Bivalirudin Anticoagulation for a Pediatric Patient with Heparin-Induced Thrombocytopenia and Thrombosis Requiring Cardiopulmonary Bypass for Ventricular Assist Device Placement

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Modified techniques were utilized. This included use of the Terumo CDI 500 (Terumo Cardiovascular Systems, Inc.) in-line blood gas monitor which contains a heparin coated arterial shunt sensor. We flushed this sensor with buffered saline preoperatively and noted no significant decrease in platelet count postoperatively. The patient was successfully placed on the ventricular assist device and was subsequently listed for heart transplantation. Keywords: Angiomax, bivalirudin, anticoagulation, heparin-induced thrombocytopenia, HIT, HITT, pediatric cardiopulmonary bypass, ventricular assist device. JECT. 2016; 48:39–42

OVERVIEW

Heparin-induced thrombocytopenia (HIT) occurs in 1–3% of adult and pediatric patients requiring cardiovascular interventions and results from an immune reaction to the heparin and platelet factor-4 complex (1). HIT manifests with a significant drop in platelet count after heparin exposure and can also present with thrombosis whereby it is termed heparin-induced thrombocytopenia and thrombosis (HITT). For these patients, an alternative medication for anticoagulation must be used during cardiopulmonary bypass (CPB). Bivalirudin is a direct thrombin inhibitor, with the trade name Angiomax® (The Medicines Company, Parsippany, NJ), that has been shown to be an effective anticoagulant in this setting for both the adult and pediatric population (1–5). Bivalirudin works by binding to both circulating and clot-bound thrombin, which prevents thrombin from activating fibrinogen to fibrin. This inhibits stabilized blood clot formation. It has a half-life of 25–34 minutes and is eliminated both by the kidneys and intravascular proteolysis (6,7). Its immediate onset of action, relatively short half-life, renal and intravascular elimination, and correlation with the activated clotting time (ACT) have made bivalirudin an attractive choice for HIT patients undergoing cardiac surgery.

DESCRIPTION

An 11-year-old male with acute onset heart failure secondary to idiopathic dilated cardiomyopathy was transferred from an outside hospital to our cardiac intensive care unit (CICU) for consideration for a ventricular assist device (VAD). He was medically managed for his heart failure and atrial tachyarrhythmias with milrinone, diuretics, and
POD 10 575,000
POD 7 370,000
POD 4 134,000
POD 1 238,000
Postoperative 230,000
Preoperative 325,000
CICU day 18 279,000
CICU day 15 216,000
CICU day 12 76,000
CICU day 11 20,000
CICU day 10 22,000
CICU day 1 242,000

This platelet count dropped to 22,000 to concern of thrombosis. On CICU admission day 10, procainamide. A heparin infusion was also initiated due to concern of thrombosis. On CICU admission day 10, his platelet count dropped to 22,000 µL$^{-1}$ and HIT was confirmed with a positive HIT serotonin-releasing assay (SRA) and positive HIT IgG antibody test. Heparin was stopped and the patient was put on the factor Xa inhibitor fondaparinux (Arixtra, GlaxoSmithKline, Brentford, United Kingdom) for anticoagulation management. The patient was scheduled for a HeartWare® VAD (HeartWare®, Framingham, MA) implant on CICU day 11, but this was postponed due to fever and the concern for HIT. Over the next several days, the platelet count was low, ranging from 20,000 to 76,000 µL$^{-1}$ as shown in Table 1. The patient suffered a near-arrest episode on CICU day 13. An echocardiogram was performed that showed significant clot in the right atrium, right ventricle, and right common femoral vein. Anticoagulation management was switched from fondaparinux to argatroban (GlaxoSmithKline).

The patient went to the operating room (OR) for VAD placement on CICU day 19. The platelet count had returned to 325,000 µL$^{-1}$ before surgery. The anticoagulation plan for the OR was to use bivalirudin with a target minimum kaolin-ACT (K-ACT) of either 2.5 × baseline or greater than 400 seconds, whichever was lower. The baseline K-ACT was 175 seconds giving a target K-ACT range of 400–500 seconds. Our institutional protocol has been to use K-ACTs for bivalirudin anticoagulation cases based on published experience of other groups using this test to monitor bivalirudin anticoagulation during bypass (8,9). A Hemochron Response Whole Blood Coagulation System was used as the point-of-care ACT monitoring device (Accriva Diagnostics, San Diego, CA).

The patient’s parameters were a weight of 58.8 kg, height of 158 cm, and body surface area of 1.61 m². A circuit was chosen consisting of a CAPIOX FX15–30 oxygenator with integrated arterial filter (Terumo Cardiovascular Systems, Inc. Ann Arbor, MI) and a custom tubing pack using 3/8” arterial, venous and arterial pump lines (Sorin Group USA, Arvada, CO). The final circuit prime consisted of 245 mL of Plasma-Lyte A pH 7.4 (Baxter Healthcare, Deerfield, IL), 530 mL of reconstituted whole blood (packed red blood cells and plasma premixed in the Blood Bank), 30 mEq of sodium bicarbonate, and 1,470 mg of cefazolin. A 50-mg bolus of bivalirudin was added to the pump prime before the pump lines were handed up to the field. This prime bolus dose of bivalirudin has been reported by several other authors for pediatric cases of varying bypass prime volumes (1,4,5). The bivalirudin prime bolus was added shortly before the bypass lines were divided at the field to prevent the potential breakdown of bivalirudin in the prime. We routinely add calcium to our heparinized pump primes to normalize values but we did not in this case due to the lack of heparin in the prime. We planned to correct ionized calcium levels on bypass. A Sorin Xtra intraoperative autotransfusion device with a 175-mL bowl (Sorin Group USA) was used throughout the case. Anticoagulation for this device was accomplished with a citrated saline drip. Also of note, we elected to use a Terumo CDI® 500 (Terumo Cardiovascular Systems, Inc.) in-line blood gas monitoring device in our bypass circuit. The arterial shunt sensor for the device is heparin coated which normally precludes its use for patients with HIT. However, after discussion with the surgical and hematology teams, exposure to the heparin coating in the shunt sensor was determined to be very low risk. The arterial sensor was calibrated and then, in an attempt to remove as much heparin as possible, the sensor was flushed with 1 L of buffered saline (9% Sodium Chloride Injection USP pH 4.5–7.0, Baxter Healthcare) before placement in the circuit.

Prophylactic antifibrinolytic therapy was initiated after induction of general anesthesia with a 2,000-mg bolus of tranexamic acid (TXA) followed by an infusion of 16 mg/kg/h. Arterial blood gas samples were obtained from the patient’s arterial line with a heparin-free syringe and immediately transferred to a heparinized syringe for analysis. Approximately 15 minutes before bypass was anticipated, the anesthesiologist gave a bivalirudin bolus of 60 mg (1 mg/kg) and started the infusion at 2.5 mg/kg/h through an internal jugular vein central line. The pump lines were passed up to the field and kept circulating until immediately before aortic cannulation. The K-ACT after bivalirudin bolus was 385 seconds. A second bolus of 50 mg bivalirudin was given and the infusion rate was increased to 3 mg/kg/h. The pump suckers were not turned on until the patient was on bypass.

Once on bypass, the bivalirudin infusion was moved to a cardiotomy port on the bypass circuit. This was done knowing that the cardiotomy filter has the greatest risk of stagnation. An additional bolus of 120 mg (2 mg/kg) TXA was also administered via the pump per our standard antifibrinolytic protocol. The bypass plan was to monitor K-ACTs frequently and to avoid areas of stasis in the pump, including keeping a lower venous reservoir level

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Platelet Count (µL$^{-1}$)</th>
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<tbody>
<tr>
<td>CICU day 1</td>
<td>242,000</td>
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<tr>
<td>CICU day 10</td>
<td>22,000</td>
</tr>
<tr>
<td>CICU day 11</td>
<td>20,000</td>
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<tr>
<td>CICU day 12</td>
<td>76,000</td>
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<tr>
<td>CICU day 15</td>
<td>216,000</td>
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<td>CICU day 18</td>
<td>279,000</td>
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<td>POD 1</td>
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<tr>
<td>POD 4</td>
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<td>POD 7</td>
<td>370,000</td>
</tr>
<tr>
<td>POD 10</td>
<td>575,000</td>
</tr>
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Table 1. Time point platelet counts.
BIVALIRUDIN ANTICOAGULATION FOR A PEDIATRIC PATIENT

Authors: M. T. Schenck, G. H. M. Edwards, R. A. Reeder, R. J. Riemenschneider, M. A. Pulcini

The use of bivalirudin for pediatric left ventricular assist device (VAD) placement was evaluated. The patient, a 3-year-old male, underwent a left VAD placement using a modified surgical technique. During CPB, bivalirudin was administered to prevent clotting. The patient experienced low platelet counts postoperatively, which were managed with argatroban. The patient was transferred to the cardiovascular intensive care unit (CICU) and discharged with no HIT-related complications. The use of bivalirudin was successful in preventing HIT, and the patient was later transplanted.

COMMENTS

We have described the successful use of bivalirudin for a pediatric left VAD placement using modified surgical and perfusion techniques. Although HIT occurs in approximately 1–3% of patients exposed to heparin for cardiovascular procedures, reports of the use of bivalirudin anticoagulation for CPB in the pediatric population are relatively limited. To our knowledge, this is the first reported use of a Terumo CDI shunt sensor in a HIT patient, adult, or pediatric. The Terumo CDI arterial shunt sensor (Model CDI510H, Terumo Cardiovascular Systems, Inc.) probe is heparin coated and its instructions for use state, “Do not use on patients with heparin sensitivity.” However, after discussions among the care team, the use of a heparin-coated shunt sensor flushed with 1 L of buffered saline was thought to be low risk. The ability to monitor blood gas values and potassium throughout the case was considered a necessary safety feature during a case with theoretically increased risk for both bleeding and clotting events. In our pediatric practice, we use pH-stat acid–base management for patients being cooled below 32°C, which most often means CO2 is blended into our ventilating gas. In an environment that includes temperature changes and variable sucker and left ventricular vent flow requiring adjustments to the supplemental CO2 flow, in-line blood gas monitoring is crucial to maintaining precise pH, PCO2, and PO2 levels. Although not as critical for this case where we maintained a temperature of 34°C, the successful use of the CDI in this patient opens the door for us to use this important tool for future complex cases involving HIT. We were not able to detect any adverse effects during this case secondary to the use of the CDI.

A search of the literature demonstrates a debate whether or not to use ultrafiltration (conventional or modified) for bivalirudin cases. Bivalirudin has a molecular weight of 2,180 daltons and can therefore pass through most hemoconcentrators where the pore size is commonly around 60,000–65,000 daltons. Bivalirudin elimination has been...
shown to be 45–69% with the use of a hemoconcentrator (12). This elimination has been shown to decrease the half-life of bivalirudin by 20% (13). This may be beneficial at the end of bypass with conventional ultrafiltration, or after bypass with modified ultrafiltration (MUF), to help achieve hemostasis and decrease transfusion requirements. MUF has been successfully used in bivalirudin cases to help decrease the ACT (1,2). When used in combination with other therapies such as dialysis and clotting factors, it can be used to control bleeding after bypass (14) and in at least one case, the use of MUF alone without clotting factors was enough for postoperative hemostasis after bivalirudin anticoagulation (4). However, at least one group reported having to discontinue MUF after bypass due to visualization of clot in the MUF circuit (2). The concern for clotting in the ultrafiltration circuit extends not only to after bypass but can also be a concern while on bypass. One author recommends not using the hemoconcentrator at all for bypass, but instead temporarily storing extra volume in citrated transfer bags (3). We used the Sorin SH14 hemoconcentrator (Sorin Group USA) for our case, which has a surface area of 1.35 m² and a pore size of 65,000 daltons. This is the same pore size as the Minntech Hemocor HPH 700 hemoconcentrator (Medivators, Minneapolis, MN), which has been shown to remove approximately 65% of bivalirudin (12). While we attempted to avoid its use during the case, it did become necessary for volume and hemocrit management. We were careful to monitor ACTs more frequently during hemoconcentrator use and we maintained flow through the hemoconcentrator once opened to prevent stasis. We hemoconcentrated a total of 1,200 mL during the case and did not experience any problems associated with this use.

When using bivalirudin, there is increased concern for excessive bleeding perioperatively. We decided to use TXA per our routine institutional protocol for CPB cases. We aimed to mitigate postoperative bleeding with the antifibrinolytic properties of TXA. Bleeding in the OR was unremarkable after bypass. The patient did not require packed red blood cells and was able to leave the OR in under 3 hours after separation from bypass. The chest tube drainage over the next few days was not excessive and transfusion requirements were similar to patients managed with heparin anticoagulation for cardiopulmonary bypass.

In conclusion, bivalirudin anticoagulation for CPB requires thoughtful communication between the surgery, anesthesiology, perfusion, and nursing teams before and during bypass. Surgical and perfusion techniques must be modified for these cases to prevent blood stasis and clot formation. We demonstrated the use of ultrafiltration and the use of the heparin-coated Terumo CDI arterial shunt sensor. Both may be used in the pediatric HIT population provided the required alterations to practice are recognized and instituted.

REFERENCES