Boucherville, Quebec, Canada). The patient’s resultant slope from HDR curve was 122 secs/IU/mL. Baseline ACT was 178 seconds. After heparinization, the ACT was >999 seconds and heparin concentration was 400 IU/kg. Because the patient had a factor XII level of .24 U/mL and the activator in the HDR cartridge is kaolin, we knew that the results from the HDR would underestimate the heparin requirements for the patient. Therefore, we erred on the side of caution by keeping the patient heparinized above the determined value from the HDR.

After completing CPB, a protamine dose of 600 mg was determined by the HMS plus. A post heparin–protamine titration sample showed that there was no remaining circulating heparin. The patient was on bypass for 148 minutes and cross-clamped for 119 minutes. All ACTs on bypass were >999 seconds and heparin concentration was no lower than 350 IU/kg. An hour into bypass, an additional 10,000 IU of heparin were administered to increase the heparin concentration from 350 IU/kg to 400 IU/kg (Table 2).

The patient was hemodynamically stable postbypass. Two grams of tranexamic acid bath mixed in 50 mL of warm (37°C) sodium chloride was applied topically into the chest wound before sternal closure, which is our practice. Intravenous tranexamic acid was not given. The patient was extubated in 12 hours and stayed in the intensive care unit for 17 hours with no postoperative complications. Total chest tube losses were 730 mL. The patient was discharged home on postoperative day 5 with a

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Table 1. Values from heparin dose response analysis.

<table>
<thead>
<tr>
<th>Clotting Times</th>
<th>Averages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel 1</td>
<td>532 seconds</td>
</tr>
<tr>
<td>Channel 2</td>
<td>512 seconds</td>
</tr>
<tr>
<td>Channel 3</td>
<td>365 seconds</td>
</tr>
<tr>
<td>Channel 4</td>
<td>387 seconds</td>
</tr>
<tr>
<td>Channel 5</td>
<td>179 seconds</td>
</tr>
<tr>
<td>Channel 6</td>
<td>182 seconds</td>
</tr>
</tbody>
</table>

Table 2. Heparin dose, heparin concentration, and activated clotting time.

<table>
<thead>
<tr>
<th>Time</th>
<th>Heparin Dose Given (IU)</th>
<th>Heparin Concentration (IU/kg)</th>
<th>Activated Clotting Time (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1400</td>
<td>0 (baseline)</td>
<td>181 (dose indicated by HDR)</td>
<td>178</td>
</tr>
<tr>
<td>1432</td>
<td>35000</td>
<td>400</td>
<td>999</td>
</tr>
<tr>
<td>1515</td>
<td>0</td>
<td>400</td>
<td>999</td>
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<tr>
<td>1545</td>
<td>0</td>
<td>350</td>
<td>999</td>
</tr>
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<td>1615</td>
<td>0</td>
<td>350</td>
<td>999</td>
</tr>
<tr>
<td>1645</td>
<td>10000</td>
<td>400</td>
<td>999</td>
</tr>
<tr>
<td>1705</td>
<td>0</td>
<td>400</td>
<td>N/A</td>
</tr>
<tr>
<td>1730</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

HDR, heparin dose-response; N/A, not available.
hematocrit of .248 L/L, hemoglobin of 83 g/L, and platelet count of 193 $10^9$/L. At a 2-month follow-up, the patient’s hematocrit was .353 L/L, hemoglobin was 115 g/L, and platelets were $200 \times 10^9$/L. This patient received no transfusions during the course of treatment.

COMMENT

Factor XII is a single-chain glycoprotein belonging to the peptidase S1 family with a molecular weight of 80,000 daltons. Factor XII is important in the intrinsic cascade, plasminogen-dependent fibrinolysis, the kallikrein–kinin system, and complement activation (5). Despite its importance, factor XII-deficient patients are not at greater risk for clinical bleeding. It has been suggested by some authors’ factor XII deficiency impairs the production of plasmin from plasminogen, thus causing thromboembolic events resulting from impaired fibrinolysis (5,6). For this reason and advisement from our hematology staff, we deferred from administering our standard practice of 2 g of tranexamic acid intravenously before initiating CPB.

Activation of factor XII by kallikrein is greatly stimulated by the presence of negatively charged substances like celite, kaolin, dextran sulfate, or sulfatides (6). The ACT contains an activator substance that will activate factor XII through contact activation. The main activator substances used are celite (diatomaceous earth), kaolin, or glass beads. ACT analysis activates the intrinsic coagulation cascade and measures the time it takes for generation of a fibrin clot using an activator to speed up the process (7).

The heparin–protamine titration (HPT) cartridges perform a semiquantitative measurement of heparin concentration in a whole blood sample by titrating known amounts of protamine against heparin in the cartridges channels. Instead of kaolin, each channel in a HPT cartridge contains a constant amount of thromboplastin for activation of the test. As ACT is ineffective in monitoring adequacy of anticoagulation in factor XII deficient patients, heparin concentration can be used to monitor proper anticoagulation for cardiac surgery.

With respect to the heparin dose and the lack of antithrombin testing, we believe we had enough information from the HDR to proceed. Four of the HDR channels contain heparin. Had there been antithrombin deficiency, the channels with heparin would have shown a reduced heparin effect even in the face of factor XII deficiency.

A drawback to monitoring only heparin concentration during CPB is that optimal heparin activity is patient-specific. Thus, defining a minimal heparin concentration level for CPB may not be possible (8). However, heparin concentration-based anticoagulation management during CPB has shown significant reduction of thrombin generation, fibrinolysis, and neutrophil activation when compared against ACT (9). It was with this in mind we chose to keep this patient’s heparin concentration above our institutionally determined level of 300 IU/kg.

Two papers describe the administration of fresh-frozen plasma to correct clotting time so that an ACT could be used to monitor anticoagulation (10,11). This method is unfavorable because it would expose the patient to blood products that may not be needed. A modified ACT technique is described in the literature; however, it involves in vitro replacement of factor XII in the patient’s blood with donor plasma (12). The successful use of heparin concentration in a patient with a kininogen or prekallikrein deficiency for CPB using the HMS has been previously reported (13). Another reported case describes heparin concentration monitoring through direct heparin assays in a factor XII-deficient 12-year-old patient undergoing CPB. These authors kept heparin levels between 3.3 and 4.0 IU/mL during bypass with no complications (14).

It is widely recognized that inadequate heparinization with exposure of blood to foreign and intrinsic surfaces leads to coagulation activation and thrombin generation. Thus, it is crucial that proper anticoagulation for CPB has been achieved.

We present the successful management of anticoagulation of a patient with factor XII deficiency during CPB for coronary artery bypass grafting with a heparin concentration method. This approach can be used to safely care for these patients in the setting of cardiac surgery. Clinicians should keep in mind patient anticoagulation requirements vary greatly. There is no defined optimal heparin concentration for adequate anticoagulation for patients on CPB. Further studies need to be conducted investigating heparin concentration and optimal anticoagulation for safe conduct of open heart surgeries.

REFERENCES