ORIGINAL ARTICLE

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The Effectiveness of Carvedilol, a New Antioxidant and Antiproliferative Beta-Blocker, on Prevention of Restenosis after Coronary Stent Implantation : a Prospective, Randomized, Multicenter Study

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ABSTRACT

Background: Carvedilol is a direct inhibitor of vascular smooth muscle cell migration and proliferation through inhibition of mitogen-activated protein kinase activity and regulation of cell cycle progression. It produced an 84% suppression of neointimal hyperplasia in rat carotid angioplasty model, but no data are available regarding its effect on stent restenosis in patients. We tested whether a sustained oral administration of carvedilol reduces restenosis after coronary stenting in patients. **Methods**: One hundred fifty nine patients were randomized to receive either carvedilol (50 mg/day, n=80) or atenolol (50 mg/day, n=79) at least 1 day before stenting and continued on the same medication over 3 months. The primary end point was angiographic restenosis (>50% diameter stenosis) at follow-up angiography. **Results**: Baseline clinical and angiographic variables were similar between the carvedilol and atenolol group. The carvedilol dose was tolerable in most patients after adjustment of other medications, but reduced in 3 patients due to hypotension and dizziness. Angiographic follow-up was done in 137 patients (86%) and the restenosis rate was not different significantly between both groups (17.1% versus 19.4%, p=0.732). **Conclusions**: A sustained oral administration of carvedilol is not effective to reduce stent restenosis. With carvedilol targeting regulators of cell cycle progression and having a profound neointimal inhibition with a high blood concentration in an experiment, further investigations using a stent-based delivery to achieve a high local concentration may be warranted. **(Korean Circulation J 2004;34(1):35-40)**

KEY WORDS: Carvedilol; Stents; Coronary restenosis; Drug therapy.

Introduction

The long-term clinical efficacy of intracoronary stenting is limited by restenosis, which occurs in 15% to 30% of patients.[1)2)] Stent restenosis is due solely to neointimal hyperplasia.[3-5)] Stent-induced mechanical arterial injury and a foreign body response to the prosthesis incite acute and chronic inflammation in the vessel wall, with elaboration of cytokines and growth factors that induce multiple signaling pathways to activate smooth muscle cell (SMC) migration and proliferation.[3-5)] Therefore, the delivery of the agents inhibiting cell cycle progression via stent platforms[6-8)] or systemically[9)] produces effective inhibition of in-stent neointimal hyperplasia.

Carvedilol is a neurohumoral antagonist with multiple actions.[10)11)] It was originally discovered to be a beta-adrenoreceptor antagonist.[11)] However, subsequent research revealed that this agent possessed potent antioxi-

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dant and free radical scavenger properties.[12] In addition, carvedilol inhibits vascular SMC proliferation induced by a broad group of mitogens, such as platelet derived growth factor, fibroblast growth factor, endothelin-1, serum and thrombin.[13][14] Recently, the mechanisms responsible for these actions of carvedilol have been proven due to the inhibition of mitogen-activated protein kinase activity and regulation of cell cycle progression.[15][16]

Carvedilol produced an 84% suppression of neointimal hyperplasia in rat carotid injury model,[13] but no data is available regarding its effect on restenosis after stenting in patients. Therefore, the purpose of this study was to test whether a sustained oral administration of high-dose carvedilol reduces restenosis after coronary stenting in patients.

Methods

Study population

One hundred fifty nine patients who underwent elective coronary stenting for single or multiple lesions were eligible for this study. Inclusion criteria were symptomatic coronary artery disease, documented myocardial ischemia with exercise stress electrocardiogram or myocardial perfusion scan, and angiographic evidence of $\geq$75% diameter stenosis of *de novo* lesion in native coronary arteries. We attempted to perform single stenting to cover a whole lesion in all patients, and patients with a long lesion over 30 mm requiring multiple overlapping stents were excluded.

Severely calcified and diffuse lesions requiring rotational atherectomy were also excluded. The other exclusion criteria included stenting for left main coronary artery stenosis, primary or rescue stenting for acute myocardial infarction, contraindication of anti-platelet agents, and inability to take high-dose β-blocker; severe left ventricular dysfunction (<30% of ejection fraction), hypotension (<90 mmHg of systolic blood pressure), sinus bradycardia (<50 bpm), second- or third-degree atrioventricular block, or obstructive lung disease. The study was carried out with approval of the institutional review board at each center, and written informed consent was obtained from every patient.

Stent implantation procedure

All eligible patients were randomly assigned to receive either carvedilol (50 mg/day) or atenolol (50 mg/day) according to a randomization list. The medications were administered at least 1 day before stenting and thereafter continued for 3 months. Dosage was reduced among other concomitant drugs causing hypotension or bradycardia, such as calcium channel antagonists, or angiotensin converting enzyme inhibitors.

Coronary angioplasty procedure was performed with the standard technique via femoral or radial approach. Aspirin (200 mg/day) and ticlopidine (500 mg/day) were administered for at least 3 days before stenting. All the procedures were performed with intravenous administration of heparin (10,000 U), and 200 μg of intracoronary nitroglycerin was repeatedly injected during the procedure, if necessary. The selection of appropriate stents for lesions was done at the discretion of the operators. The stents were deployed using an inflation pressure of 12 to 16 atmosphere for 15 to 30 seconds. After intracoronary administration of 200 μg nitroglycerin, angiography was repeated to confirm adequate stent expansion and vessel patency. Procedural success was defined as successful stenting at the desired position with <25% residual stenosis (visual estimation) and normal antegrade flow.

Follow-up and end points

All patients underwent clinical examination as outpatients every 4 weeks after discharge. Follow-up coronary angiography was performed approximately 6 months after stenting, or earlier if clinically indicated. The primary end point was angiographic restenosis (>50% diameter stenosis) at the follow-up angiography. The secondary end points were minimal luminal diameter (MLD), late luminal loss, and loss index at the angiography and major adverse cardiac events (MACE) at 6 months, such as death of cardiac origin, myocardial

infarction, and percutaneous or surgical target lesion revascularization (TLR).

Restenosis was defined as >50% diameter stenosis of the treated lesion. Myocardial infarction was diagnosed when creatine kinase-MB level was elevated 2-fold or more with chest pain lasting ≥20 minutes or when new electrocardiographic changes were seen. TLR was performed in patients with stenosis of ≥90% or of ≥75% with symptoms.

Quantitative coronary angiography

One experienced angiographer blinded to the patients' assigned groups analyzed the angiographic results with the off-line method using an electronic caliper. The measurements were performed on the end-diastolic frames. Reference diameter, lesion length, and MLD were measured before and immediately after stenting and at the time of follow-up angiography. Acute gain (MLD after stenting-MLD baseline), late loss (MLD after stenting-MLD at follow-up), and late loss index (the ratio of late loss to acute gain) for each lesion were determined.

Statistical analysis

Sample size was determined based on the assumption that the restenosis rate would be less than 10% in the carvedilol group and around 25% in the atenolol group, with a 2-tailed α of 0.05 and a β of 0.20, and required 89 cases in each group. The data are expressed as mean±standard deviation or frequency (%) based on the characteristics of variables. Comparison of clinical and angiographic variables between the 2 groups was performed with independent samples using the t-test for the continuous variables and the χ^2 test or Fisher's exact test for the categorical variables. Differences were considered statistically significant at a $p<0.05$.

Table 1. Baseline clinical characteristics

	Carvedilol (n=80)	Atenolol (n=79)	p
Age (year)	58.9± 9.8	56.7± 8.8	0.190
Male gender	50 (62.5%)	46 (58.2%)	0.582
Clinical diagnosis			0.506
Stable angina	31 (38.8%)	37 (46.8%)	
Unstable angina	24 (30.0%)	23 (29.1%)	
Acute or recent myocardial infarction	25 (31.3%)	19 (24.1%)	
Previous myocardial infarction	8 (10.0%)	9 (11.4%)	0.776
Risk factors			
Hypertension	45 (56.3%)	40 (50.6%)	0.478
Diabetes mellitus	24 (30.0%)	26 (32.9%)	0.693
Current smoking	18 (22.5%)	21 (26.6%)	0.550
Hypercholesterolemia	27 (33.8%)	24 (30.4%)	0.649
Left ventricular ejection fraction (%)	60.8±10.7	58.5±13.0	0.367

Table 2. Angiographic and lesion characteristics and stent types

	Carvedilol (n=80)	Atenolol (n=79)	p
Extent of coronary artery disease			0.631
1 vessel disease	34 (42.5%)	34 (43.0%)	
2 vessel disease	34 (42.5%)	37 (46.8%)	
3 vessel disease	12 (15.0%)	8 (10.1%)	
Lesion location			0.048
Left anterior descending	24 (30.0%)	38 (48.1%)	
Left circumflex	15 (18.8%)	14 (17.7%)	
Right coronary	41 (51.3%)	27 (34.2%)	
ACC/AHA lesion type			0.486
A or B1	49 (61.3%)	45 (57.0%)	
B2	21 (26.3%)	27 (34.2%)	
C	10 (12.5%)	7 (8.9%)	
Lesion morphology			
Bifurcation lesions	15 (18.8%)	17 (21.5%)	0.406
Ostial lesions	6 (7.5%)	7 (8.9%)	0.490
Calcification, mild to moderate	10 (12.5%)	7 (8.9%)	0.314
Diffuse disease	8 (10.0%)	6 (7.6%)	0.400
Thrombus-containing lesions	5 (6.3%)	10 (12.7%)	0.133
Total occlusion, non-thrombotic	5 (6.3%)	7 (8.9%)	0.374
Stent diameter (mm)	3.24±0.44	3.17±0.34	0.329
Stent length (mm)	16.10±4.50	17.40±5.12	0.126
Stent types			0.693
Tube-typed	56 (70.0%)	53 (67.1%)	
Coil-typed	24 (30.0%)	26 (32.9%)	

ACC/AHA: American college of cardiology/American heart association

Table 3. Results of quantitative angiographic analysis

	Carvedilol (n=80)	Atenolol (n=79)	p
Lesion length (mm)	14.37± 5.95	12.34± 5.21	0.197
Baseline			
Reference diameter (mm)	3.14± 0.39	3.16± 0.31	0.810
MLD (mm)	0.58± 0.39	0.45± 0.29	0.395
Stenosis (%)	82.47±11.64	87.86±18.39	0.189
Immediately after stenting			
Reference diameter (mm)	3.11± 0.47	3.17± 0.36	0.240
MLD (mm)	3.41± 0.44	3.36± 0.29	0.605
Residual stenosis (%)	0.85± 4.36	−0.68± 1.75	0.070
Acute gain (mm)	2.83± 0.44	2.91± 0.70	0.634
Follow-up			
Reference diameter (mm)	3.09± 0.23	3.11± 0.44	0.763
MLD (mm)	2.08± 0.85	2.13± 0.70	0.748
Stenosis (%)	34.24±25.14	32.50±21.23	0.708
Late loss (mm)	1.31± 0.81	1.40± 0.81	0.699
Loss index	0.46± 0.27	0.48± 0.29	0.799
Follow-up angiography	70 (87.5%)	67 (84.8%)	0.623
Angiographic restenosis	12 (17.1%)	13 (19.4%)	0.732

MLD: minimal luminal diameter, Acute gain: post-stenting MLD-baseline MLD, Late loss: post-stenting MLD-follow-up MLD, Loss index: late loss/acute gain

Results

Clinical, angiographic, and procedural characteristics

A total of 159 patients were recruited in the carvedilol or atenolol groups. Both patient groups were not different with respect to age, gender, diagnosis, previous myocardial infarction, risk factors, and heart function (Table 1). Except for lesion location, the vessels affected, lesion type and morphology, and stent size and types were not significantly different between the two groups (Table 2).

Angiographic results

Successful stent implantation was achieved in all cases. At the time of stenting, the target vessel lesion length, reference diameter and MLD as well as percent stenosis were similar between the carvedilol and atenolol groups. There were no statistically significant differences in angiographic variables immediately after the stenting or at follow-up (Table 3). Acute gain and late loss were not different between the two groups. These translated into a non-significant difference of angiographic restenosis rates between the two groups (17.1% vs. 19.4%, p=0.732).

Table 4. Major adverse cardiac events at 6 months after stenting

	Carvedilol (n=80)	Atenolol (n=79)	p
Death of cardiac origin	0	0	–
Myocardial infarction	0	0	–
Surgical revascularization	0	0	–
Percutaneous revascularization	7 (8.8%)	8 (10.1%)	0.767

Clinical follow-up

After dose reduction of other concomitant medications, the initial carvedilol dose (50 mg/day) was tolerable and continued for 3 months after stenting in most patients. In 3 patients, however, the dose was reduced to 25 mg/day after 1 week due to persistent hypotension and dizziness. The rate of MACE at 6 months was not different in both groups (Table 4).

Discussion

This study shows that a sustained oral administration of carvedilol is not effective to reduce stent restenosis in patients. The results imply that the inhibition of neointimal hyperplasia in experiments, usually based on higher concentrations of carvedilol, cannot be achieved by oral administration of tolerable high-dose carvedilol in patients.

The ineffectiveness of carvedilol to reduce stent restenosis might result primarily from the inability of achieving a sufficient local or tissue concentration by oral administration, although carvedilol blood levels were not measured concomitantly in this study. Any significant antiproliferative effect in *ex vivo* studies[14)17)] was observed with a high concentration of carvedilol (>1 μmol), and the profound inhibition of neointimal growth in rat was achieved at the concentration of approximately 5 (mol/kg/day by intraperitoneal delivery of 1 mg/kg carvedilol twice daily for 17 days.[13)] Oral administration of carvedilol (50 mg/day) in human provided the plasma concentration of 66 μg/mL (0.157 μmol) in a study,[18)] although it was suggested that the concentration of carvedilol needed to produce antiproliferative effects might be achievable in *in vivo* settings.[14)]

Oral administration of carvedilol to prevent restenosis in patients was attempted in a trial (the EUROCARE) of directional coronary atherectomy (DCA), but failed to reduce restenosis after atherectomy.[19)] At the time the EUROCARE trial was planned in 1994, stenting was in the early phase of clinical evaluation; the BENESTENT and STRESS trials had not yet been completed. It was assumed that restenosis after DCA was due to neointimal hyperplasia. For this reason, the investigation of an agent with antioxidant, antichemotactic, and direct antiproliferative effects seemed ideally suited to an atherectomy-treated patient population. Intravascular ultrasound studies have since demonstrated that vessel remodeling accounts primarily for the restenotic response after DCA,[20)21)] which reduces the target for antiproliferative drugs. This study represents the first clinical trial regarding the effect of oral administration of carvedilol on neointimal hyperplasia in stented patients, the population with an appropriate target for carvedilol.

In spite of the negative result from oral administration, carvedilol may deserve further investigations using a stent-based delivery[22)] to achieve a high local concentration, because carvedilol targets regulators of cell cycle progression and the extent of neointimal inhibition with a high blood concentration in rat model far exceeds those reported for other compounds in animal models.

Limitations

The type and length of the stents used were not homogenous and might be biased upon each operator's experience although he wanted to choose an appropriate stent for a specific lesion. The late loss obtained from quantitative coronary angiography was used as an index of neointimal hyperplasia in this study. However, intravascular ultrasound study would allow closer observation of in-stent neointimal formation. Follow-up angiography was not performed in all the study patients, although patients who did not receive follow-up study did not show any recurrence of symptoms. The randomization was performed in each center and single-blinded.

Conclusions

This first clinical study shows that a sustained oral administration of carvedilol is not effective to reduce stent restenosis in patients. With carvedilol targeting regulators of cell cycle progression and having a profound neointimal inhibition with a high blood concentration in an experiment, further investigations using a stent-based delivery to achieve a high local concentration may be warranted.

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