Carvedilol Compared With Metoprolol on Left Ventricular Ejection Fraction After Coronary Artery Bypass Graft

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A number of elective coronary artery bypass graft (CABG) surgery patients have impaired underlying left ventricular function (poor ejection fraction). This study was performed to compare the effect of postoperative oral carvedilol versus metoprolol on left ventricular ejection fraction (LVEF) after CABG compared with metoprolol. In a double-blind clinical trial, 60 patients with coronary artery disease, aged 35 to 65 years, who had an ejection fraction of 15% to 35% were included. Either carvedilol or metoprolol was administered the day after CABG. The patients were evaluated by the same cardiologist 14 days before and 2 and 6 months after elective CABG. The results demonstrated better improvements in LVEF in the carvedilol group. No difference regarding postoperative arrhythmias or mortality was detected. The results suggest that carvedilol may exert more of an improved myocardial effect than metoprolol for the low ejection fraction patients undergoing CABG in the early postoperative months.

Keywords: *carvedilol, metoprolol, coronary artery bypass graft surgery.*

A NUMBER OF elective coronary artery bypass graft (CABG) surgery patients have impaired underlying left ventricular function (poor ejection fraction [EF]).[1] After CABG, these patients typically do not improve left ventricular ejection fraction (LVEF) more than 10%.[2] Repeated hospitalizations are a frequent problem during the postoperative months, primarily because of preexisting heart

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failure. This preexisting heart failure leads to increased postoperative mortality and morbidity and impaired quality of life.[2,3]

β-adrenergic blockers have been shown to decrease the mortality and morbidity of heart failure patients.[2-4] Carvedilol, a nonselective third-generation adrenergic blocker, is more effective than other β-adrenergic blocking agents, especially in patients who have experienced myocardial infarction (MI).[3-7] This study was designed and performed to compare the effect of postoperative oral carvedilol versus oral metoprolol on increasing EF after CABG.

Materials and Methods

This research study received approval from the Institutional Review Board Committee for Ethical Considerations, Research Deputy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The research project was accomplished during a 24-month period from January 2008 through December 2009. Patients gave written informed consent before enrollment in the study.

In a prospective randomized double-blind clinical trial, 60 patients with coronary artery disease were enrolled. The study included 22 women and 38 men, whose ages ranged from 35 to 65 years and who had an EF of 15% to 35%. The EF was confirmed by the same cardiologist during echocardiography and angiography.

The patients also each had a history of recent MI. The MI had occurred more than 4 weeks before the study and was documented by electrocardiographic (ECG) and dipyridamole-thallium imaging results. Those patients who had a recent MI during the last 4 weeks were excluded because those who have had a recent MI within 4 weeks are not usually considered appropriate candidates for elective CABG. Viability of the myocardium was determined by single-photon emission computed tomography (SPECT) and stress echocardiography.

Those patients older than 65 or younger than 35 years were excluded from the study. Also, the following items were considered as exclusion criteria:

- urgent surgery
- history of recent MI during the last 4 weeks
- evidence of atrioventricular block or severe sinoatrial node dysfunction, according to the ECG assessments
- no viable myocardium
- any contraindications for administration of β-blockers

The patients were assigned randomly into one of two study groups using a computer table of random numbers for random allocation. The first group (group 1), which included 30 patients, received oral carvedilol, and the second group (group 2), also including 30 patients, received oral metoprolol tartrate. Both groups received the drugs after elective CABG.

All the patients underwent echocardiography during 14 preoperative days before the surgical operation and again at 2 and 6 months after CABG. The echocardiography examination was again performed by the same cardiologist and echocardiographic machine (GE Vingmed Vivid 5 Echocardiography System; All Imaging Systems, Inc., Irvine, CA) in the same hospital. During the postoperative period, the patients were evaluated regarding atrial arrhythmias and 1-month mortality.

Conventional on-pump CABG was performed in all 60 patients. After establishing cardiopulmonary bypass, mild hypothermia (32°C, passive cooling) was used, with crystalloid cardioplegia solution. The β-blocker drugs were begun the day after the operation. Low-dose oral carvedilol (3.125 mg) twice daily was started for the first group. If the patient tolerated the drug, the dose was gradually increased over 2 weeks to reach a maximum of 12.5 mg twice daily. Low-dose oral metoprolol tartrate (50 mg/day) was used for the second group by the same pattern of administration. If the patient tolerated the drug, the dose was gradually increased over 2 weeks to reach a maximum of 200 mg twice daily to reach a maximum of 400 mg per day. These doses are comparing equipotent dosages of the two drugs. For both drugs, the signs of intolerance that were critical markers were intolerable fatigue, sinus bradycardia with a heart rate of less than 45 per minute, and shortness of breath. If any of these occurred with drug administration, the drug would be discontinued and the patient would be excluded from the study. Fortunately, none of the patients had any

signs or symptoms of intolerance in any of the two groups.

These medications were controlled to prevent their effect on the myocardial function: digoxin, angiotensin-converting enzyme inhibitors, and diuretics. No other variables with a possibility for affecting the myocardial function were considered necessary to be controlled and monitored. This is a possible limitation of the study.

Statistical Analysis

The study data were recorded and extracted from each patient's data sheet. Statistical analysis was performed using SPSS (version 11.5; SPSS Inc, Chicago, IL). For statistical data analysis, Student *t* test, chi-square test, and analysis of variance were used. A value for *P* less than .05 was considered significant.

Results

The two groups had no statistically significant difference regarding age and the number of coronary grafts in the operation (Table 1). There were no differences between the two groups regarding gender or in the incidence of diabetes mellitus, hyperlipidemia, hypertension, previous history of MI, smoking, and preoperative arrhythmias (*P* value for all the variables greater than .05). The two groups did not differ regarding their medications, including digoxin, angiotensin-converting enzyme inhibitors, and diuretics.

The results also demonstrated that there was no difference regarding lengths of surgery, pump run, intensive care unit stay, and hospitalization between the two groups. All CABG operations were performed by the same surgeon.

Table 1. Distribution of Age and Graft Numbers in the Study

Variables	Carvedilol Group	Metoprolol Group	*P* Value
Age (y)	56 ± 6.5	57 ± 5.4	.33
Number of grafts	3.4 ± 0.8	3.6 ± 0.7	.8

Figures are demonstrated as mean ± standard deviation.

There was only one death in the second group (metoprolol group), which occurred in the fifth postoperative day after a cerebral vascular accident.

Both groups had increased performance of the left ventricle as demonstrated in their EF of the left ventricle (LVEF), 2 and 6 months after CABG, when compared with their preoperative echocardiography assessments. In group 1 (ie, carvedilol), EF was increased from baseline values to higher ranges in the assessments performed at 2- and 6-month periods. In group 2 (ie, metoprolol), the EF had a similar pattern. The improvements in LVEF were significantly increased in group 1 (carvedilol group) compared with group 2 (metoprolol group) (Table 2). However, the two groups had no significant difference regarding functional status assessed by the New York Heart Association classification, 6 months after the operation.

Although bradycardia was more common in the carvedilol group (three patients versus one patient), the incidence of other arrhythmias (atrial fibrillation [AF] or flutter, premature atrial beats, or premature ventricular contractions) was not significantly different. No difference may have been secondary to low sample size.

Discussion

The study demonstrated an increase in LVEF in carvedilol group. The study suggests that carvedilol is more effective in patients than metoprolol to increase EF after CABG. EF may rise 5% to 10% after CABG surgery, however, in this study, the assessments performed after 6 months demonstrated that the increase was greater than 10% in both groups. The carvedilol group increased approximately 18%. Much of this increase occurred during the first

Table 2. Left Ventricle Performance Assessment (Demonstrated as LVEF)

Variables	Carvedilol Group	Metoprolol Group	*P* Value
Before the operation	26.5 ± 5.1	28.2 ± 4.5	.33
2 mo after CABG	41.1 ± 6.3	34.5 ± 5.2	.02
6 mo after CABG	44.3 ± 6.2	38.7 ± 5.4	.02

LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft.

Figures are demonstrated as mean ± standard deviation.

2 months after CABG, and this increase continued during the next 4 months (Table 2).

In a 2005 study that looked at LVEF after CABG in 20 patients with chronic hibernated myocardium studied before and after revascularization, the effect of carvedilol on hibernating myocardium was significantly better than that of metoprolol. The authors of the study described their finding related "partially" to the "reduced cardiomyocyte degeneration" after carvedilol administration.[8] All our patients had a history of previous MI that was evidenced by ECG, stress echocardiography, or SPECT, but the patients in the above study had hibernating myocardium that would be accompanied with a better response to revascularization, and the sample size was smaller than that in our study.

Carvedilol was demonstrated to produce better effects on the performance of the LVEF than metoprolol (with equal doses), especially when prescribed long term.[9] The difference in patient mortality after metoprolol and carvedilol administration is due to the greater counteradrenergic properties of carvedilol. Both drugs are β-blocking agents, but it is only carvedilol that is both a nonselective β-blocker and also an α-1 blocker.[10] To strengthen these findings, other studies have assessed the effects of carvedilol when used in the postoperative period after landiolol administration. Landiolol was not assessed in our study; but in other studies, landiolol has demonstrated an enhanced protective effect against tachycardia during AF in post-CABG patients.[11] Another study demonstrated that in post-CABG patients, therapeutic landiolol in "low doses" can decrease the prevalence of AF.[12] However, our study did not demonstrate any difference regarding the incidence or prevalence of arrhythmias or postoperative 6-month mortality. These issues differed from previous research, but the results of this study could demonstrate the effect of carvedilol on LVEF to be superior to metoprolol, a therapeutic effect of the drug that could be because of its effects as a counteradrenergic agent.[9-12] Therefore, it would demonstrate this effect as better performance on the poorly functioning myocardium during the early post-CABG months.

Conclusion

Carvedilol could improve LVEF in the early postoperative period after CABG. When compared with metoprolol in patients with low EF, the patients demonstrate better early postoperative performance of left ventricle. Evaluating patients with at least 1-year follow-up is recommended to assess the long-term outcome of such cases.

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