Use of Bivalirudin for Anticoagulation during Implantation of Total Artificial Heart

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Abstract: Heparin-induced thrombocytopenia presents a challenge for anticoagulation techniques during cardiac surgery and ventricular assist device implantation. Bivalirudin is currently recommended for use during cardiopulmonary bypass for patients with heparin-induced thrombocytopenia but requires the use of special techniques to avoid blood stagnation. We report the successful use of bivalirudin during cardiopulmonary bypass for implantation of the Total Artificial Heart with late operative bleeding likely resulting from heavy cell saver use. Keywords: bivalirudin, cardiopulmonary bypass, anticoagulation, circulatory assist device, Total Artificial Heart.

Successful bivalirudin use has been reported for both adult and pediatric cardiac surgical procedures for patients with heparin-induced thrombocytopenia (1–4). There are isolated reports of use of bivalirudin during the implantation of ventricular assist devices (5) and bivalirudin has been used for anticoagulation after implantation (6,7), but the use of bivalirudin during implantation of the SynCardia Total Artificial Heart has not been reported. We report the successful use of bivalirudin for cardiopulmonary bypass during Total Artificial Heart implantation.

DESCRIPTION

A 19-year-old man was transferred to our institution for management of newly diagnosed idiopathic dilated cardiomyopathy and for heart transplant evaluation. On admission, his ejection fraction was 15% and noted on echo was the presence of a large mural thrombus in the left ventricle. He reported chest pain and shortness of breath on admission. He was admitted to the pediatric intensive care unit and treated with a milrinone infusion and diuretic therapy, which provided some symptomatic relief. He was also started on a heparin infusion as a result of the large left ventricular thrombus. After admission, he developed intermittent episodes of nonsustained ventricular tachycardia that were initially treated with a lidocaine infusion. Lidocaine was stopped after several days because of poor tolerance and because he was not symptomatic from ventricular tachycardia episodes. On Day 9 of his hospitalization, he developed heparin-induced thrombocytopenia (HIT), Type II (platelets 64 × 10E3/uL, normal 143–398 × 10E3/uL) with positive heparin-associated platelet antibody titer (2.455 O.D., normal <1.0) and positive serotonin release assay (36% release, normal <20% release); therefore, he was transitioned to an argatroban infusion for ongoing anticoagulation. He remained stable on milrinone and diuretic therapy for approximately another week and was listed for heart transplantation during this time. On Day 20 of his hospitalization, he developed longer runs of ventricular tachycardia requiring the initiation of an amiodarone infusion and also clinical signs of worsening cardiac function requiring an epinephrine infusion. Secondary to ongoing clinical deterioration, it was determined that he required mechanical support and, as a result of the ventricular thrombus and dysrhythmias, the decision was made to implant the SynCardia Total Artificial Heart (SynCardia Systems Inc., Tucson, AZ). As a result of the presence of HIT, bivalirudin (Angiomax; The Medicines Company, Parsippany, NJ) was used for anticoagulation during cardiopulmonary bypass (CPB) and Total Artificial Heart (TAH) implantation. Platelet count
has normalized $352 \times 10^3$ uL (normal 143–398 $\times 10^3$ uL) on the day of surgery.

The perfusion technique focused on reducing areas for stagnation within the CPB circuit with specific efforts to provide sufficient nonsucker blood flow to the cardiomyotomy and ensuring adequate mixing with the bivalirudin drip. The CPB circuit consisted of a nonheparin-coated circuit with a Terumo FX25 oxygenator (Terumo Cardiovascular Systems Incorporation, Elkton, MD). Circuit modifications included using the recirculation line off the top of the oxygenator to provide flow into the cardiomyotomy with an in-line hemoconcentrator and using a second shunt off the arterial line that returned to the venous line for arterial and venous sampling. Pump suckers were not used until CPB was started, antifibrinolytics were not used, and the arterial cannula was flushed every 3 minutes until decannulation. The prime consisted of 1200 mL Plasmalyte, 25 mEq sodium bicarbonate, and 50 mg bivalirudin. Before bypass, only a cell saver was used to scavenge blood from the periocardial well. The patient received a 1-mg/kg bolus dose of bivalirudin and was placed on cardiopulmonary bypass after confirmation of desired activated clotting time (ACT). The aorta was cross-clamped, antegrade cardioplegia was administered through the aortic root, and vena cavae were snared. Once CPB was initiated, both shunts were opened and remained open until the patient was weaned off of CPB. The infusion of bivalirudin during the pump run was initially delivered at a rate of 2.5 mg/kg/h into the top of the cardiomyotomy reservoir, per our institutional practice, to ensure adequate mixing of the anticoagulant with the pump sucker return. The cell saver used 2.6 g citrate phosphate dextrose for intraoperative cell salvage and postpump salvage.

The surgical technique used was standard for TAH implantation. The left ventricle was opened and apical thrombus was evacuated. The right ventricular outflow tract was incised and the incision carried around the right atrioventricular groove. The interventricular septum was incised and the entire cardiac ventricular mass was amputated at the level of the atrioventricular valves. Both the mitral and tricuspid valves leaflets were excised. The aorta and pulmonary arteries were divided at the sinotubular junctions. The sewing cuff of the left ventricular half of the TAH was completed first using a running suture, and then the right side was sutured to the atrioventricular fibrous rim. The aortic and pulmonary outflow grafts were trimmed to the appropriate length and then sutured to the great vessels using a continuous suture technique. All suture lines were treated with Coseal® (Baxter Healthcare Corporation, Hayward, CA) to obtain hemostasis. The TAH was then inserted into the atrioventricular sewing cuffs and outflow grafts. The device was deaired and initiated as the patient was weaned off CPB. During the entire case, cardiomyotomy suckers were only used inside the heart. All pericardial suction was performed using a cell saver. Modified ultrafiltration (MUF) was carried out at the end of the case. Initial coagulation studies after CPB and MUF showed a prolonged international normalized ratio (INR) of 2.6 and partial thromboplastin time of 73.4 seconds (normal 23.8–32.2 seconds). He received fresh-frozen plasma, cryoprecipitate, and platelet transfusions in the operating room for bleeding, but at the end of the case, there was complete hemostasis at all the anastomotic sites. The lowest platelet count during surgery was $86 \times 10^3$ uL (normal 143–398 $\times 10^3$ uL). The chest was closed 60 minutes after discontinuation of bivalirudin and 42 minutes after termination of CPB.

In terms of bivalirudin dosing and bivalirudin response during TAH implantation, the patient received a bolus of 1 mg/kg bivalirudin and bypass was initiated 28 minutes later with an ACT of 519 seconds. Our practice when using bivalirudin for CPB anticoagulation is to target an ACT of 480 seconds or 2.5 times the patient’s baseline ACT, whichever value is higher. Therefore, because our patient’s baseline ACT was 132 seconds, the target ACT was 480 seconds. The ACT decreased to 405 seconds after 50 minutes of bypass at which time bivalirudin infusion was increased from 2.5 to 2.75 mg/kg/min. The ACT increased to 447 seconds and remained above 480 seconds for subsequent samples. The bivalirudin infusion was discontinued 18 minutes before coming off of CPB. MUF was initiated and maintained for 40 minutes post-CPB. MUF was discontinued as a result of a thrombus visualized in the MUF circuit. The ACT decreased from an initial ACT of 456 seconds to 313 seconds at the end of the MUF.

Throughout the surgical case, approximately 2.5 L of cell saver blood was transfused to the patient. Soon after chest closure, the patient started bleeding profusely from the mediastinal and pleural drainage tubes as well as the incision. He continued to have significant chest tube output for the first 6 hours postoperatively requiring red blood cell, fresh-frozen plasma, and cryoprecipitate transfusions and Factor VII administration (NovoSeven® RT; Novo Nordisk Inc., Plainsboro, NJ) as well as calcium administration for hypocalcemia. He did not require platelet transfusion postoperatively. Bleeding improved after about 6 hours and he did not require re-exploration for bleeding. He was extubated on postoperative Day 1 and chest tubes were removed the next day. Antiplalet therapy was initiated postoperative Day 1 with aspirin and dipyridamole. Warfarin was started postoperative Day 2 and argatroban was used as a bridge until the INR was in the therapeutic range. He was eventually transitioned to the Freedom driver with plans for discharge home, but he received a heart transplant approximately 6 weeks after TAH implantation. Heparin-associated platelet antibody titer several days before transplant was only weakly positive (.663 O.D., normal <1.0) and serotonin release assay.
was negative so heparin was used without complication for CPB during the transplant. He was discharged home 7 days after transplantation.

**COMMENT**

To our knowledge, this is the first report of the use of bivalirudin during CPB for TAH implantation. Bivalirudin provided excellent anticoagulation while on CPB using special techniques to avoid blood stagnation, and our standard approach to using bivalirudin during cardiac surgery with CPB was appropriate in this case. This case was complicated by intra- and postoperative bleeding, which likely was the result of heavy cell saver use. We believe that the cell saver blood may have contained enough bivalirudin to have contributed to a profound coagulopathy that resulted in significant blood loss. In addition, the cell saver blood likely was the cause of the hypocalcemia secondary to the citrate component, which also contributed to his coagulopathy. No surgical sites of bleeding were identified.

Heparin-induced thrombocytopenia is reported in children and adults who require heparin for various reasons for anticoagulation. The incidence is approximately 2–3% in both populations and may be as high as 5–10% in patients undergoing ventricular assist device implantation (8,9). Bivalirudin, a direct thrombin inhibitor, is currently recommended by the American College of Chest Physicians for patients with acute HIT who require cardiac surgery as long as the team of surgeons, anesthesiologists, and perfusionists are aware of the unique features of bivalirudin pharmacology (10). Special techniques are required because bivalirudin undergoes progressive, non-enzymatic degradation if blood stagnation occurs, which can lead to thrombus formation (11). Consideration should be given to the fact that bivalirudin may remain active in cell saver blood. Removal of bivalirudin by cell saver devices is not complete, although it can approach 90% (11). Therefore, a more rigorous protocol of double washing of cell saver blood or testing for bivalirudin levels should be considered, if available. ACT was used to assess the anticoagulation effect of bivalirudin in our patient, but ecarin clotting time, a more specific assay for direct thrombin inhibitors, can more accurately estimate the effect of bivalirudin and bivalirudin levels (12). In addition, there are studies suggesting that bivalirudin may negatively affect platelet function (13), which can also contribute to bleeding complications.

In summary, bivalirudin can be used during cardiopulmonary bypass during TAH implantation without altering standard approach to bivalirudin anticoagulation or TAH implantation. The surgical and medical teams must understand bivalirudin’s pharmacologic properties and effects.

**REFERENCES**