A Case Report of Heparin Resistance due to Acquired Antithrombin III Deficiency

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Abstract

A case of heparin resistance and its management during cardiopulmonary bypass is reported. A patient with a history of post-infarct angina and arrhythmias was treated with intravenous heparin infusion for five days prior to myocardial revascularisation surgery. He required 13,500 IU/kg of heparin to increase his activated clotting time to a therapeutic level for safe institution of cardiopulmonary bypass. This phenomenon of heparin resistance was postulated to be due to consumption of circulating antithrombin III as a result of prior heparinisation. Treatment with fresh frozen plasma restored heparin effectiveness.

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Key words: Activated clotting time, Cardiopulmonary bypass, Fresh frozen plasma, Intravenous heparin therapy, Preoperative heparin infusion

Introduction

Intravenous heparin therapy is used in the management of angina and myocardial infarct with increasing frequency in recent years. Those patients who have been on heparin therapy for several days may exhibit resistance to heparin given before cardiopulmonary bypass. The postulated mechanisms include heparin-induced thrombocytopenia,[1-3] heparin-induced decrease in the circulating antithrombin III (AT III) level[4,5] and enhancement of factor VIII activity.[6] We report a case of acquired AT III deficiency following preoperative heparin therapy, resulting in resistance to the anticoagulant effects of heparin given for cardiopulmonary bypass (CPB), and its management.

Case Report

A 75-year-old Chinese man had an inferior myocardial infarct presenting with chest discomfort, sweating and dizziness. This was complicated by polymorphic ventricular tachycardia and atrial flutter-fibrillation. He also had post-infarct angina. Cardiac catherisation revealed left main coronary artery stenosis (50%) and severe triple vessel disease. His estimated ejection fraction was 30% with mild mitral valve regurgitation. Coronary artery bypass surgery was planned for the patient.

The patient continued to have episodes of atrial flutter and chest pain. He was started on continuous intravenous heparin infusion, the rate adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2 times control. This was continued for five days and stopped on the morning of the operation.

Preoperatively, the prothrombin time (PT) was 14.2 seconds (control 12.5 seconds) and aPTT was 43 seconds (control 23.6 seconds). The platelet count was 523 000 per mm^3. The patient underwent an uneventful general anaesthesia.

The baseline celite activated clotting time (ACT) was 132 seconds. The patient was given 50,000 units of aprotinin intravenously with another 50,000 units added to the pump prime. After harvesting the left internal mammary artery, heparin was administered as an intravenous bolus of 300 IU / kg (a total dose of 20,000 IU), which is the standard regime at this hospital. The resulting ACT taken 5 minutes later was only 266 seconds. Additional doses of heparin were given repeatedly. After a total dose of 900 IU / kg (60,000 IU), the ACT was 428 seconds. In view of the use of aprotinin, a celite ACT of 750 seconds or greater was deemed necessary to institute bypass safely. Kaolin ACT was not available in our hospital.

At this time, a presumptive diagnosis of heparin resistance due to antithrombin III (AT III) deficiency was made since the patient had been on intravenous heparin infusion for 5 days prior to surgery. Blood was sampled for measurement of AT III activity. 500 ml of fresh frozen plasma (FFP) was administered to the patient empirically. The time between the last dose of heparin administration to completion of FFP transfusion was 45 minutes.

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Additional 450 IU / kg (30,000 IU) of heparin was given after the completion of the FFP. A satisfactory ACT of 784 seconds was finally achieved and CPB instituted. The ACT was maintained above 750 seconds during hypothermia, but fell to 466 seconds when the patient was warmed to 36°C. Additional 10,000 IU of heparin was given. The patient was weaned off cardiopulmonary bypass without difficulty. Heparin was reversed with 300 mg of protamine. The ACT after protamine administration was 131 seconds.

The AT III activity before the FFP was given was 65% (normal range 80% to 120%). A repeat blood sample for AT III activity was taken on the fifth postoperative day with a result of 90%.

Discussion

Anticoagulation is a fundamental prerequisite for the institution of cardiopulmonary bypass (CPB). This is usually achieved by administration of a fixed dose of heparin based on the patient's body weight or surface area. Heparin binds to antithrombin III (AT III) which is the naturally occurring thrombin inhibitor. AT III acts by irreversibly binding to thrombin thus neutralizing the effect of thrombin on fibrinogen and prevents clot formation. The rate of AT III-thrombin reaction is greatly enhanced by the presence of heparin. Heparin has no anticoagulant effect in AT III-depleted plasma.

Activated clotting time (ACT) is a commonly used monitor of heparin levels during CPB. Satisfactory anticoagulation is defined as a celite ACT of 400 seconds or more, and mechanical circulation is not instituted until this value is reached. In patients given aprotinin, this value is increased to 750 seconds, because aprotinin artificially prolongs celite ACT as a result of the drug's inhibition of kallikrein and contact activation of the intrinsic coagulation pathway. Therefore, celite ACT should be maintained in the range of 600 to 750 seconds during CPB to prevent inadequate anticoagulation and thromboembolic complications in aprotinin-treated patients.[7] Kaolin is not affected by apotinin. Cardiopulmonary bypass can be instituted safely when kaolin ACT is above 400 seconds.

The baseline ACT in our patient was normal. Esposito et al[8] maintained that a low baseline ACT could predict heparin resistance because they observed lower values in 8 resistant patients than in 38 controls. The observation was not found in studies by Cloyd et al and Staples et al.[9,10] They concluded that baseline ACTs could not be used to forecast heparin resistance preoperatively.

Patients who received intravenous heparin therapy preoperatively showed diminished anticoagulant response to heparin during operation.[8-11] Staples et al[10] recommended modification of the standard heparin dose schedule with close surveillance of ACT for the duration of CPB in this subgroup of patients. Dietrich et al[11] recommended a larger (500 IU / kg) initial bolus of heparin be given before CPB in heparin-pretreated patients.

Marciniak and Gockerman[4] reported that when present in the blood for long periods, heparin significantly reduced circulating AT III levels, which returned to normal 2 to 3 days after heparin was stopped. Dietrich[11] noted a decrease in circulating AT III levels in patients who were treated with heparin infusion. Preoperative heparin therapy resulting in decreased circulating AT III level was the most likely cause of heparin resistance in our patient. Indeed his AT III levels were low. Buller and Ten Cate[12] reported that AT III levels decreased to a nadir on the third day after major surgery, followed by a return to normal by the fifth postoperative day. A blood sample taken from the patient on the fifth day after surgery demonstrated a normal AT III level. This confirms the diagnosis of acquired AT III deficiency.

The treatment options available when a presumptive diagnosis of AT III deficiency is made include the use of whole blood, fresh frozen plasma (FFP) or pooled AT III preparations. Transfusion of blood and blood products carries the risk of transmission of viral infections. It also depletes a rare commodity and involves wastage of time while waiting for the blood product. AT III preparations are heat treated in a wet condition for 10 hours at 60°C to reduce the infectious risk. It is also convenient to use. Unfortunately, this product is expensive, has a short shelf life and is not available in our institution. Therefore, at this point in time, FFP is the most appropriate treatment.

In summary, we presented a patient with decreased heparin response due to acquired AT III deficiency following preoperative intravenous heparin therapy. Infusion of fresh frozen plasma restores heparin effectiveness, resulting in a satisfactory ACT for safe institution of cardiopulmonary bypass. This case serves to remind us that a history of preoperative heparin therapy should trigger concern about the possibility of heparin resistance and the prospect that greater-than-usual amounts of heparin may be necessary for achieving safe intraoperative anticoagulation. Close surveillance of ACT is essential for the entire duration of anticoagulation.

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