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The safety of bivalirudin during elective percutaneous coronary interventions in heart transplant patients

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Abstract

Background: *Bivalirudin has been shown to be safe and effective during percutaneous coronary interventions (PCI) of native coronary arteries in the REPLACE 2 trial. The safety of bivalirudin during PCIs in heart transplant patients is not known.*

Methods: *Heart transplant patients who had undergone PCI of* de novo *lesions and received bivalirudin during the procedure were included in the study. Medical records were reviewed for the occurrence of death, myocardial infarction, target vessel revascularization or major bleeding up to 30 days after discharge. The results were compared with the REPLACE 2 trial and with a control group of heart transplant recipients who received heparin during their procedures.*

Results: *There were 51 separate PCIs performed in 30 patients in the study group. The mean age was 56 ± 12 years and 6 (20%) were women. The control group consisted of 24 patients who had undergone 35 PCIs. There were no deaths, myocardial infarctions or target vessel revascularization during the follow-up period in the study group. The combined endpoint of death, myocardial infarctions, target vessel revascularization and major bleeding requiring two or more units of packed red blood cells occurred in 2 (3.9%) patients compared to 275 (9.2%) patients in the REPLACE 2 trial ($p = 0.195$) and 5 (14.3%) in the control group ($p = 0.115$).*

Conclusion: *Bivalirudin is a safe antithrombotic medication to use during elective PCI in heart transplant patients with cardiac allograft vasculopathy.* (Cardiol J 2007; 14: 458–462)

Key words: bivalirudin, safety, percutaneous coronary interventions, heart transplant

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Introduction

Cardiac allograft vasculopathy (CAV) occurs in 42% of heart transplant patients three years after transplantation and is the leading cause of death in these patients within one and three years [1]. Although CAV is pathologically distinct from native coronary artery disease [2], percutaneous coronary intervention (PCI) is effective and safe in this patient population [3–7]. Heparin is the traditional antithrombotic agent used during PCI in heart transplant recipients. Interest in the use of bivalirudin in this population has increased in the light of

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studies that have shown its safety and effectiveness during PCI of native coronary artery disease [8–11]. We report on the safety of bivalirudin use in one center during PCI in heart transplant patients and compare the results with historical controls from the Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events (REPLACE) 2 trial that was performed in non-transplant patients and to heart transplant patients from our center who received heparin during their PCI.

Methods

Patient population

The records of heart transplant recipients who had undergone a PCI at the University of Alabama at Birmingham from June 2003 to December 2005 were retrospectively reviewed. Patients who had a PCI of one or more *de novo* lesions and who received bivalirudin during the index procedure were included in the study. Patients who underwent PCI solely for in-stent restenotic lesions were excluded. A control group of heart transplant patients who underwent PCI from January 2002 till January 2007 and received heparin during the procedure was identified.

Study protocol

Bivalirudin was administered as a bolus of 0.75 mg/kg prior to the start of the intervention, followed by an infusion of 1.75 mg/kg/h for the duration of the intervention. Glycoprotein 2b3a inhibitors were used at the operator's discretion. Patients who underwent PCI of multiple vessels or lesions during the same visit to the catheterization laboratory were considered to have a single procedure, and each visit to the catheterization laboratory was considered a separate procedure.

Outcomes

As in the REPLACE 2 trial, the primary endpoint consisted of a composite of death, myocardial infarction, target vessel revascularization or major bleeding within 30 days of the intervention. The secondary endpoint consisted of a composite of death, myocardial infarction or target vessel revascularization. Single endpoints from the above listed composite endpoints were also compared.

Major bleeding was defined as intracranial, intraocular or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 mg/dl, any decrease in hemoglobin of more than 4 mg/dl or transfusion of two or more units of packed red blood cells or whole blood. Cardiac markers were collected every 8 hours and for at least three sets after each procedure. Myocardial infarction was defined as new significant Q waves in two or more contiguous leads or elevation of CPK or CK-MB ≥ 3 times the upper limit of the norm within two days of revascularization and ≥ 2 times the upper limits of the norm outside the setting of revascularization. Therefore both the bleeding and the clinical endpoints were identical to REPLACE 2.

Statistical analysis

Statistical analysis was performed using the SPSS software (Version 11.5, SPSS Inc., Chicago, Illinois). The results are expressed as a percentage frequency or mean ± 1 standard deviation (SD) where appropriate. Categorical variables were compared using a χ^2 test. A two-tailed p-value < 0.05 was considered statistically significant.

Results

The study group consisted of 30 heart transplant recipients who underwent 51 coronary procedures using bivalirudin as an antithrombotic agent. The control group included 24 patients who underwent 35 PCIs. The patients' baseline characteristics at the time of the procedure are shown in Table 1. The two groups are comparable, with the exception that patients who received heparin during their procedures had a higher likelihood of having a history of CAV or having undergone a PCI. The results of coronary angiography and the procedural characteristics are shown in Table 2. In the study group stents were deployed in 48 (94%) procedures. The remaining 3 (6%) procedures consisted of pressure wire or intravascular ultrasound evaluations of intermediate coronary lesions with no intervention performed. We elected not to exclude these patients, although they did not undergo an intervention since they had received bivalirudin and were at risk of complications. All except 1 patient (98%) received clopidogrel before, during or after the procedure. The patient who did not receive clopidogrel had pressure wire evaluation of a lesion and did not require PCI.

The mean hospitalization duration was 2.7 ± ± 2.0 days (range 2–13) for the study group compared to 2.9 ± 1.9 days (range 1–10) in the control group, both groups having a median of two days. In the patients who received bivalirudin there were two episodes of major bleeding, one of which occurred during the index hospitalization and involved right femoral artery blood loss that required 5 units

Table 1. Baseline characteristics.

Characteristics	Bivalirudin (n = 30)	Heparin (n = 24)	p
Age (years)	56 ± 12	58 ± 13	NS
Women	6 (20%)	6 (25%)	NS
Race			
Caucasian	20 (67%)	17 (71%)	NS
African American	9 (30%)	7 (29%)	
Other	1 (3%)	0 (0%)	
Reason for heart transplant			
Ischemic cardiomyopathy	17 (57%)	12 (50%)	NS
Non-ischemic cardiomyopathy	8 (27%)	9 (38%)	
Congenital heart disease	2 (7%)	0 (0%)	
Other	3 (10%)	3 (12%)	
Diabetes mellitus	16 (53%)	13 (54%)	NS
Hypertension	25 (83%)	22 (92%)	NS
Peripheral vascular disease	2 (7%)	4 (17%)	NS
Prior stroke	3 (10%)	3 12%)	NS
Chronic kidney disease	15 (50%)	15 (63%)	NS
History of coronary vasculopathy	24 (80%)	24 (100%)	0.028
Prior coronary intervention	15 (50%)	20 (83%)	0.004
Medications*			
Aspirin	48 (96%)	33 (94%)	NS
Clopidogrel — on admission	38 (75%)	31 (89%)	NS
Clopidogrel — on discharge	50 (98%)	33 (94%)	NS
Warfarin	4 (8%)	0 (0%)	NS
Statin	37 (73%)	29 (83%)	NS
Beta-blocker	7 (14%)	6 (17%)	NS
Calcium channel blocker	46 (90%)	27 (77%)	NS
Nitrates	1 (2%)	5 (14%)	0.039
Oral rapamycin	18 (35%)	8 (23%)	NS

*Medications relate to time of procedure and are relative to the number of procedures rather than to the number of patients

of packed RBC transfusion. The second episode occurred 30 days after the index procedure, when the patient presented with maroon stools and fatigue. She was hospitalized and was transfused with 4 units of packed red blood cells and 2 units of platelets. Upper gastrointestinal endoscopy revealed two duodenal ulcers with a visible vessel and an overlying clot in one of the ulcers. The patient was on aspirin and clopidogrel, which were suspected as the culprits of her upper gastrointestinal bleed. Both were stopped and the bleeding was controlled with no further interventions. There were no deaths, myocardial infarctions or urgent target vessel revascularizations. The composite endpoint of death, myocardial infarction, urgent target vessel revascularization or major bleeding occurred in 2 (3.9%) procedures in the first 30 days. The summary of events and the comparisons with the REPLACE 2 results and with the control group are presented in Table 3. Glycoprotein 2b3a inhibitors were provisionally used in 4 (8%) procedures in addition to bivalirudin (3 patients received Reopro and 1 patient eptifibatide) at the operator's discretion, but none had any complication and the hospital stay was two days for all 4 patients. In the control group, glycoprotein 2b3a inhibitors were used in 16 (46%) procedures. The two myocardial infarctions as well as the three major bleeding episodes in the control group occurred in the patients who received glycoprotein 2b3a inhibitors on top of heparin.

Discussion

In this observational study we examined the safety of bivalirudin as the anticoagulant during elective coronary procedures for coronary vascu-

Table 2. Procedural characteristics.

Characteristics	Bivalirudin (n = 51)	Heparin (n = 35)
Vasculopathy > 50% of lumen*		
Left main**	1 (2%)	2 (6%)
Left anterior descending**	35 (69%)	26 (74%)
Left circumflex**	23 (45%)	25 (71%)
Right coronary artery**	18 (35%)	16 (46%)
Target vessel (not mutually exclusive)		
Left main**	1 (2%)	2 (6%)
Left anterior descending**	28 (55%)	19 (54%)
Left circumflex**	13 (25%)	13 (37%)
Right coronary artery**	10 (20%)	5 (14%)
Procedure type		
Balloon angioplasty alone	0 (0%)	0 (0%)
Drug-eluting stent***	47 (92%)	25 (71%)
Heparin coated stent***	0 (0%)	9 (26%)
Bare metal stent***	1 (2%)	1 (3%)
Pressure wire or intravascular ultrasound	3 (6%)	0 (0%)

*Lesion severity as determined by cardiologist reading the angiogram for clinical purposes; **stated artery or any of its major branches; ***either primary stenting alone or included pre- or post-dilatation with balloon angioplasty

Table 3. Events during the first 30 days and comparison with the REPLACE 2.

Events	Bivalirudin (n = 51)	Heparin (n = 35)	p*	REPLACE 2 (n = 2994)	p*
Death	0 (0%)	0 (0%)	Not applicable	7 (0.2%)	0.729
Myocardial infarction	0 (0%)	2 (5.7%)	0.163	207 (7%)	0.052
Target vessel revascularization	0 (0%)	0 (0%)	Not applicable	35 (1.2%)	0.437
Major bleeding	2 (3.9%)	3 (8.6%)	0.393	71 (2.4%)	0.473
Any transfusion	2 (3.9%)	1 (2.9%)	1.000	50 (1.7%)	0.218
Transfusion of ≥ 2 U of PC RBC	2 (3.9%)	1 (2.9%)	1.000	39 (1.3%)	0.108
Death + MI + TVR + major bleeding	2 (3.9%)	5 (14.3%)	0.115	275 (9.2%)	0.195
Death + MI + TVR	0 (0%)	2 (5.7%)	0.163	227 (7.6%)	0.041

*Compared to the bivalirudin group; PC RBC — packed cell red blood cells; MI — myocardial infarction; TVR — target vessel revascularization

lopathy in heart transplant recipients. Since there are no data in the literature about the safety of the traditional anticoagulant, heparin, we compared our data for this population with the bivalirudin arm of the REPLACE 2 trial, which showed that bivalirudin with provisional glycoprotein 2b3a inhibition was not inferior to heparin with planned glycoprotein 2b3a inhibition in relation to ischemic events and was associated with statistically fewer bleeding events [8]. We also compared our results with a control group of heart transplant recipients who underwent PCI using heparin at our center. Our findings, which were tailored to mirror the events monitored in REPLACE 2, showed significantly lower rates of ischemic events (0% for the composite of death, myocardial infarction and target vessel revascularization) and a non-significant trend to a lower rate for the composite endpoint of ischemic events and bleeding at 30 days in comparison with patients with native coronary arteries undergoing a PCI (Table 3). Neither outcome was statistically different from the control group. Unlike REPLACE 2, only a small minority of patients received bare metal stents (Table 2).

We believe that these findings are of practical value to the cardiologist caring for heart transplant patients with CAV. The pathophysiology of CAV is different from that of native coronary artery disease, making it impossible to extrapolate that bivalirudin is safe to use in this patient population without this data being available. Previous reports have established the benefit of PCI in CAV, with procedural

success rates higher than 90% and at acceptable restenosis rates, especially with the use of drug-eluting stents [12–14]. Most of these studies included a small number of patients and did not address the 30-day outcomes of these patients but rather the long-term clinical and angiographic outcomes, making a direct comparison between different antithrombotic agents in this population difficult.

Study limitations

We are aware of the limitations on the conclusions of our single-center retrospective study of a small group of patients. It is important to realize that in order to include this number of patients we surveyed all the heart transplant patients at our center that had had PCI over several years. It is also of note that we did not perform routine angiography at one month and that the lack of ischemic events could be secondary to the fact that transplant recipients have denervated hearts and rarely present with chest pain [15]. We did, however, check routine cardiac markers, including troponins, after PCI on all patients.

Conclusion

Bivalirudin is a safe antithrombotic medication to use during elective PCI in heart transplant patients with CAV. Future multicenter randomized studies are needed to compare the efficacy of heparin with that of bivalirudin in this unique subset of patients undergoing PCI.

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