Anticoagulant Monitoring Techniques in a Heparin-Induced Thrombocytopenia Patient Undergoing Cardiopulmonary Bypass Using Bivalirudin Anticoagulant

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Abstract: Heparin is widely used as the anticoagulant of choice for cardiopulmonary bypass. However, some patients exposed to heparin therapies develop heparin-induced thrombocytopenia (HIT). Severe complications of HIT-induced thrombosis may lead to end-organ dysfunction and death. Bivalirudin, a hirudin analog, is an alternative anticoagulant that may be used in the patient with HIT without inducing thrombotic disorders. This case report provides a look at the successful use of bivalirudin as the sole anticoagulant in a patient diagnosed with HIT undergoing minimally invasive cardiothoracic surgery requiring cardiopulmonary bypass for severe mitral insufficiency. An 80-year-old male presented to the operating room for a minimally invasive mitral valve repair. Past medical history included mitral valve prolapse, atrial fibrillation, hypertension, and congestive heart failure. Preoperative evaluation noted the existence of HIT with heparin exposure 2 months prior. The decision was made to use bivalirudin as the sole anticoagulant for the operative procedure. Anticoagulation evaluation was performed with both high-dose thrombin time (HiTT) and Celite activated clotting time tubes for comparison using a Hemochron device. Cardiopulmonary bypass was initiated, and the patient’s mitral valve was repaired using a 34-mm annuloplasty ring. The patient was successfully weaned from bypass. No complications or evidence of HIT exacerbation were noted in the postoperative course.

Keywords: bivalirudin, heparin-induced thrombocytopenia (HIT), high-dose thrombin time (HiTT), cardiopulmonary bypass (CPB).

One of the most widely used anticoagulants for the treatment and prevention of thrombotic disorders and the drug of choice for extracorporeal circulation is heparin. It is estimated that some 12 million patients are exposed to heparin every year (1). One of the most common and severe side effect seen in these patients is the development of heparin-induced thrombocytopenia (HIT). Two clinically distinct forms of HIT have been identified: HIT type I and HIT type II. Type I is characterized by a transient, asymptomatic, nonimmunogenic reduction in platelet count (1–3). Platelet levels are seen to resolve spontaneously with or without the discontinuation of heparin therapies (2). The origin of HIT type I is not completely understood, but is thought to be the result of heparin induced platelet clumping and/or sequestration (2). HIT type II, or heparin-induced thrombocytopenia and thrombosis (HITT), is an immune mediated thrombocytopenia, with platelet counts dropping to below 100 × 10⁹/L (1, 2). Identifiable drop in platelet counts generally occur 4 or more days after the initiation of heparin therapy and are often associated with thromboembolic complications (1–3). Associated complications include arterial and venous thrombosis, stroke, myocardial infarction, end-organ dysfunction, disseminated intravascular coagulation, and death (2). Given the reported incidence rate of 2–7%, approximately 360,000 individuals are at risk for HIT, and some 120,000 are at risk of developing thromboembolic complications (1).

In the clinical setting, patients with HIT who are scheduled to undergo cardiothoracic surgery requiring cardiopulmonary bypass (CPB) present unique challenges as to the management of anticoagulation and hemostasis. Bivalirudin (Angiomax®, The Medicines Company, Cambridge, MA), a synthetic analog of hirudin, is a 20 amino acid polypeptide that acts as a direct, reversible thrombin inhibitor that does not show cross reactivity with the HIT antibodies present in HIT type II (1,4–7). Prolongation of the activated partial thromboplastin time, thrombin time, prothrombin time, and activated clotting time (ACT) with the use of bivalirudin occurs in a concentration-dependent manner (1,4). The following case report presents the successful use of bivalirudin as the sole anticoagulant in a patient with HIT undergoing cardiothoracic surgery re-
quiring CPB for the repair of a mitral valve prolapse. Monitoring of anticoagulation was guided by the use of ACT as well as the empirical use of high-dose thrombin time (HiTT) to evaluate its effectiveness in monitoring thrombin inhibition.

CASE REPORT

An 81-year-old male was admitted to the hospital in September 2002 for increased shortness of breath and dyspnea on exertion. Evaluation of patient history revealed the existence of a known posterior mitral valve leaflet prolapse for 10 years. Echocardiography showed severe mitral regurgitation, mild aortic insufficiency, and moderate tricuspid regurgitation. Additional history included atrial fibrillation, congestive heart failure, pulmonary hypertension, and gout. Two months prior to admission, during an exploratory laparoscopy to release abdominal adhesions from a prior surgery, the patient experienced an onset of thrombocytopenia after the administration of heparin, with platelet counts dropping to below $20 \times 10^9/L$. Although no thrombotic complications were noted, laboratory tests were ordered to confirm a differential diagnosis of HIT. An enzyme-linked immunosorbent assay was performed to evaluate for the presence of anti-heparin-platelet factor 4 antibodies. Positive titer results confirmed the diagnosis of HIT type II. Because of the decline in the patient’s condition, the decision was made to move ahead with a mitral valve repair surgery 4 days later using bivalirudin as the sole anticoagulant.

The patient was brought to the operating room, anesthetized, prepped, and draped in standard fashion. A right side thoracotomy incision was made. The patient was anticoagulated with an intravenous bolus of bivalirudin, 1.5 mg/kg (patient weight = 51 kg), and 0.75 mg/kg was added to the pump prime. Aortic and right atrial cannulation was performed. Bypass was initiated, and the patient was cooled down to 24°C. A continuous bivalirudin infusion was started at a rate of 3 mg/kg/h. Additional boluses were administered as needed throughout the case. Cold blood cardioplegia was administered in antegrade fashion via an angiocatheter in the aortic root until arrest was achieved. A mitral valve repair using a 34mm annuloplasty ring was performed. Radio-frequency ablation of the left atria was also performed to attenuate the reoccurring atrial fibrillation. Celite ACT (Celite Corporation, Santa Barbara, CA) and HiTT values were monitored using the Hemochron 801 device (International Technidyne, Edison, NJ) every 15–30 minutes (Figure 1). The patient was weaned from bypass with a cross clamp time of 98 min and total CPB time of 136 min. One unit of packed red blood cells (PRBCs) was administered during bypass to augment a hematocrit of 22%. No clot formation was noted in the circuit after the discontinuation of CPB. Two units of PRBCs and one unit of fresh-frozen plasma were given after CPB. Proper hemostasis was achieved, the chest was

![Figure 1. ACT and HiTT monitored concomitantly during the course of CPB.](image-url)
closed, and the patient was transferred to the intensive care unit in stable condition.

At 5 h after surgery, blood loss via chest tube and pericardial drainage was a total of 2500 mL; 1450 mL from the right chest tube and 950 mL from the pericardial sump. The patient had received 8 units of PRBCs, 8 units of fresh-frozen plasma, 4 units of platelets, and 2 units of cryoprecipitate during that time to attenuate for the loss of blood components. The decision was made to reopen the chest to explore for a bleeding site. The chest was opened, blood clots were observed and removed, and the chest was irrigated. A constant ooze of blood was found coming from the angiocatheter site in the aortic root. A pledgetted stitch was placed to seal the wound site, and the chest was reclosed. Five hours after exploration blood output was measured; 200 mL from the pericardial sump and 250 mL from the right chest tube. The pericardial sump was removed 1 h later. The right chest tube was removed 2 days later, with drainage of only 500 mL during the next 48 hours. The rest of the postoperative course was uneventful, with no signs of HIT exacerbation. The patient was discharged on postop day 8.

DISCUSSION

In this case, because of the prior history of HIT antibody formation, the use of heparin as an anticoagulant was deemed inappropriate. Bivalirudin was chosen as the sole anticoagulant because of absence of cross-reactivity with HIT antibodies. Bivalirudin has been approved for use in percutaneous transluminal coronary angioplasty, but its use in CPB, at the time of this case, was largely unreported. Bivalirudin is thrombin specific and does not bind to other plasma proteins or red blood cells (4). It is a direct thrombin inhibitor with the ability to bind both soluble and fibrin bound thrombin thereby inhibiting any further clot formation (4,6). Bivalirudin is unique in that it undergoes thrombin-mediated cleavage allowing re-expression of thrombin’s active site, which enables recovery of its functional properties (1,4–7). This proteolytic cleavage coupled with renal elimination, translates to half-life 25 min in the absence of renal insufficiency (1,4–7). The short half-life and rapid elimination allows timely recovery of coagulation.

Because of its short half-life and rapid reinstitution of coagulation, precise monitoring of patients anticoagulation status when employing the use of bivalirudin is imperative. At the time of surgery little information was available regarding the monitoring of anticoagulation at the higher doses needed to perform CPB. Koster et al. (7) recently reported the monitoring of bivalirudin anticoagulation using ecarin clotting time. They found a close correlation between the ecarin clotting time and the plasma concentration of bivalirudin, as measured by an anti-IIa assay. Unfortunately at the time of this case, neither ECT nor specific anti-IIa assays were readily available in our institution to monitor bivalirudin concentration. Following the manufacturer’s recommendations, we incorporated the use of ACT as our guide in monitoring proper anticoagulation. Because of the anticoagulant mechanism of bivalirudin, we also empirically instituted the use of HiTT to evaluate the direct anti-IIa effects.

Past studies have evaluated the use of HiTT as a monitor for heparin anticoagulation in patients receiving aprotonin therapy and preoperative heparin (8,9), but its use as a monitor for direct thrombin inhibitors has gone unreported. HiTT has the ability to measure anti-IIa activity without being affected by hemodilution, hypothermia, antifibrinolytic drugs, or the accumulation of fibrin degradation products (8–10). In comparison to the ACT, which measures both the intrinsic and common pathways of the coagulation cascade, the HiTT may be less susceptible to error as it measures only the final common pathway (9). HiTT test tubes are easily attainable and compatible for use in the Hemocron device. The HiTT test tube contains a lyophilized thrombin reagent. The test tube is hydrated with 0.5 mL of distilled water, prewarmed, and 1.5 mL of whole blood is added. The test tube is then inserted into the Hemocron device, and the clotting time is measured.

Comparison of the intra-operative ACT/HiTT results can be seen in Figure 1. The large discrepancy between the ACT and the HiTT points to the inefficiency of one of the methods in correlating with the true plasma concentration of bivalirudin. This discrepancy could be the result of outside influences of hypothermia and hemodilution on the ACT. HiTT clotting times showed a more consistent response, which presumably represented a correlation with the continuous infusion rate. Unfortunately, the absence of a reliable monitor of bivalirudin plasma concentration makes it impossible to validate which method most closely represents the true plasma concentration.

There are inherent limitations in drawing final conclusions about the use of bivalirudin in CPB and the efficacy of monitoring its anticoagulant effects via HiTT from the single case presented here. Although it is impossible to conclusively state that bivalirudin is the optimal anticoagulant of choice from one case, initial results from this and other recent reports (6,7) point to its effectiveness in the HIT patient population. The empirical use of HiTT in this case appears to show a correlation with plasma concentrations of bivalirudin, but because of laboratory limitations, this could not be validated. Future investigation may reveal HiTT’s effectiveness in monitoring anticoagulation with bivalirudin. Further studies are warranted to evaluate bivalirudin effectiveness, optimal concentration levels, and proper anticoagulation monitoring when used as the sole anticoagulant in a patient undergoing CPB.

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REFERENCES


