

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 anes-

thetic 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

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The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

and pericardial spaces has been proposed. Shunt lines that are normally clamped during bypass need to be temporarily opened to allow fresh anticoagulated blood to flush through (8,11). Maintaining low blood levels in the hard-shell venous reservoir, especially with those models exhibiting poor mixing, ensures an adequate turnover of anticoagulated blood in the reservoir (8). Excess blood can be bagged up in citrate-based anticoagulant, monitoring blood calcium levels on retransfusion (8,11) to prevent hypocalcemia. With blood primes, blood is added to the perfusion circuit just prior to initiation of bypass thus minimizing the contact time with bivalirudin (11).

A number of recommendations are found in the literature describing the target-activated clotting time (ACT) permitting institution of CPB following the loading dose of bivalirudin. Federman et al. (3) set their ACT cutoff to 480 seconds or $2.5 \times$ baseline ACT, whichever was the higher. Others recommend solely a $2.5 \times$ baseline ACT cutoff (8,11), whereas Nicolaidis et al. (1) opted for the conventional 400 seconds target ACT. Both point-of-care ACT analysis and other coagulation tests available at the hematology laboratories (i.e., activated partial thromboplastin time ratio [APTT_r], prothrombin time, thromboelastogram [TEG]) rise linearly with an increasing bivalirudin concentration (4,5,11). However, some studies have demonstrated poor ACT sensitivity (kaolin and celite) around the critical cutoff level permitting institution of CPB (3,5,11,12). This is evident in the case study presented by Nicolaidis et al. (1), where at an APTT_r of 4.98, the ACT fell short of the targeted 400 seconds, however exceeded the $2.5 \times$ baseline ACT. In review of the aforementioned data, we opted for a cutoff limit of $2.5 \times$ patient baseline ACT, confirmed by an APTT_r greater than 5.

Other modifications made to our protocol are illustrated in Table 1. This change in practice reflects the pharmacological properties of bivalirudin that differ from those of heparin, routinely used during CPB in our center. The proposed changes were extensively discussed and ultimately approved in multidisciplinary meetings. This process was instigated following the referral of a patient for cardiac revascularization presenting with heparin hypersensitivity. This was the first ever such case in over 20 years of cardiac surgery in Malta. The implementation of the final protocol is described in the case study below.

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.

The patient's allergy to heparin was diagnosed 10 years prior after being exposed to intravenous unfractionated heparin for the treatment of the ischemic cerebral infarct. He developed a generalized rash 24 hours after initiation of treatment which resolved following the cessation of the intravenous heparin and the administration of intravenous steroids and antihistamines.

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., APTT_r, TEG, and ACT. Baseline ACT was 129 seconds, whereas APTT_r was 1.05. 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 (APTT_r = 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).

Table 1. Adaptations made to the established protocol for cardiac surgery on CPB reflecting the use of bivalirudin as an alternative anticoagulant to heparin.

	Normal Protocol—Using Heparin	Changes Affected for Using Bivalirudin	Reference
HLM setup			
Prime	+10,000 IU heparin	+50 mg bivalirudin	(8,11)
Pressure monitoring on bypass	Postmembrane (line) pressure	Pre- and postmembrane pressure	
Cardioplegia	Cold blood cardioplegia using dual head roller pump	Cold crystalloid cardioplegia delivered using single roller pump	
Anticoagulation			
Anticoagulation monitoring	ACT	ACT, APTTr	
ACT threshold	ACT >400 seconds to proceed to bypass, >480 seconds on bypass	At least 2.5 × baseline ACT	(11)
APTTr threshold	Not applicable	>5.0	(3,8)
Anticoagulation maintenance on bypass	5,000–10,000 IU bolus heparin if required	Continuous infusion of Bivalirudin at 2.5 mg/kg/h on CPB direct into venous line	
Conduct on bypass			
Avoiding stagnation of blood in the circuit	Nil	Recirculation of blood through all closed shunts every 15–20 minutes	(2,11)
Collection of blood pools in the surgical field to avoid stagnation of blood (postloading dose of anticoagulant)	Nil	Every 15–20 minutes Any blood pools laying stagnant for more than 20 minutes are to be aspirated into the cell saver and processed	(2,8)
Displacement of excess blood in reservoir during CPB	In plasma transfer bags with no preservatives	In CPDA-1 bags, monitoring blood calcium levels on reinfusion	(8)
Conduct off bypass			
Anticoagulant in bypass circuit	Nil	50 mg into oxygenator + 50 mg/h infusion	(8)
Recirculation of blood in circuit	Slow recirculation of blood through all shunt/recirculation lines	Recirculate blood through all shunt/recirculation lines with ongoing infusion of bivalirudin	(1)
	Nil	Connect table lines after decannulation and recirculate blood until patient is stable enough to empty out CPB circuit for cell washing	(1,8,11)
Others			
Cell salvaging	35,000 IU heparin in 1 L 0.9% heparin for priming cell saver reservoir and anticoagulation of suctioned blood	Citrate-based saline for priming cell saver reservoir and anticoagulation of suctioned blood	(8)
Anesthesia			
Pressure/infusion lines	Heparinized saline	Sterile saline 0.9% with no added anticoagulant	
Anticoagulant loading dose prebypass	300–400 mg/kg loading dose	1 mg/kg loading dose plus 2.5 mg/kg/h continuous infusion (until initiation of CPB)	(8,11)
Surgical nurses			
Preservation of vein graft	Heparinized blood	Sterile saline 0.9%	

CPDA-1, citrate phosphate dextrose adenine; HLM, heart–lung machine.

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 nasopharyngeal 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

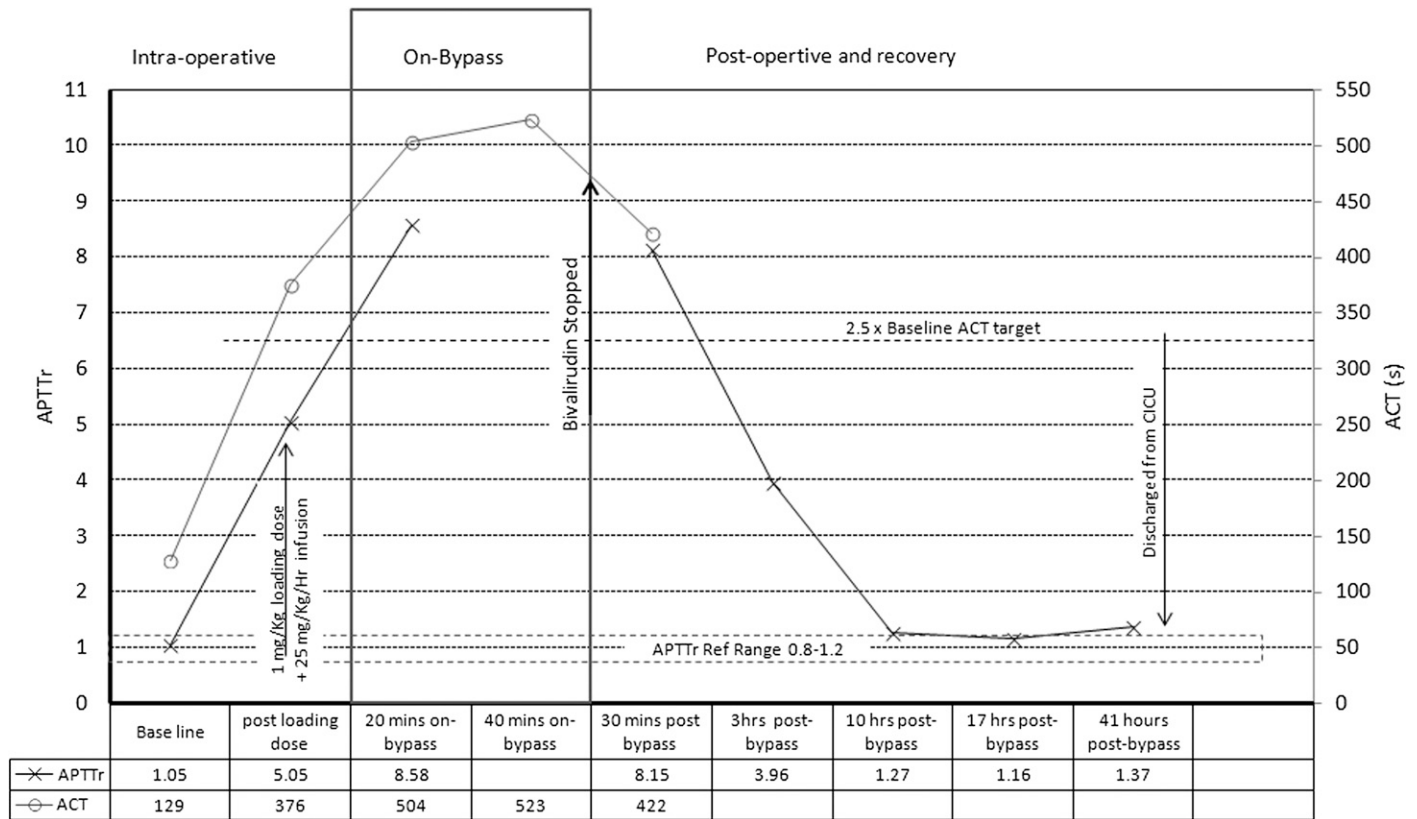


Figure 1. Results of coagulation analysis performed intra- and postoperatively until discharge from CICU. APTTr reference range and 2.5 × baseline ACT limit are represented on the graph.

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.

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