

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

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Abstract: The direct thrombin inhibitor bivalirudin is an option for anticoagulation in patients with heparin induced thrombocytopenia (HIT) requiring cardiopulmonary bypass (CPB). There are a limited number of reports of pediatric patients in which bivalirudin has been used for anticoagulation for CPB. We present the case of an 11 year old male with acute onset heart failure secondary to idiopathic dilated cardiomyopathy that developed heparin induced thrombocytopenia with thrombosis (HITT). The patient was anticoagulated in the operating room with bivalirudin and placed on CPB for insertion of a HeartWare® Ventricular Assist Device (Heartware®).

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 pre-operatively 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

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Table 1. Time point platelet counts.

Time Point	Platelet Count (μL^{-1})
CICU day 1	242,000
CICU day 10	22,000
CICU day 11	20,000
CICU day 12	76,000
CICU day 15	216,000
CICU day 18	279,000
Preoperative	325,000
Postoperative	230,000
POD 1	238,000
POD 4	134,000
POD 7	370,000
POD 10	575,000

procainamide. A heparin infusion was also initiated due to concern of thrombosis. On CICU admission day 10, his platelet count dropped to $22,000 \mu\text{L}^{-1}$ 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 $76,000 \mu\text{L}^{-1}$ 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 $325,000 \mu\text{L}^{-1}$ before surgery. The anticoagulation plan for the OR was to use bivalirudin with a target minimum kaolin-ACT (K-ACT) of either $2.5\times$ 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 m^2 . 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 headlines (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 cardiectomy port on the bypass circuit. This was done knowing that the cardiectomy 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

to avoid stagnation in the integrated cardiectomy venous reservoir. All shunts on the pump were kept open once blood primed and a flow probe was used on the arterial line for accurate flow monitoring. The venous sampling line was the only shunt that could not be left open so it was flushed with air after use to avoid stagnation. The target hematocrit on bypass was 30–35%, which is within normal range at our institution. To achieve this, 3 units of packed red blood cells were required during CPB in addition to the blood prime. Transfusion of red blood cell units and crystalloid dilutes the concentration of circulating bivalirudin. Therefore, when transfusing volume, the bivalirudin infusion was prophylactically increased. The infusion rate was also titrated as needed to maintain K-ACTs > 400 seconds, ranging from 2.5 to 5.0 mg/kg/h resulting in a K-ACT range on bypass of 343–531 seconds, close to our target of 400–500 seconds.

We had concerns about using ultrafiltration on bypass due to surface area exposure, the potential for clots, and the removal of bivalirudin by the hemoconcentrator. However, it became necessary to use the hemoconcentrator to increase hematocrit while still maintaining a reasonably lower reservoir level. During hemoconcentrator use, the bivalirudin infusion was increased and K-ACTs were monitored every 5 minutes. Blood flow through the hemoconcentrator was maintained once initiated to prevent stasis.

A modified surgical technique, previously described by Morshuis et al., was used to avoid stagnation of blood in the VAD (10). Clot, which was noted preoperatively, was removed from the right atrium and right ventricle. Once the VAD was pumping, the bivalirudin infusion was stopped. It was off for 11 minutes before terminating bypass. The last ACT on bypass was 405 seconds. Once off bypass, the pump suckers were stopped immediately and flushed with saline to prevent stasis and clot formation. The venous and aortic cannulas were removed shortly after coming off bypass and the arterial and venous pump lines were connected at the field to allow for recirculation. The volume in the bypass circuit was immediately chased through with crystalloid to the intraoperative autotransfusion device and once this was completed, an additional 50-mg bolus of bivalirudin was administered to the pump to ensure it was ready in case another bypass run was needed. A venous thrombectomy was performed via the right femoral vein after bypass.

After protamine administration, the patient received 2 units of single donor platelets, 2 units of cryoprecipitate, 1 unit of fresh frozen plasma, a single 90 mcg/kg dose of recombinant factor VII (NovoSeven® RT, Novo Nordisk, Inc., Plainsboro, NJ), and 1,070 mL of processed blood, which included the volume from the pump circuit and field suction volume sent to the intraoperative transfusion device. The patient was transferred to the CICU less than 3 hours after coming off bypass. The first platelet count in

the CICU was $230,000 \mu\text{L}^{-1}$ and subsequent platelet counts never dropped below $100,000 \mu\text{L}^{-1}$. The patient was managed on argatroban postoperatively and later transitioned to warfarin (Coumadin, Bristol-Myers Squibb, New York, NY). On the postoperative day (POD) 1, the patient's chest tube drainage was 520 mL and he was transfused 2 units of red blood cells. Over the next few days his chest tube drainage was between 350 and 560 mL and he did not receive any further transfusions. On POD 13, SRA testing was negative and on POD 20 he was transferred from the CICU to a step down unit where he was listed for heart transplantation. He later received a transplant and was managed on heparin for that surgery with no HIT-related complications.

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 CO_2 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 CO_2 flow, in-line blood gas monitoring is crucial to maintaining precise pH, PCO_2 , and PO_2 levels (11). 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 hematocrit 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, anes-

thetology, 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

1. Argueta-Morales IR, Olsen MC, DeCampi WM, Munro HM, Felix DE. Alternative anticoagulation during cardiovascular procedures in pediatric patients with heparin-induced thrombocytopenia. *J Extra Corpor Technol.* 2012;44:69–74.
2. Federman M, Dragomer D, Grant S, Reemtsen B, Biniwale R. Use of bivalirudin for anticoagulation during implantation of total artificial heart. *J Extra Corpor Technol.* 2014;46:170–2.
3. Garland C, Somogyi D. Successful implantation of a left ventricular assist device in a patient with heparin-induced thrombocytopenia and thrombosis. *J Extra Corpor Technol.* 2014;46:162–5.
4. Gates R, Yost P, Parker B. The use of bivalirudin for cardiopulmonary bypass anticoagulation in pediatric heparin-induced thrombocytopenia patients. *Artif Organs.* 2010;34:667–9.
5. Almond CSD, Harrington J, Thiagarajan R, et al. Successful use of bivalirudin for cardiac transplantation in a child with heparin-induced thrombocytopenia. *J Heart Lung Transplant.* 2006;25:1376–9.
6. Zhang D, Wang Z, Zhao X, Lu W, Gu J, Cui Y. Pharmacokinetics, pharmacodynamics, tolerability and safety of single doses of bivalirudin in healthy chinese subjects. *Biol Pharm Bull.* 2011;34:1841–8.
7. DiNisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. *N Engl J Med.* 2005;353:1028–40.
8. Jones PM, Bainbridge D, Dobkowski W, et al. Comparison of MAX-ACT and K-ACT values when using bivalirudin anticoagulation during minimally invasive hybrid off-pump coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth.* 2011;25:415–8.
9. Wasowicz M, Vegas A, Borger M, Harwood S. Bivalirudin anticoagulation for cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. *Can J Anaesth.* 2005;52:1093–8.
10. Morshuis M, Boergermann J, Gummert J, Koster A. A modified technique for implantation of the HeartWare™ left ventricular assist device when using bivalirudin anticoagulation in patients with acute heparin-induced thrombocytopenia. *Interact Cardiovasc Thorac Surg.* 2013;17:225–6.
11. Matte GS. *Perfusion for Congenital Heart Surgery: Notes on Cardiopulmonary Bypass for a Complex Patient Population.* Hoboken, NJ: Wiley-Blackwell; 2015:159.
12. Koster A, Chew D, Grundel M, et al. An assessment of different filter systems for extracorporeal elimination of bivalirudin: An in vitro study. *Anesth Analg.* 2003;96:1316–9.
13. Koster A, Buz S, Krabatsch T, et al. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary bypass grafting: An assessment of different filtration strategies. *J Card Surg.* 2008;23:655–8.
14. Stratmann G, deSilva Am, Tseng EE, et al. Reversal of direct thrombin inhibition after cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. *Anesth Analg.* 2004;98:1635–9.