Case Reports

Bivalirudin as an Alternative Anticoagulant for Cardiopulmonary Bypass During Adult Cardiac Surgery—A Change in Practice

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Abstract: The referral of patients for open heart surgery, presenting with a history of heparin hypersensitivity instigated a multidisciplinary effort to find an alternative anticoagulant to heparin. The various options mentioned in the literature call for changes in the routine practice of open heart surgery on cardiopulmonary bypass. These changes involve mostly the perfusion setup and conduct on bypass and to a lesser extent the anesthetic and surgical practice. Nevertheless, the different professions involved in the cardiac surgical firm discussed the proposed changes in a multidisciplinary effort. A new protocol was drafted, endorsed, and executed. The authors highlight these changes and their successful use in the subsequent case study. Keywords: anticoagulation, adult cardiac surgery, bivalirudin, cardiopulmonary bypass, protocol. J Extra Corpor Technol. 2017;49:49–53

Bivalirudin has been successfully used in invasive cardiology (1,2). Its effective use during cardiopulmonary bypass (CPB) has also been extensively reported (3–6), making it the anticoagulant of choice as an alternative to (1) and in conjunction with (7) heparin in patients presenting with hypersensitivity to heparin. Its popularity over other alternative anticoagulants is attributed to a number of advantages linked to its pharmacological properties (2,8).

The use of an alternative anticoagulant to heparin is required in patients undergoing on-pump cardiac surgery and who have been diagnosed with heparin hypersensitivity. Four types of hypersensitivity reactions against heparins and heparinoids have been described (9). The immediate-type or type I reaction affects up to 10% of patients subjected to heparin. It is caused by the direct interaction of heparin with platelets leading to platelet clamping and is clinically manifested within 48–72 hours of initiation of treatment. Heparin-induced thrombocytopenia is a type II reaction involving polyclonal antibodies against heparin-platelet factor 4 complex that activates circulating platelet. Although up to 8% of patients receiving heparin are at risk of developing antibodies, only 1–5% will manifest thrombocytopenia (10). The other two types of hypersensitivity reactions to heparin are type III, presenting Arthus reaction, and type IV delayed-type hypersensitivity reaction (9).

Bivalirudin is an oligopeptide analogue of hirudin acting on thrombin through direct inhibition. It has a half-life of approximately 25 minutes, and is mostly cleared from the circulation by proteolytic enzymes. Approximately 20% is cleared by the renal system (11). In patients with poor renal function, the half-life of circulating bivalirudin is prolonged as a result of impaired renal clearance (2). The absence of an antidote for bivalirudin (1,2) may raise concerns regarding an increased risk of postoperative blood loss (2). However, mechanical blood filtration has been mentioned as an alternative means of removing bivalirudin from the circulation (2).

As a consequence of the blood’s proteolytic activity that eliminates circulating bivalirudin, stagnant blood tends to clot (2). During bypass, the frequent suctioning of blood pools from surgical cavities such as the pleural...
CASE DESCRIPTION

A 68-year-old male patient with a history of hypertension and atrial fibrillation was referred for coronary artery bypass grafting (CABG). He had suffered from an ischemic infarct in the right middle cerebral artery territory with resultant apraxia and dysphasia with subsequent postinfarct epilepsy. He was admitted to hospital with dizzy spells that was deemed cardiac in origin and subsequently underwent an angiogram that showed triple-vessel disease with a preserved left ventricular function. This was in concordance with the echocardiogram finding of an ejection fraction of 62% by biplane Simpson. The patient thus underwent a CABG with left internal mammary artery being anastomosed to the left anterior descending artery and a saphenous vein graft to the posterior descending artery.

A Maquet VKMO 780000 oxygenator (QUADROX-i Adult HMO 70000 + VHK 70000; Maquet, Rastatt, Germany) was set up on a Jostra HL20 heart–lung machine (Maquet) in accordance with the institutional protocol. A blood cardioplegia delivery set (Vanguard; LivaNova Group, Mirandola, Italy) was used with minor modifications for the delivery of cold crystalloid cardioplegia. The circuit was primed with 1,500 mL Hartmann’s Solution (Baxter Healthcare, Norfolk, UK), 150 mL of 15% mannitol solution (Baxter Healthcare), and 50 mg of bivalirudin (Angiox 250 mg; The Medicines Company UK Ltd, Oxfordshire, UK). In view of the patient’s low prebypass hematocrit of 23%, two units of packed red blood cells (PRBC) were added to the prime, removing an equivalent volume of the crystalloid prime from the circuit.

On induction and intubation, blood samples were taken for baseline arterial blood gases (which include electrolytes, hemoglobin/hematocrit level, and metabolites) and coagulation studies, i.e., APTTr, TEG, and ACT. Baseline ACT was 129 seconds, whereas APTTr was 400 seconds, however exceeded the 2.5 × baseline ACT. After the harvesting of the mammary artery was completed, a loading dose of 1 mg/kg bivalirudin was administered through the central line, and a continuous infusion of 2.5 mg/kg/h of the anticoagulant was initiated in accordance with the approved protocol. Coagulation studies were performed 3 minutes after the loading dose of bivalirudin was administered. These were found to be adequate to proceed to CPB (APTTr = 5.05; ACT = 376 seconds).

Following recirculation of the blood prime, de-airing, and completion of the prebypass checklist, the table lines were clamped and divided at the table. The patient was cannulated centrally with a 22-Fr EOPA 3D aortic cannula (Medtronic, Minneapolis, MN) and a MC2 34/46 dual stage venous cannula (Medtronic).
On proceeding to CPB, the bivalirudin infusion was administered through the perfusion circuit at a rate of 2.5 mg/kg/h. Sevoflurane (Piramal Healthcare, Northumberland, UK) was administered at 2% via the oxygenator. The blood flow of 4.32 L/min calculated at a cardiac index of 2.4 L/min/m², (patient’s height 1.60 m, weight 75.5 kg, and body surface area 1.83 m²) was maintained throughout bypass. The patient’s nasopharageal temperature was maintained at 35°C while on CPB. Arterial blood gases and coagulation status were monitored at 20-minute intervals. Coagulation results were satisfactory throughout the case (Figure 1), with no adjustment being required to the infusion rate of bivalirudin.

A loading dose of 800 mL cold crystalloid cardioplegia (20 mL Sterile Cardioplegia Solution [Martindale Pharmaceuticals, Essex, UK] in 1 L nonlactated Ringer’s Solution [Baxter Healthcare]) was administered through a 14-Ga aortic root cannula (DLP; Medtronic) after the clamping of the aorta. This was delivered at a line pressure of approximately 150 mmHg at a temperature of 4°C–6°C.

Throughout CPB, the pressure gradient across the oxygenator was monitored as an early indication of inadequate anticoagulation leading to clotting. The gradient remained constant throughout the case.

To avoid stagnation of blood, all shunt lines within the circuit were temporarily unclamped every 20 minutes to allow fresh anticoagulated blood through. Blood pools in the surgical field were also suctioned back to the circuit. Furthermore, the blood volume in the cardiotomy reservoir was maintained below the 500 mL level to ensure a fast turnover, thus avoiding possible stagnation. As a
result, 2,500 mL of blood were displaced into CPDA-1 bags (Terumo; Pempol Ltd, Trivandrum, India), most of which was processed with an XTra cell saver (LivaNova Group). The resultant washed cells were transferred to the oxygenator to help raise and maintain adequate hematocrit levels on bypass. The remaining citrated blood was added to the circuit at the end of bypass so as to have adequate volume for weaning off the heart–lung machine.

After an aortic cross clamp time of 28 minutes and on completion of the proximal anastomosis, CPB was terminated uneventfully with normal sinus rhythm and satisfactory hemodynamics. Total bypass time was 56 minutes. Following this, a 50 mg bolus of bivalirudin was added to the pump in addition to an infusion of 50 mg/h. The remaining volume in the perfusion circuit was circulated through all the shunt lines and recirculation lines to avoid stagnation. Once decannulated, the venous line was siphoned with normal saline. Following the decannulation of the aorta, the aortic line was reconnected to the venous line and oxygenator blood was circulated through. Once the patient was stable and the heart–lung machine no longer required, the residual pump blood, amounting to 1,500 mL, was processed with the cell saver. This decision was taken to ensure the total removal of bivalirudin from the blood prior to reinfusing. In total, 1,186 mL of processed blood at a hematocrit of 52% was returned to the patient during the procedure.

The patient was admitted to cardiac intensive care unit (CICU) for postoperative recovery. The average blood loss via the chest drain was of 5 mL/h for the first 5 hours increasing to 20 mL/h for the subsequent 12 hours. Consequently, cell salvaging was not required. Within 10 hours postbypass, APTTr had decreased significantly although remained slightly elevated (Figure 1). During the 48-hour recovery period in CICU, a total of 570 mL of blood was collected from the chest drains while 1 unit of PRBCs and 2 units of fresh frozen plasma were transfused. The patient had an uncomplicated postoperative recovery and was discharged from hospital 5 days postoperatively. He was found to be doing well at the first follow-up clinic 4 months after surgery.

COMMENTS

Bivalirudin is a direct thrombin inhibitor that has been previously used as an alternative anticoagulant to heparin
mostly for percutaneous coronary interventions and also during CPB. Its pharmacological properties make it an attractive alternative anticoagulant to heparin for patients presenting with heparin hypersensitivity requiring cardiac surgery on CPB. However, the normal surgical protocol needs adjusting to reflect these properties. These changes mostly affect the perfusion setup and conduct on bypass.

Alterations to an established protocol is a challenging task especially for a unit like ours that has been using heparin in adult cardiac surgery for more than 20 years. A positive outcome can be achieved with the involvement of all the professions associated with cardiac surgery (2).

Changes in our protocol were based on an extensive literature search. CPB in the presented case was conducted successfully and uneventfully, indicating a thorough and effective multidisciplinary team effort and strict adherence to the consented protocol.

As a consequence of the limited data collected, the lacking sensitivity (or otherwise) of ACT to an increasing blood concentration of bivalirudin, as reported by various studies (1,3,11,12) cannot be demonstrated. However, after the loading dose of bivalirudin, the ACT did exceed the $2.5 \times$ baseline target adopted by Federman et al. (3) but fell short of the traditional 400 seconds ACT threshold at an APTTr >5.0. This is congruent with the findings of Nicolaidis et al. (1). In future cases, both APTTr and ACT should be used as standard analytical tools to assess the patient’s coagulation status when using bivalirudin as an alternative anticoagulant. The target values permitting initiation of bypass have been set to APTTr >5.0 and $2.5 \times$ baseline ACT.

Following termination of CPB, APTTr declined steadily, reaching half the bypass value after approximately 3 hours postbypass and returned to near baseline within 10 hours. The excessive postoperative bleeding during the first few hours of recovery encountered by other authors (2) was not experienced by our unit and as a result cell salvaging was not required.

In conclusion, the new protocol for the use of bivalirudin as an alternative anticoagulant during CPB in our unit has been shown to be satisfactory. Following a postoperative consultation with the professions involved, the new protocol was made official. Nevertheless other changes might be required in the future to keep it updated with ongoing evidence and developments in this area.

REFERENCES