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Routine Use of the Direct Thrombin Inhibitor Bivalirudin for Off-Pump Coronary Artery Bypass Grafting is Safe and Effective

George J. Palmer, MD,[1] Iyer S. Sankaran, MD,[2] Gary M. Sparkman, PA-C,[2] Andreas Koster, MD,[3] Cornelius M. Dyke, MD,[4] George Ebra, EdD[1]

[1]Florida Hospital Cardiovascular Institute, Orlando, Florida; [2]Central Florida Regional Hospital, Sanford, Florida, USA; [3]Department of Anesthesia, Deutsches Herzzentrum, Berlin, Germany; [4]Gaston Memorial Hospital, Gastonia, North Carolina, USA

ABSTRACT

Anticoagulation with unfractionated heparin has been the standard of care for more than a half-century for patients undergoing cardiac surgery. The risk of heparin-induced adverse reactions dictates the need for a safe and effective alternative, particularly in off-pump coronary artery bypass (OPCAB) surgery, an approach associated with a perioperative prothrombotic condition that may negatively influence graft patency. Between March 2003 and January 2005, 243 consecutive patients underwent OPCAB with bivalirudin (0.75 mg/kg bolus with 1.75 mg/kg per hour infusion). There were 171 men (70.4%) and 72 women (29.6%). The mean age was 64.9 ± 10.9 years (age range 32-88 years). There were 147 patients (60.5%) with 3-vessel disease; 46 (18.9%) had substantial (>50%) stenosis of the left main coronary artery; 104 (42.8%) had a moderately reduced (0.30 to 0.50) ejection fraction; and 9 (3.7%) had a severely reduced (<0.30%) ejection fraction. Five patients (2.1%) required conversion to cardiopulmonary bypass and subsequently received heparin. Postoperative complications included perioperative myocardial infarction in 6 patients (2.5%), stroke in 3 (1.2%), prolonged ventilation in 4 (1.6%), reoperation for bleeding in 3 (1.2%), renal insufficiency in 14 (5.8%), atrial fibrillation in 26 (10.7%), low cardiac output in 3 (1.2%), and deep sternal infection in 1 (0.4%). Blood products were used in 117 patients (48.1%). The overall hospital mortality rate was 0.4% (1 of 243). Bivalirudin is a safe and effective anticoagulant that may be routinely used as an alternative to heparin and protamine in patients undergoing OPCAB. This is evidenced by low hospital mortality and morbidity rates. Further follow-up is warranted to discern the influence of bivalirudin on long-term clinical outcomes.

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Correspondence: George Palmer, Cardiovascular Surgeons, P.A., 217 Hillcrest Street, Orlando, FL 32801; 407-425-1566; fax: 407-422-016 (e-mail: cutter9512@hotmail.com).

INTRODUCTION

Heparin has been used since 1953 as the anticoagulant of choice in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) [Cohn 2003]. Advantages of heparin include reproducible effect, relative ease of monitoring with point-of-care testing, and rapid reversibility with protamine sulfate. However, heparin has several serious limitations that detract from its effectiveness as an anticoagulant agent in cardiac surgery. The use of heparin may lead to antithrombin depletion, which may result in adverse outcomes [Ranucci 2001]. Heparin clinically activates platelets, requires a cofactor for effect (anti–thrombin III), remains inactive against clot-bound thrombin, and exhibits nonlinear dosing characteristics. Moreover, patients with prolonged exposure to heparin may develop a resistance and require a transfusion of antithrombin III or plasma protein to achieve an adequate level of anticoagulation. In addition, heparin may cause a series of adverse effects including heparin-induced thrombocytopenia (HIT), a catastrophic complication [Bartholomew 2005], and heparin-induced thrombosis syndrome. HIT may occur in a small number of patients even when heparin is not given postoperatively [Warkentin 2001].

These adverse reactions create a serious condition manifested by platelet activation and thrombin reliance caused by antibody binding to the heparin/platelet factor 4 complex and the platelet Fc receptor. Anti–platelet factor 4-heparin (PF4/H) antibodies may occur in approximately 70% of the patients exposed to heparin during CPB [Warkentin 2003], resulting in increased lengths of hospital stay [Williams 2003; Bennett-Guerrero 2005] and other adverse clinical events. Limiting heparin in acute coronary syndrome patients is difficult because many receive multiple exposures over subsequent hospitalizations. The use of bivalirudin in patients with acute coronary syndrome undergoing percutaneous coronary intervention may avoid the need for heparin [Lincoff 2003; Matar 2006].

Despite the many years of experience with heparin, the optimal dose for cardiac surgery patients remains undefined, particularly for patients undergoing off-pump CAB (OPCAB) grafting. Patients undergoing OPCAB may receive a full- or half-dose of heparin, with or without protamine

reversal, and varying postoperative antiplatelet regimens [D'Ancona 2001].

Recognizing the limitations and adverse effects inherent in using heparin in percutaneous coronary intervention and cardiac surgery, a hospital-wide initiative was implemented at our institution to limit heparin use. Bivalirudin (Angiomax), a short-acting (25-30 minutes) direct thrombin inhibitor that exhibits primarily nonorgan metabolism through proteolysis [Warkentin 2005] and has no interaction with the PF4 complex, became the anticoagulant of choice for cardiovascular intervention. Although bivalirudin has been used in clinical trials, its use in large series has not been investigated. We performed this single-center, single-surgeon study to discern the effectiveness, safety, and clinical benefits of using bivalirudin in a large cohort of patients undergoing OPCAB.

MATERIALS AND METHODS

Patient Population

The study population consisted of 243 consecutive patients treated during the time period between March 2003 and January 2005 who underwent OPCAB performed by a single-surgeon who used bivalirudin as an anticoagulant agent. This study was approved by the institutional review board, and a waiver of informed consent was granted because of the study's retrospective nature. The clinical characteristics of the patient population are summarized in Table 1.

Patients were classified functionally and symptomatically according to the New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) systems. Preoperatively, heart disease in 34 patients (14.0%) was classified as NYHA class I, in 36 (14.8%) as class II, in 155 (63.8%) as class III, and in 18 (7.4%) as class IV. According to the CCS system, 51 patients (21.0%) were in class 0 (no angina), 5 (2.1%) in class I, 28 (11.5%) in class II, 143 (58.8%) in class III, and 16 (6.6%) in class IV.

Significant coronary artery disease (CAD) that required surgical intervention was defined as an estimated reduction in luminal diameter of ≥50%. The procedure investigated in this study was a first operation in 232 patients (95.5%) and a reoperation in 11 patients (4.5%). Surgery was performed electively in 213 patients (87.7%), urgently in 21 patients (8.6%), and emergently in 9 patients (3.7%). Emergency surgery was performed in cases of intractable angina that did not respond to aggressive clinical measures, impending infarction, or decompensation during cardiac catheterization that required measures such as defibrillation, extended cardiac massage, balloon counterpulsation, or inotropic support were required. All other procedures in the series were considered elective operations.

Table 1. Preoperative Clinical Variables of Study Patients (N = 243)

Variable	Value*
Preoperative Risk Factors	
Male	171 (70.4%)
Female	72 (29.6%)
Age, y	
Mean	64.9 ± 10.9
Range	32-88
Age groups	
<50 y	19 (7.8%)
50–59 y	57 (23.5%)
60–69 y	82 (33.7%)
70–79 y	67 (27.6%)
≥80 y	18 (7.4%)
Coronary risk factors	
Family history of CAD	127 (52.3%)
Hypertension (diastolic pressure >90 mm Hg)	181 (74.5%)
Dyslipidemia (cholesterol >200 mg/dL)	149 (61.3%)
Smoking history	149 (61.3%)
Diabetes mellitus	83 (34.2%)
Perioperative risk factors	
Renal dysfunction (creatinine >2.0 mg/dL)	14 (5.8%)
Cerebrovascular disease	26 (10.7%)
Peripheral vascular disease	29 (11.9%)
Prior myocardial infarction	90 (37.0%)
History of congestive heart failure	33 (13.6%)
Unstable angina	158 (65.0%)
Chronic lung disease	31 (12.8%)
Myocardial infarction (<8 days)	51 (21.0%)
Coronary angiography	
Single-vessel disease	28 (11.5%)
Double-vessel disease	67 (27.6%)
Triple-vessel disease	147 (60.5%)
Left main disease (stenosis >0.50)	46 (18.9%)
Left ventricular ejection fraction	
>0.50	130 (53.5%)
0.30–0.50	104 (42.8%)
<0.30	9 (3.7%)

*Values are n (%) or mean ± SD.

Decision to Use an Alternative Anticoagulant Agent

The routine use of bivalirudin for OPCAB at our institution followed a hospital-wide effort to limit heparin exposure for patients undergoing coronary artery bypass graft (CABG) surgery. The use of bivalirudin was initially limited. Because intraoperative use of heparin resulted in increasing rates of circulating anti-PF4/H antibodies following surgery, however, a decision was made to seek an alternative anticoagulant agent. This effort was initiated to reduce the incidence of anti-PF4/H antibodies, HIT, and thrombosis syndrome [Francis 2003].

A multidisciplinary team of surgeons, anesthesiologists, hematologists, pharmacists, and hospital administrators was assembled to examine alternative strategies for patients undergoing cardiac surgery. The team decided to increase the use of off-pump techniques for CABG to avoid the deleterious effects of CPB [Kirklin 1983; Edmunds 1995] and reduce patient exposure to heparin. Bivalirudin was selected as the anticoagulant of choice for OPCAB patients because of its linear dosing characteristics and short biologic half-life. Results have been favorable at our institution with ongoing

use of bivalirudin in the cardiac catheterization laboratory and for peripheral vascular surgical procedures.

The era of heparin-free cardiac surgery at our institution began in March 2003 when anticoagulation with bivalirudin was used for all patients undergoing OPCAB. Following the initial 40 cases, outcomes were reviewed for quality assurance and to ensure the safety and efficacy of bivalirudin during this initial experience. After no adverse effects were observed during the initial trial phase, a heparin-free OPCAB program at our institution flourished and continues to this date.

Data Collection and Management

Preoperative, intraoperative, and postoperative demographic and clinical variables were collected prospectively by reviewing the patient hospital records, catheterization reports, and cineangiogram and echocardiography results. Data were collected in a standardized manner using prespecified definitions. At the time of the operation a patient registration form was completed for each patient in the study. Data were entered into a cardiac surgery clinical database and subsequently retrieved for analysis.

Data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as the mean ± SD. Data collected were analyzed using the Number Cruncher Statistical Systems (NCSS, Kaysville, UT, USA).

Operative Technique

Surgery was performed using a median sternotomy and standard anesthesia and OPCAB surgical techniques, including apical suction, epicardial stabilization, and the mister/blower for increased visualization. A cell saver was used throughout the series, and citrate was used as the anticoagulant of choice for the cell saver. The use of the cell saver did not cause any adverse effects on anticoagulation parameters during the procedure, and the cell saver was not associated with episodes of air embolism or excessive intraoperative and postoperative bleeding.

The anticoagulation protocol consisted of a 0.75 mg/kg loading dose given at the completion of the harvesting of the internal mammary artery (IMA). A bivalirudin infusion was also initiated (1.75 mg/kg per hour) and continued until the completion of the last proximal anastomosis. The activated clotting time (ACT) was routinely measured to assure appropriate drug delivery. If an initial ACT was greater than 300 seconds then no further measurements were conducted; otherwise, no additional bivalirudin bolus dosing was used.

Epicardial stabilization was used for all distal anastomoses. The left IMA anastomosis to the left anterior descending artery was completed first, followed by saphenous vein graft distal anastomoses. Saphenous vein grafts were filled with a bivalirudin solution (0.2 mg/m^2) on completion of the distal anastomoses and prior to completing the proximal anastomosis. Following each completed anastomosis, a bulldog clamp was placed adjacent to the distal anastomosis to prevent backflow of blood and ensure stasis within the vein graft until the proximal anastomosis was completed.

In the initial 40 cases, the proximal anastomosis was created by partially occluding the ascending aorta. Subsequently, the proximal anastomosis was created using a clampless technique/heartstring device (Boston Scientific, Natick, MA, USA) An advantage of the clampless technique for patients in whom bivalirudin is administered is that imperfect hemostasis occurs during the anastomosis procedure, allowing for the mixing of blood and the avoidance of stasis. Following the completion of the last proximal anastomosis, the bivalirudin infusion was discontinued. The use of bivalirudin did not lead to increased operative times.

Postoperative management of patients was routine, with the administration of antiplatelet therapy and aspirin initiated within 24 hours of surgery. Platelet counts were monitored using an aggressive protocol to diagnose and treat patients with suspected HIT. Any patient with a platelet count of 100,000/μL was tested for anti-PF4/H antibodies and was tested again if the platelet count did not return to baseline at the time of discharge from the hospital. Patients who experienced a suspected or confirmed thrombotic event were also tested for anti-PF4/H antibodies. Patients who required anticoagulation therapy for atrial fibrillation or dialysis were screened for anti-PF4/H prior to the initiation of heparin therapy.

Operative Data

A total of 832 coronary artery grafts were performed (mean, 3.4 per patient; range, 1 to 7). Eleven patients (4.5%) had 1 graft, 40 patients (16.5%) 2 grafts, 75 patients (30.9%) 3 grafts, 77 patients (31.7%) 4 grafts, and 40 patients (16.5%) 5 or more grafts. The left IMA was used in 222 patients (91.3%), the right IMA in 1 patient (0.4%), and the radial artery in 6 patients (2.5%). Conversion to CPB was necessary in 5 patients (2.1%). In this subset of patients, bivalirudin was discontinued and heparin was initiated as the anticoagulant.

RESULTS

Hospital Morbidity and Mortality

A series of hospital complications was documented, which included reoperation for bleeding, prolonged mechanical ventilation, cerebral vascular accident, perioperative myocardial infarction, renal insufficiency, atrial fibrillation, low cardiac output, and deep sternal infection. The overall incidence of postoperative morbidity for the series was low, with 197 patients (81.1%) experiencing no hospital complications. The hospital complication rates are shown in Table 2.

Table 2. Hospital Complications of Study Patients (N = 243)

Complications	n (%)
Reoperation for bleeding	3 (1.2%)
Ventilator prolonged	4 (1.6%)
Cerebral vascular accident	3 (1.2%)
Perioperative myocardial infarction	6 (2.5%)
Renal insufficiency	14 (5.8%)
Atrial fibrillation	26 (10.7%)
Low cardiac output	3 (1.2%)
Deep sternal infection	1 (0.4%)

Prolonged mechanical ventilation was defined as required ventilatory support for more than 24 hours postoperatively, cerebral vascular accident as a neurological deficit that remained unresolved for more than 24 hours, perioperative myocardial infarction as a new onset of Q waves with or without elevation of myocardial enzymes, or a substantial elevation of myocardial enzymes alone. Renal insufficiency was defined as a creatinine level greater than or equal to 2.0 mg/dL. Low cardiac output syndrome was defined as clinical evidence of hypotension, oliguria, and peripheral vascular constriction with normal or supranormal left ventricular filling pressure or a measured cardiac index of less than 2 L/min per m^2, necessitating the administration of catecholamines or the use of an intraaortic balloon pump (IABP)—or both. Deep sternal infection included sternal instability with positive wound cultures necessitating an additional surgical procedure such as incision and drainage, debridement, or secondary closure.

Placement of the IABP was required in 4 patients (1.6%), but none of the patients requiring use of the IABP experienced a major vascular complication. Blood products were used by 117 patients (48.1%), and the average postoperative length of stay was 7.6 ± 6.7 days.

Hospital mortality was defined as death occurring during surgery or the hospitalization period during which the procedure was performed or death occurring after discharge from the hospital but within 30 days of the surgical procedure, unless the cause was unrelated to the operation. The hospital mortality rate was 0.4 % (1 of 243 patients). The patient who died was a 73-year-old woman in CCS class IV with unstable angina who presented with multiple comorbidities. During surgery the patient became hemodynamically unstable and conversion to CPB was required. This patient experienced a myocardial infarction postoperatively, low cardiac output, and cardiac arrest. She died on postoperative day 4.

DISCUSSION

CABG continues to be the most widely performed cardiac surgical procedure in the world and has been frequently accomplished with the use of CPB. The application of CPB has afforded the surgeon a bloodless and motionless heart on which to carry out the operation. Although CABG using CPB has been successful, it has long been recognized that the application of this technology has some short- and long-term deleterious effects [Kirklin 1983; Edmunds 1995].

Advances in technology have made off-pump myocardial revascularization an attractive alternative for both the medical community and the patient. For more than a half-century, heparin has been used as the anticoagulant of choice in cardiac surgery. Limitations of this anticoagulant agent, however—including incomplete anticoagulation, heparin resistance, and the development of heparin antibodies—have raised serious concerns. These limitations have led to the search for an alternative anticoagulant in cardiac surgery.

Bivalirudin, a short-acting, nonreversible, direct thrombin inhibitor, has emerged as a viable candidate to replace heparin in cardiac surgery. This drug is characterized by a relatively short half-life (approximately 25 minutes), with 80% eliminated primarily through proteolytic cleavage and the remainder through renal excretion [Bates 2000]. Several studies have demonstrated the benefits of bivalirudin in OPCAB grafting [Merry 2004; Smedira 2006], in patients undergoing cardiac surgery with CPB [Koster 2004; Dyke 2006], and in patients with thrombocytopenia [Bott 2003; Koster 2004]. The use of bivalirudin in patients undergoing percutaneous intervention is well documented [Lincoff 2003; Matar 2006].

The present study represents a single-surgeon experience using standardized techniques in a large cohort of patients. In the current investigation, the use of bivalirudin did not lead to any hemodynamic side effects or anaphylaxis. Neither early graft failure nor an excessive rate of reoperation for bleeding occurred. The hospital mortality rate of 0.4% (1 of 243 patients) was low. The only death occurred in a patient with hemodynamic instability who required conversion to CPB and the subsequent use of heparin.

Hospital morbidity in the series was also low, with more than 3/4 of the patients (81.1%; n = 197) experiencing no in-hospital complications. The reoperation rate of 1.2% (3 of 243 patients) is lower than reported in other OPCAB studies [Angelini 2002; Khan 2004; Smedira 2006]. The amount of chest tube drainage observed in this series was unremarkable. The myocardial infarction rate was low at 2.5% (6 of 243 patients) and less than that reported in other OPCAB series [Van Dijk 2001; Angelini 2002; Puskas 2003; Khan 2004]. The stroke rate of 1.2% (3 of 243 patients) was comparable to that reported in a large metaanalysis [Sedrakyan 2006].

Previously conducted studies in the use of bivalirudin in cardiac surgery have been limited by small sample sizes and the participation of several surgeons. In recently reported, rigorous clinical trials, bivalirudin has been demonstrated to be a safe and effective anticoagulant for patients undergoing coronary revascularization, with or without CPB [Dyke 2006; Smedira 2006]. In the EVOLUTION-OFF trial, there was no difference observed in outcomes between patients anticoagulated with heparin versus bivalirudin; although, the incidences of transfusion and reexploration in both groups were higher than our single-center experience.

The superior outcomes in our single-center experience may be a function of the learning curve, because the number of patients in this series exceeds the total EVOLUTION-OFF enrollment. In another single-center, single-surgeon study, patients treated with bivalirudin were found to have superior early graft patency compared with a cohort anticoagulated with heparin/protamine [Merry 2004]. These single-center studies suggest that greater experience with bivalirudin may serve to improve clinical results.

Specific technical issues regarding the use of bivalirudin for OPCAB surgery must be considered. A greater understanding of the pharmacokinetics must be achieved to maximize the benefits of this drug. How best to monitor the anticoagulation state and reverse the drug's effects, without creating thrombosis, is an important consideration. Careful attention must be focused on how to manage the operative field. Discontinuing infusion during the creation of the last proximal anastomosis allows bivalirudin to metabolize before chest closure and minimizes the length of time spent achieving hemostasis.

Also, an active effort to avoid stasis of blood within the chest cavity during surgery can minimize the coagulum that occurs, thus reducing the consumption of circulating clotting factors. Additionally, bivalirudin's pharmacodynamic characteristics dictate careful postoperative medical management to minimize bleeding and transfusion.

Although this study was not designed to assess the economic impact of heparin versus bivalirudin, it is well recognized that the latter is a more expensive anticoagulant agent. However, the use of bivalirudin precludes the occurrence of heparin-induced thrombocytopenia and associated thrombosis, which can be a potentially devastating and costly complication for a patient receiving heparin in cardiac surgery. Recognizing the cost associated with bivalirudin, the data in this investigation clearly demonstrate that bivalirudin is an effective anticoagulant agent in OPCAB surgery, offering a safe and practical option that may serve to improve clinical outcomes in cardiac surgery.

Limitations of the Study

This study has provided some important clinical information regarding the use of bivalirudin in OPCAB surgery. However, there are several limitations which deserve consideration. This investigation was observational, nonrandomized, and conducted by retrospective review of prospectively collected data and has the inherent limitations of this type of study design. Moreover, the lack of a control group detracts from the efficacy of this study. The absence of follow-up to assess the long-term benefits of bivalirudin use in OPCAB surgery is also a limiting factor. A strength of the study is that the data collected on preoperative, intraoperative, and postoperative clinical variables were gathered in a standardized manner using prespecified definitions.

CONCLUSION

The use of bivalirudin shows promise, from a technology assessment perspective, as a replacement for heparin as the anticoagulant of choice in cardiac surgery. The outcome data generated from this large cohort of patients clearly demonstrate that bivalirudin is a safe and effective anticoagulant agent in OPCAB surgery. Bivalirudin is an efficient and practical option that improves clinical outcomes. Continued clinical evaluation and further follow-up are warranted to confirm the long-term benefits of bivalirudin as an anticoagulant in cardiac surgery.

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