Amiodarone versus digoxin and metoprolol combination for the prevention of postcoronary bypass atrial fibrillation

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Abstract

Objective: This prospective randomized study aims at evaluation and comparison of the prophylactic effects of amiodarone versus digoxin and metoprolol combination in postcoronary bypass atrial fibrillation. Methods: A total of 241 consecutive patients undergoing elective coronary artery bypass grafting were randomly allocated into three groups. Patients in Group 1 (n = 77) received metoprolol 100 mg/24 h per oral (P.O.), preoperatively, 2 × 0.5 mg digoxin intravenously on the operating day and digoxin 0.25 mg P.O. + metoprolol 100 mg P.O. on the first postoperative day until discharge. Patients in Group 2 (n = 72) received totally 1200 mg intravenous/24 h amiodarone which the 300 mg – bolus dose/1 h was given as soon as the operation had been finished. On the next day patients were administered 450 mg/24 h amiodarone i.v. and 600 mg/day in three doses P.O. were given until discharge. Group 3 (n = 92) was the control group with no antiarrhythmic prophylaxis. Results: Preoperative patient characteristics and operative parameters were similar in three groups. Atrial fibrillation occurred in 13 patients (16.8%) in Group 1, six patients (8.3%) in Group 2 and 31 patients (33.6%) in Group 3. Conclusion: Both study groups were effective in the prevention of postcoronary bypass atrial fibrillation with respect to control (P < 0.01 in Group 1 and P < 0.001 in Group 2). © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Coronary artery bypass grafting; Atrial fibrillation; Amiodarone

1. Introduction

New onset of atrial fibrillation (AF) is a frequent event after coronary artery bypass grafting (CABG) with an incidence of 15–40% [1]. The loss of normal atrial contraction reduces the cardiac output in most patients and a rapid ventricular response increases myocardial oxygen consumption, so it may result in hemodynamic compromise during the postoperative period. An increased risk ratio for stroke or peripheral embolization also has been associated with postoperative AF, thus these minor or major complications may cause prolonging hospital stay and increasing costs [2–4].

A variety of pharmacological agents such as beta blockers [5,6], digoxin [5,7,8], calcium channel blockers [9,10], quinidine [5], and amiodarone [11–14] has been used to prevent the occurrence of AF after CABG; none of those agents however has been uniformly accepted as a routine treatment.

This is a prospective randomized study to evaluate the efficacy of the prophylactic effects of amiodarone versus digoxin + metoprolol combination on post coronary bypass AF.

2. Patients and methods

The study was approved by Medical Ethics Committee of the institution and informed consent was obtained from each patient included in the study.

2.1. Patients

In a 9-month period, 241 consecutive patients undergoing elective CABG without concomitant procedures were included in the study. Patients with preoperative rhythm abnormalities (sick sinus syndrome, atioventricular conduc- tion abnormalities, history of chronic or intermittent AF, etc.), pretreatment with classes I and III antiarrhythmic agents, receiving anti-hypertensive drugs except ACE inhibitors, thyroid disease, renal or liver disease, peripheral arterial...
atherosclerotic disease and chronic obstructive pulmonary disease were not included in the study. Patients were randomly allocated into three groups. Patients in Group 1 received metoprolol 100 mg/24 h per oral (P.O.), preoperatively and 2 × 0.5 mg digoxin intravenously (i.v.) was administered in the early postoperative period in intensive care unit (ICU), and on the first postoperative day digoxin 0.25 mg P.O. and metoprolol 100 mg P.O. were administered. The efficacy of therapy was monitored by blood digoxin levels in therapeutic range. This regimen was continued until discharge. Patients in Group 2 received totally 1200 mg i.v. amiodarone in 24 h, of which the 300 mg (bolus dose) was given in 1 h as soon as the operation had been finished. On the next day patients were given 450 mg/24 h amiodarone i.v. and 600 mg/day in three doses P.O. until discharge (Fig. 1). The thyroid toxicity of amiodaron was controlled by daily blood thyroid hormone levels throughout the study. Group 3 was the control group with no specific anti-arrhythmic medication. The preoperative characteristics of patients are summarized in Table 1. Ventricular performance score (VPS) as seen in Table 1 is a scoring system of left ventricular function due to wall motions of seven segments at the left and right oblique left ventriculography (normal: one, hypokinesia: two, akinesia: three, dyskinesia: four and aneurysm: five).

2.2. Surgical procedure

After premedication with diazepam (10 mg I.M.), a radial artery catheter, two peripheral intravenous catheters and a pulmonary artery catheter were inserted in the operating room.

Hemodynamic parameters; heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, rectal temperature and arterial blood gases were monitored throughout the procedure.

Anesthesia was induced by fentanyl (35 mg/kg) and muscle relaxation was established with pancuronium (0.1 mg/kg). Patients were intubated endotracheally and ventilated with 100% oxygen.

Standard median sternotomy incision was used for the exposure of the heart. Left internal mammary artery was harvested and saphenous vein was prepared, if necessary.

All operations were performed under cardiopulmonary bypass (Polystan Safe II) and moderate hypothermia (28–32°C). Cardiac arrest was performed by initial crystalloid cardioplegia (Plegisol, 4°C, 15 cc/kg) and myocardial preservation was supported with 400 cc cold blood cardioplegia in every 20 min and topical ice slush. A hot shut was performed just before removal of the cross clamp. Venous cannulation was done with two stage single cannulae through the right
atrial appendix, the arterial cannula was placed into the ascending aorta.

2.3. Monitoring

All patients were monitored continuously at the ICU with electrocardiography (ECG), three-channel pressure, cardiac output via pulmonary artery catheter and with finger probe for oxygen saturation within 48 h. When the patients were transferred to wards, continuous ECG monitoring and non-invasive blood pressure for every 30 min were recorded until discharge.

2.4. Data analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS Inc. Chicago, IL). Data were expressed as the mean ± standard deviation. Significant differences between nominally scaled and ordinally scaled variables were determined with a χ² test. Unpaired t-test for independent samples was used for interval scaled variables. A P value of less than 0.05 was considered significant.

3. Results

Age, gender, and incidence of hypertension, smoking and diabetes mellitus were similar in the three groups. Furthermore the groups did not differ significantly in extent of coronary artery disease, right coronary artery disease (RCAD), VPS, left ventricular end diastolic pressure (LVEDP) and left ventricular ejection fraction (LVEF %) as demonstrated in Table 1.

Thyroid hormone levels were within normal range in Group 2 throughout the study. Cardiac output and cardiac index levels were stable in especially amiodarone group. Atrial size did not demonstrate any difference among groups. Minimal mitral regurgitation was observed in four patients in Group 1, three patients in Group 2 and four patients in Group 3.

Number of grafts per case, cross-clamp time (CCT), cardiopulmonary bypass time (CPBT) and use of internal mammary artery were also similar in three groups (Table 2).

AF occurred in 13 patients (16.8%) in Group 1, six patients (8.3%) in Group 2 and 31 patients (33.6%) in Group 3 (Fig. 2). The duration of AF was 30 ± 9 min in Group 1, 24.6 ± 8 min in Group 2 and 35.2 ± 9 min in Group 3. Time dependent analysis of AF did not demonstrate any dominant specific interval. AF occurred in nine patients within the period of 08:00–14:00 h; 11 patients in 14:00–20:00 h, 16 patients in 20:00–02:00 h and 14 patients in 02:00–08:00 h.

Seven patients in Group 1, three in Group 2 and 16 in Group 3 had clinical deterioration following AF occurrence.

Table 1
Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>77</td>
<td>72</td>
<td>92</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.6 ± 18.7</td>
<td>57.5 ± 8.4</td>
<td>59.5 ± 18.3</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male %)</td>
<td>77.9</td>
<td>76.3</td>
<td>77.1</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>41.5</td>
<td>41.6</td>
<td>42.3</td>
<td>NS</td>
</tr>
<tr>
<td>DM (%)</td>
<td>19.4</td>
<td>20.8</td>
<td>21.7</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>61</td>
<td>61.1</td>
<td>59.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean atrial size (cm)</td>
<td>3.2 ± 0.6</td>
<td>2.99 ± 0.6</td>
<td>3.18 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral regurgitation (pts)</td>
<td>4 (minimal)</td>
<td>3 (minimal)</td>
<td>4 (minimal)</td>
<td>NS</td>
</tr>
<tr>
<td>CAD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel disease</td>
<td>15.5</td>
<td>13.8</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>2 vessel disease</td>
<td>29.8</td>
<td>27.7</td>
<td>23.9</td>
<td>NS</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>54.5</td>
<td>58.3</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>RCAD (%)</td>
<td>71.4</td>
<td>69.4</td>
<td>70.6</td>
<td>NS</td>
</tr>
<tr>
<td>VPS</td>
<td>8.6 ± 1.7</td>
<td>8.6 ± 1.5</td>
<td>8.4 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>12.7 ± 6.9</td>
<td>12.4 ± 2.8</td>
<td>12.5 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60.6 ± 18.1</td>
<td>59.6 ± 12.3</td>
<td>60.6 ± 19.5</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular arrhythmia (pts)</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>

a DM, diabetes mellitus; CAD, coronary artery disease; RCAD, right coronary artery disease; VPS, ventricular performance score; LVEDP, left ventricular enddiastolic pressure; and EF, ejection fraction.

Table 2
Perioperative parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMA usage (%)</td>
<td>98.7</td>
<td>100</td>
<td>98.9</td>
</tr>
<tr>
<td>Graft per case</td>
<td>2.9 ± 1.8</td>
<td>2.8 ± 1.0</td>
<td>3.1 ± 1.1</td>
</tr>
<tr>
<td>CCT (min)</td>
<td>27.6 ± 10.5</td>
<td>32.1 ± 12.1</td>
<td>29.8 ± 10.0</td>
</tr>
<tr>
<td>CPBT (min)</td>
<td>54.0 ± 18.1</td>
<td>60.4 ± 20.8</td>
<td>60.4 ± 18.3</td>
</tr>
<tr>
<td>AF (No. of pts) (%)</td>
<td>13 (16.8)</td>
<td>6 (8.3)</td>
<td>31 (33.6)</td>
</tr>
<tr>
<td>AF duration (min)</td>
<td>30 ± 9</td>
<td>24.6 ± 8</td>
<td>35.2 ± 9</td>
</tr>
<tr>
<td>Clinical AF (pts)</td>
<td>7</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Inotropie use (pts)</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

a IMA, internal mammary artery; CCT, cross clamp time; and CPBT, cardiopulmonary bypass time.
Normal sinus rhythm was maintained by additional anti-arrhythmic medication or electrical cardioversion technique in every patient. Ventricular arrhythmia was observed in eight patients in Group 1, seven in Group 2, ten in Group 3, which did not yield clinical significance.

Both study groups were effective in the prevention of postcoronary bypass AF with respect to control group ($P < 0.01$ in Group 1 and $P < 0.001$ in Group 2 versus control).

Two patients in Group 1, one in Group 2 and four in Group 3 needed inotropic support within the perioperative period. Among these patients, two in Group 1 and three in Group 3 suffered from postoperative AF.

The relation between AF and age, sex, hypertension, diabetes mellitus (DM), RCAD, VPS, EF %, LVEDP, CCT, CPBT, inotropic use, preoperative atrial size and incidence of mitral regurgitation was studied by using multivariable regression analysis and none of them except age and inotropic use were found to have significant relationship with AF. AF was documented in higher incidence in older patients (38.1% >65 years old and 16.5% ≤65 years old).

In Group 1 medication was stopped in four patients due to side effects of the drugs (one sinusal bradycardia and three hypoxia). In Group 2 medication was stopped in two patients due to atrioventricular block. No cerebrovascular complication was observed in any of the patients suffering from AF.

4. Discussion

Older age, hypertension, poor left ventricular function, prolonged duration of operative ischemic period, poor myocardial preservation, metabolic changes, temperature flux, fluid and electrolyte changes, lack of preoperative use of beta blocker and ICU stress might increase the incidence of postoperative AF. Although there are many etiologic and predisposing factors little consensus exists regarding these factors. But it is not easy to prove the single causal factor. Perhaps interaction between these factors is important in the occurrence of AF.

The efficacy of pharmacologic prophylaxis in reducing the incidence of AF has been investigated in several studies and also there were different studies for prevention postcoronary bypass AF with digoxin, beta blocker or combination of two [6-8,17,18]. In these studies it was emphasized that the effectiveness of digoxin + beta blocker combination was more effective than using these drugs alone. In the study of Peter and colleagues the incidence of postoperative AF was 17% with digoxin + acebutolol combination whereas the 32% with digoxin alone [8]. In addition the ineffectiveness using single, digoxin had the potential to increase the incidence of ventricular arrhythmias [17]. In our study incidence of ventricular arrhythmias did not differ among groups. A variety of beta blocking agents have been studied with different results and none of them was sufficient in prevention of postoperative AF [17,18,20]. In the study of Patrick and colleagues the incidence of postoperative AF was 16% in sotalol group whereas 48% in the control group. In this study it was emphasized that low dose oral sotalol provided considerable and reliable protection in patients especially with selected non-depressed cardiac function [20]. We combined digoxin and beta-blocker therapy, planning to test amiodarone versus these previous effective results. There were many studies with amiodarone for prevention of postcoronary bypass AF and their results were controversial [13–15]. Amiodarone increases the refractory period of atrial, ventricular muscle and atrioventricular node. In addition to its class III antiarrhythmic activity it has mild beta blocker and calcium channel blocker activity. Cardiac toxicity from amiodarone is uncommon. The incidence of amiodarone induced ventricular arrhythmia is low even in the presence of structural heart disease. It has no negative inotropic effect, is a powerful after load reducing agent and has coronary vasodilatory effects [16]. However these effects would be rather marginal when compared to the powerful vasodilators or ACE inhibitors. It is usually difficult to understand the pharmacological effects of amiodarone between the pure Classes I and II activity by intravenous administration and the beta blocking activity occurring by the metabolism of oral intake. In this study, amiodarone was only administered intravenously in the ICU period as well as digoxin, but metoprolol exclusively per os. It must be remembered that enteral absorption of drugs might be disturbed following extracorporeal circulation. Blood levels of metoprolol and amiodarone were not monitored. This was one of the limitations of our study.

Different regimen doses of amiodarone has been reported [13–16,19]. In the study Daoud and associates amiodarone was used preoperatively and postoperatively in 125 patients who had coronary bypass. The drug was given for 7 days preoperatively at a dosage of 600 mg per day and proceeded with 200 mg per day postoperatively until the discharge day. AF occurred in 25% patients in the amiodarone group whereas 53% in the placebo group at the postoperative period ($P < 0.003$) [19]. In this study the occurrence of AF was decreased 52.9% with amiodarone. In our study
with amiodarone the occurrence of AF was decreased 75.3%; with digoxin + metoprolol 50% with respect to control group. When the two studies were compared we believe the lower AF incidence in our study was due to the higher dosage of amiodarone. We have preferred a high dose over coming a need for testing different doses. Since we have not observed any side-effects and got better results, we have not tried other amiodarone doses.

Giri et al. also demonstrated in their study that oral amiodarone prophylaxis in combination with beta-blockers prevented atrial fibrillation and symptomatic fibrillation and reduced the risk of cerebrovascular accidents and ventricular tachycardia [21]. No cerebrovascular events have been reported in our series. We have also not observed any hemodynamic negative effect of amiodarone in our patients. No thyroid hormone instability occurred as well.

Dörgê et al. found no beneficial effect of amiodarone prophylaxis, when they compared two different doses of amiodarone with placebo [13]. But as we mentioned before, there were many predisposing factors, which may trigger a new onset of AF. Study groups of Dörgê et al. had larger CCT and CPB times than our groups. Also the percentage of patients with diminished ventricular function were higher than our groups.

In conclusion; both medical groups were effective for prevention postcoronary bypass AF. But the effects of amiodarone seem dose dependent compared to the literature. Also the patient’s preoperative ventricular function, myocardial ischemic period, age and inotrop use may have important role on the trigger and prevention of AF.

References