Intravenous Administration of Metoprolol Is More Effective Than Oral Administration in the Prevention of Atrial Fibrillation After Cardiac Surgery

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Background—Atrial fibrillation (AF) is the most common arrhythmia to occur after cardiac surgery, with an incidence of 20% to 40%. AF is associated with postoperative complications, including increased risk of stroke and need of additional treatment, as well as prolonged hospital stay and increased costs. It has been shown that prophylactic oral administration of β-blocker therapy reduces the incidence of postoperative AF after cardiac surgery. However, it is possible that absorption of drugs is impaired after cardiopulmonary perfusion associated with cardiac surgery. The purpose of this prospective, controlled, randomized trial was to study compare intravenous and per oral metoprolol administration in the prevention of AF after cardiac surgery.

Methods and Results—240 consecutive patients who were scheduled to undergo their first on-pump coronary artery bypass graft (CABG), aortic valve replacement, or combined aortic valve replacement and CABG were randomized to receive 48-hour infusion of metoprolol or oral metoprolol starting on the first postoperative morning. Patients were excluded if they had contraindications for β-blocker or had to stay >1 day in the intensive care unit. Dosage of metoprolol was adjusted according to heart rate. The dosage was 1 to 3 mg/h in the intravenous group and from 25 mg twice per day to 50 mg 3 times per day in the oral group. The incidence of postoperative AF was significantly lower in the intravenous group than in the oral group (16.8% versus 28.1%, P=0.036). No serious adverse effects were associated with intravenous metoprolol therapy.

Conclusions—Our study suggests that intravenous metoprolol is well-tolerated and more effective than oral metoprolol in the prevention of AF after cardiac surgery. (Circulation. 2006;114[suppl I]:I-1–I-4.)

Key Words: atrial fibrillation β beta adrenergic receptors antagonists cardiac surgery prevention

Atrial fibrillation (AF) is the most common arrhythmia to occur after cardiac surgery. Studies have reported an incidence ranging from 20% to 40% after coronary artery bypass surgery (CABG), with a peak incidence occurring between the second and fourth postoperative days.1–4 Patients undergoing CABG and combined valve surgery have a higher incidence of postoperative AF than patients undergoing CABG alone.5 Postoperative AF is associated with complications, including increased risk of stroke, and need of additional treatment, as well as prolonged hospital stay and increased costs.4–7

The results of 5 meta-analyses have shown that prophylactic β-blocker therapy reduces the incidence of AF after cardiac surgery.8–12 However, the relative benefits of any one β-blocker over another have not been demonstrated.13 In a recently published meta-analysis consisting of 27 prospective randomized trials involving 3840 patients, the incidence of AF ranged from 33% in the control group to 19% in the group treated with β-blockers. However, according to this meta-analysis the incidence of AF still remains high, even though the incidence was decreased with β-blocking therapy. It is not known how orally administrated B-blockers are absorbed after cardiac surgery.

We hypothesized that intravenous metoprolol administration after cardiac surgery would be more effective than oral metoprolol administration in the prevention of AF. A randomized prospective trial was designed to test this hypothesis.

Methods

From September 2004 to August 2005, 240 consecutive patients who were scheduled to undergo first on-pump CABG, aortic valve replacement or combined aortic valve replacement and CABG were enrolled in the study. The exclusion criteria were previous episodes of AF or flutter, sick sinus syndrome, II-degree or III-degree
atrioventricular block, and uncontrolled heart failure. Patients were also excluded if they had had an AF occurrence before the first postoperative morning or if they would have had to stay in the intensive care unit before the first postoperative day. Patients were also excluded if the systolic pressure was <100 mm Hg, if the pulse rate <60 beats per minute (bpm) at the time of randomization, or if temporary pacing was not functioning properly, when tested before randomization. The reasons for exclusion and numbers of enrolled patients who were excluded before randomization were as follows: experiencing AF before first postoperative morning (3 patients), staying in the intensive care unit >1 day (18 patients), pulse rate <60 bpm (12 patients), systolic pressure <100 mm Hg (17 patients), inaccurate function of temporary pacemaker (11 patients), new II-degree or III-degree atrioventricular block (15 patients), operation was unexpectedly performed off-pump (7 patients), mitral valve repair (2 patients), and replacement of ascending aorta (2 patients unexpectedly needed this), and 2 patients died before the first postoperative morning.

The study protocol was approved by the local ethics committee, and all patients gave informed consent. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Operative Treatment

The ascending aorta was cannulated for arterial line placement and a single-stage venous cannula was inserted through the auricle of the right atrium. Aortic root venting was used in CABG patients. Cardiopulmonary bypass with moderate systemic hypothermia (temperature of venous blood 32°C) and moderate hemodilution (hematocrit >0.22) was used with flow rates of 2.2 to 2.4 L/m² and mean perfusion pressure of 50 to 85 mm Hg. Intermittent cold crystalloid cardioplegia was administered through the antegrade route in CABG patients. Peripheral and central anastomoses were constructed during single aortic occlusion. In aortic valve replacement both antegrade and retrograde intermittent cold crystalloid cardioplegia were given and the vent was placed into the left ventricle through the right upper pulmonary vein. The cardioplegia solution consisted of management 16 mmol/L, and no extra magnesium substitution was given. Epicardial temporary pacing wires were sutured to the epicardium of the right ventricle. After the operation, patients were followed-up in the intensive care unit and were weaned off the ventilator when they fulfilled the following criteria: hemodynamic stability, peripheral temperature >32°C, cooperativeness, and no major bleeding. Chest drains were removed on the first postoperative day and the patients were moved to the surgical ward.

Postoperative Treatment

Randomization was performed on the first postoperative morning. Treatment allocations were sealed in numbered envelopes in a blinded randomized manner. Each enrolled subject was assigned to an intravenous group or oral group according to the allocation designated in the next envelope opened in sequence. Patients in the intravenous group were administered metoprolol according to the heart rate as follows: when heart rate was 60 to 70 bpm, the metoprolol dose was 1 mg/h; when heart rate was 70 to 80 bpm, the dose was 2 mg/h; and when the heart rate was >80 bpm, the dose was 3 mg/h. If heart rate decreased to <60 bpm or systolic blood pressure decreased to <100 mm Hg during treatment, intravenous metoprolol administration was discontinued for 1 hour and then continued according to heart rate, as described. Patients in the oral metoprolol group were administered metoprolol according to heart rate as follows: when heart rate was 60 to 70 bpm, the metoprolol dose was 25 mg 3 times per day; when heart rate was 70 to 80 bpm, the dose was 50 mg 2 times per day; and when heart rate was >80 bpm, the dose was 50 mg 3 times per day. The study period was 48 hours for both groups.

All the patients were connected to ward monitors for continuous ECG monitoring for the whole study period. The ward monitor stored the ECG recordings for subsequent analysis. A 12-lead ECG recording was performed if necessary to confirm the rhythm. The endpoint of the study was the occurrence of the first AF episodes or the completion of 48 hours protocol. After the first episode of AF, the study protocol was discontinued. The rhythm was defined as AF when there were no consistent P waves before each QRS complex and ventricular rate was irregular. AF episodes lasting >5 minutes were recognized. Perioperative myocardial infarction was defined as the development of new Q waves. A stroke was defined as a new neurological symptom verified by correlative changes in the computer tomography.

The sample size was determined on the assumption that the incidence of AF could be reduced from 30% in the oral metoprolol treatment group to 15% in the intravenous metoprolol treatment group. At a level of α=0.05 with a power >0.80, the sample size was calculated to be 121 patients in each group.

Statistical Analysis

The difference in continuous variables was analyzed using unpaired Student t test. Differences in categorized variables were tested using the χ² test for independence or, in the case of low expected frequencies, by the Fisher exact test. The limit for statistical significance was P<0.05. All statistical procedures were performed with statistical software SPSS for Windows, Release 11.5.1 (SPSS Inc, Chicago, Ill).

Results

Most (72.5%) of the patients were men. The mean age of patients was 65.5±9.6 years, and there were no differences between the groups. There was no difference between the groups concerning left ventricle ejection fraction, the presence of diabetes, unstable angina pectoris, hypertension, 3-vessel disease, preoperative β-blocker use, Canadian Class Score or history of stroke or transient ischemic attack, and history of claudication. The preoperative data of the patient groups are presented in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1. Demographics of the Patient Groups</th>
</tr>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>-----------------</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender: male/female (n)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>History of COPD (%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>CCS class (%)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Preoperative use of β-blockers (%)</td>
</tr>
<tr>
<td>History of stroke or TIA (%)</td>
</tr>
<tr>
<td>History of claudication (%)</td>
</tr>
<tr>
<td>Unstable angina pectoris (%)</td>
</tr>
<tr>
<td>Three-vessel disease (%)</td>
</tr>
</tbody>
</table>

Data are means±standard deviation or percentages of patients or number of patients.
CCS indicates Canadian Cardiac Society; COPD, chronic obstructive pulmonary disease; IV, intravenous metoprolol; LVEF, left ventricle ejection fraction; PO, per oral metoprolol; TIA, transient ischemic attack.
TABLE 2. Perioperative Data of the Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PO Group</th>
<th>IV Group</th>
<th>Univariate P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of operation (%)</td>
<td>0.753</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated CABG</td>
<td>81.9</td>
<td>79.6</td>
<td></td>
</tr>
<tr>
<td>Isolated AVR</td>
<td>7.8</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Combined CABG and AVR</td>
<td>10.3</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery bypass (%)</td>
<td>77.1</td>
<td>79.0</td>
<td>0.726</td>
</tr>
<tr>
<td>Pump time (min)</td>
<td>92.4 ± 42.3</td>
<td>93.2 ± 36.8</td>
<td>0.875</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>83.4 ± 49.3</td>
<td>79.5 ± 31.6</td>
<td>0.500</td>
</tr>
<tr>
<td>N of peripheral anastomoses (n)</td>
<td>3.7 ± 1.1</td>
<td>3.9 ± 1.1</td>
<td>0.336</td>
</tr>
<tr>
<td>First post-operative CK-MBm (mg/l)</td>
<td>23.8 ± 11.1</td>
<td>25.2 ± 13.3</td>
<td>0.408</td>
</tr>
</tbody>
</table>

Data are means ± standard deviation or percentages of patients.

AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; CK-MBm, creatinine kinase–MB mass.

Most of the operations in both groups were isolated CABG and there were no differences between the groups in the number of distal anastomoses (Table 2). There was no difference between groups with respect to pump time, cross-clamp time, or first postoperative creatinine kinase–muscle brain mass. The operative data of the patient groups are presented in Table 2.

The incidence of postoperative AF was significantly lower in the intravenous group (16.8%) than in the oral group (28.1%), P = 0.036 (Table 3). In addition, the average time from the start of the metoprolol medication to the first AF episode was slightly longer in the intravenous group than in the peroral group (30.1 hours ± 10.1 hours versus 26.5 hours ± 11.8 hours, respectively, P = 0.08). The patient’s serum potassium concentration when AF occurred did not differ between the groups.

Intravenous metoprolol administration was discontinued for 1 hour during the study period in 18 of 119 patients (15.1%). The reasons for this were a decrease in systolic blood pressure <100 mm Hg in 14/119 (11.8%) patients, and a decrease in heart rate <60 bpm in 4 of 119 (3.4%) patients.

There was no mortality in the study groups during the study period, but 1 patient in the intravenous group died on the fourth postoperative day because of myocardial infarction. The incidence of postoperative stroke, conduction disturbances, postoperative mediastinitis, perioperative myocardial infarction or resternotomy caused by bleeding did not differ between groups. The postoperative data of the patient groups are presented in Table 3.

Discussion

The main finding of our study is that the intravenous administration of metoprolol is significantly more effective than oral administration in the prevention of AF after cardiac surgery. There was no difference between the study groups regarding any known preoperative or perioperative risk factor for postoperative AF, so our study groups were well comparable. Metoprolol is absorbed over a large part of the intestine.14 Despite complete gastrointestinal absorption, only approximately 50% of single oral therapeutic doses reach the systemic circulation, because of presystemic elimination.15,16 The bioequivalent metoprolol dosage in the intravenous and oral groups in our study was the same, because of this presystemic elimination. One possible explanation for our finding is that orally administered metoprolol is not absorbed from the gastrointestinal tract during the very first postoperative days after cardiac surgery. Diminished visceral blood flow and gastrointestinal motility as well as the use of opioids can reduce the absorption of metoprolol after surgery. The absorption of metoprolol, or β-blockers in general, after cardiac surgery has not been studied. Another reason could be that intravenous administration provides more stable serum metoprolol concentration than oral administration.

One previous study has compared the efficacy and safety of intravenous β-blocker and oral β-blocker: intravenous esmolol was compared with oral β-blocker in the pilot study by Balckley-Harris et al.17 This study was terminated when interim analysis revealed a significantly greater incidence of adverse effects in the group receiving esmolol, and the lack of any reduction in AF incidence. We found no serious adverse effects associated with intravenous metoprolol therapy. Administration of intravenous metoprolol had to be interrupted in 15.1% of the patients because of a decrease in blood pressure or heart rate, but medication could be continued in all patients as soon as heart rate or blood pressure had recovered.

The efficacy and safety of intravenous propranolol18 and intravenous timolol19 have been studied earlier in the prevention of AF after cardiac surgery. These studies concluded that both β-blockers were effective in AF prophylaxis when compared with placebo. However, a trend toward more frequent adverse effects in the propranolol treatment group was reported.18

The feasibility of atrial pacing, oral or intravenous amiodarone and magnesium supplementation have also been studied in the prevention of AF after cardiac surgery. There are conflicting results concerning the efficacy of atrial pacing in the prevention of postoperative AF. A recent meta-analysis concluded that only bi-atrial pacing decreases the incidence of AF after CABG.11 Both oral11,20 and intravenous21 amiodarone administration have been found effective in the prophylaxis of AF after cardiac surgery. Mahoney et al assessed the cost-effectiveness of intravenous amiodarone therapy and found that the routine use of intravenous amiodarone after...
CABG is not cost-effective. Older patients undergoing valve surgery with concomitant CABG, or who had chronic obstructive pulmonary disease, were likely to benefit most from intravenous amiodarone therapy.\textsuperscript{22} The efficacy of magnesium supplementation has also been reported in the prevention of AF after cardiac surgery.\textsuperscript{23,24} Further studies are needed to compare the efficacy and safety of intravenous metoprolol administration with amiodarone therapy, magnesium supplementation, and bi-atrial pacing therapy in the prevention of AF after cardiac surgery.

The main limitation of our study is that many enrolled patients had to be excluded before randomization. Because adverse effects associated with intravenous $\beta$-blocker therapy have been reported after cardiac surgery,\textsuperscript{17,18} we excluded all patients at risk for development of complications associated with intravenous metoprolol therapy. For example, we excluded 11 patients because the functioning of a temporary pacemaker was not reliable at the time of randomization. However, the results of our study suggest that this is not necessary, because none of the patients developed bradycardia requiring temporary pacing.

We conclude that intravenous metoprolol therapy is more effective than oral metoprolol therapy in the prevention of AF after cardiac surgery. In addition, we found that intravenous metoprolol turned out to be well-tolerated after cardiac surgery.

**Disclosures**

None.

**References**

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