Effectiveness of Metoprolol in Preventing Atrial Fibrillation and Flutter in the Postoperative Period of Coronary Artery Bypass Graft Surgery

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Objective - *To assess the effectiveness of metoprolol in preventing clinically detectable atrial fibrillation (AF) and flutter after coronary artery bypass graft (CABG) surgery .*

Methods - *An open, randomized study was carried out to treat 200 patients who had undergone isolated CABG surgery with extracorporeal circulation. The patients were randomized to either receive metoprolol orally or not to receive the medication in the postoperative period. The outcomes were the detection of sustained atrial AF and flutter, which were symptomatic or required treatment. The patients with the following characteristics were excluded from the study: baseline left ventricular ejection fraction < 35%; previous AF; history of bronchospasm; second- and third-degree atrioventricular blocks, low cardiac output, and heart failure.*

Results - *Arrhythmias occurred in 11 out of 100 patients in the metoprolol group and in 24 out of 100 patients in the control group (P=0.02). The relative risk (RR) was 0.46 (95% CI = 0.24-0.88), and the number necessary to treat (NNT) and avoid the outcome was 8 patients. AF was the arrhythmia most frequently observed (30/35). In 38 patients aged 70 years or more, the arrhythmias occurred in 2 out of 19 patients in the metoprolol group and in 10 out of 19 patients in the control group ($\chi 2$ Yates: P=0.01). The relative risk was 0.20 (95% CI = 0.05-0.79) and the number necessary to treat was 2 patients.*

Conclusion - *Metoprolol is effective in preventing AF and flutter in the postoperative period of CABG surgery, and this effect was more evident in the group of elderly patients.*

Keywords: metoprolol, atrial fibrillation, coronary artery bypass graft surgery

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Atrial fibrillation and flutter are arrhythmias frequently observed in the first days following coronary artery bypass graft surgery. Its incidence ranges from 17 to 33% [1-8] and varies according to the method used for its detection and the criteria for arrhythmia definition [9]. Atrial fibrillation is by far the most common, and it sometimes coexists with atrial flutter in the same patient [10]. Little is known about the etiology of atrial fibrillation, and stimuli, such as intraoperative atrial ischemia, pericarditis, and excessive adrenergic stimulation, play an important role in its appearance in vulnerable patients [11-13]. Although most of the time these arrhythmias are benign and transient, they have been associated with embolic cerebral events [4,5,8,14] and with an increase in the length of hospitalization and in costs [6,7,15]. Several pharmacological strategies for preventing atrial fibrillation have been used in the past 3 decades, beta-blockers being the most frequently used agents for this finality. Clinical studies with these medications have shown variable results, most of which were positive [9,16]. However, maybe due to the heterogeneity of these studies and their nonuniform criteria for characterizing the outcomes, no consistency existed in regard to the use of beta-blockers to prevent atrial fibrillation and flutter at the time of these clinical studies [16,17]. Currently, however, the use of beta-blockers as the medication of choice to prevent those arrhythmias in the postoperative period of myocardial revascularization surgery is a consensus [18].

The present study aimed at assessing the effectiveness of metoprolol in preventing clinically detectable atrial fibrillation and flutter after coronary artery bypass graft surgery. The postoperative routines, such as the administration of beta-blockers and electrocardiographic monitoring, used in our service were maintained, and they were reproduced according to our clinical practice.

Methods

From February 1997 to October 1998, 383 patients underwent isolated coronary artery bypass graft surgery at the Hospital São Francisco of the Santa Casa de Misericór-

dia of Porto Alegre, in the state of Rio Grande do Sul. The study had been previously approved by the committee on ethics in research of that institution, and a written informed consent had been signed by all potentially eligible patients prior to the surgical procedure.

All medications being used in the preoperative period, including beta-blockers, were administered until 6 or 12 hours prior to surgery. Patients with the following characteristics were not included in the study: a) history of bronchospasm; b) left ventricular ejection fraction < 35% in the preoperative period; c) if they had an implantable cardiac pacemaker, chronic atrial fibrillation, history of paroxysmal supraventricular arrhythmias or if they were using amiodarone; d) congestive heart failure, low cardiac output (cardiac index < 2.2 L/min/m^2 or suggestive clinical signs), and dependence on inotropic agents, or the use of an intra-aortic balloon in the postoperative period; e) bradyarrhythmias (heart rate < 60 bpm, junctional rhythm, atrioventricular dissociation, or second- and third-degree blocks). Randomization was then performed in the 12th postoperative hour with the patient hemodynamically stable. The use of medications interfering with atrioventricular conduction or having antiarrhythmic properties was not allowed.

Of the 383 patients operated on, the following patients were not included in the study: 121 due to the above-cited reasons, 38 because the extracorporeal circulation technique was not used during their surgeries, and 24 who refused to participate in the study. The remaining 200 patients were randomized (fig. 1).

All randomized patients were operated on through a sternotomy while implementing extracorporeal circulation, moderate hemodilution (hematocrit around 25%), and moderate systemic hypothermia (32°C). For myocardial protection, a cardioplegic, anterograde, intermittent, isothermal blood solution was injected into the aortic root. In the postoperative period, potassium and magnesium serum levels were maintained above 4 mEq/L and 2 mEq/L, respectively.

An open, randomized clinical analysis was carried out based on the principle of intention to treat. Initially, blocks of 100 patients were randomly selected, and, after a provisional analysis, other blocks of 100 patients were randomly drawn adding up to a total of 200 patients. Two groups of 100 patients were randomized to receive metoprolol or not to receive the medication, which was administered either orally or with a nasogastric feeding tube if the patient was still intubated, from the 12th hour to the 7th postoperative day or hospital discharge, whichever happened first. The dosages of metoprolol ranged from 100 to 300 mg/day, were administered 2 or 3 times, and adjusted to maintain the heart rate between 60 and 90 bpm. This adjustment was performed during the first 2 to 3 days, while the patient was still in the intensive care unit. Then the dosages were maintained unaltered until the end of the study.

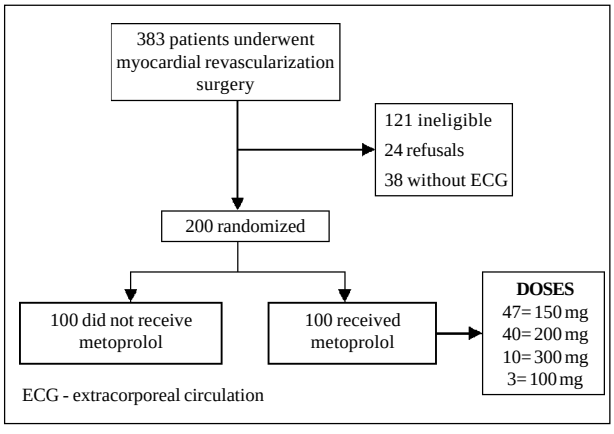

Fig. 1 - Study design.

The presence of arrhythmias was assessed with continuous electrocardiographic monitoring in the first 2 to 3 days, on average, while the patient remained in the intensive care unit. In this situation, the presence of sustained atrial fibrillation or flutter confirmed on surface electrocardiography was considered the outcome of interest. The transient arrhythmias not documented on that examination were not included in the study. After the patient was sent to the ward, these arrhythmias were detected based on the presence of symptoms or clinical examination, and were also confirmed on electrocardiography. The outcomes were initially analyzed by the physician on duty at the intensive care unit or by the resident physician at the ward; later, the outcomes were analyzed by the author of the study. On the day of hospital discharge or on the seventh postoperative day, all patients underwent electrocardiography to reassure the presence of sinus rhythm.

Data were put into table format and analyzed with the EPIINFO 6.0 statistical program for Windows, compatible with an IBM personal computer. The size of the sample for the study was estimated based on a 25%-incidence of atrial fibrillation obtained in the literature. Metoprolol was assumed to reduce that incidence to 15%, and, therefore, a sample with 200 patients would be required to reach statistical significance for a P value < 0.05 and power of 80%.

Data are shown as mean ± standard deviation. To analyze the differences between the treatment and control groups, the Student *t* test was used for the continuous variables, the chi-square test for the qualitative variables, and the Mann-Whitney test for the variables with an asymmetric distribution.

Results

Similarity was found between the metoprolol and control groups in regard to the following preoperative baseline characteristics: mean age; percentage of patients > 70 years; male sex; systemic hypertension; old myocardial infarction; left ventricular ejection fraction obtained on echocardiography or cineventriculography; and use of beta-blockers. In addition, in regard to the intraoperative characteristics, both groups had the following similarities: time of extracorporeal circulation, time of aortic clamping, internal

Table I - Baseline characteristics

Variable	Metoprolol n=100	Control n=100	P
Preoperative period			
Age (years)	59 ± 10	62 ± 11	NS
> 70 years (%)	19	19	NS
Male sex (%)	72	74	NS
SAH (%)	59	63	NS
Previous MI (%)	42	42	NS
Ejection fraction			
> 0.50 (%)	85	82	NS
0.35-0.50 (%)	15	17	NS
Use of beta-blockers (%)	65	63	NS
Intraoperative			
ECC (min)	68 ± 27	72 ± 21	NS
Ischemia duration (min)	45 ± 17	46 ± 14	NS
Internal thoracic artery (%)	78	71	NS
N. of revascularized vessels	3.7 ± 1	3.7 ± 1	NS

Results presented as mean ± standard deviation or as a percentage. SAH- systemic arterial hypertension; MI- myocardial infarction; ECC- extracorporeal circulation; NS- nonsignificant.

thoracic artery implantation, and number of vessels revascularized (tab. I).

The group of patients receiving metoprolol had significantly fewer arrhythmias than the control group did, their respective incidences being 11% and 24% (P=0.02). The relative risk was 0.46 (95% CI = 0.24-0.88), and the number necessary to treat to avoid the outcome was 8 patients (tab.II). Atrial fibrillation was the most frequent arrhythmia observed in both groups (fig. 2), and, in 86% of the cases, these arrhythmias were detected between the first and third postoperative days, the maximum peak on the second day (fig.3). During the arrhythmic episodes, the mean heart rate of the patients in the metoprolol group was significantly lower than that in the control group (134 ± 26 versus 157 ± 26; P= 0.02).

Of the 200 patients studied, 38 were 70 years old or more, 19 in each group. Ten patients in the control group had arrhythmias, but only 2 patients in the metoprolol group had those complications (χ^2 Yates: P=0.01). The relative risk was 0.20 (95% CI = 0.05-0.79), and the number necessary to treat to avoid the outcome was 2 patients (tab.II). On the other hand, among those patients aged less than 70 years, no difference was observed in the incidence of arrhythmias between both groups (P=0.3).

Of the 100 patients in the control group, those using beta-blockers before the surgery (n=65) had more arrhythmias than those who did not use them, their respective incidences being 29% and 16%, but with no significant difference (P=0.2).

Table II - Incidence of atrial fibrillation and flutter (AFF)

Variable	Control n=100	Metoprolol n=100	P	RR / 95% CI	NNT
AFF (all)	24%	11%	0.02	0.46 / (0.24-0.88)	8
AFF (≥ 70 y)	10/19 (53%)	2/19 (11%)	0.01*	0.20 / (0.05-0.79)	2

RR- relative risk; CI- confidence interval; NNT- number necessary to treat. *χ^2 Yates.

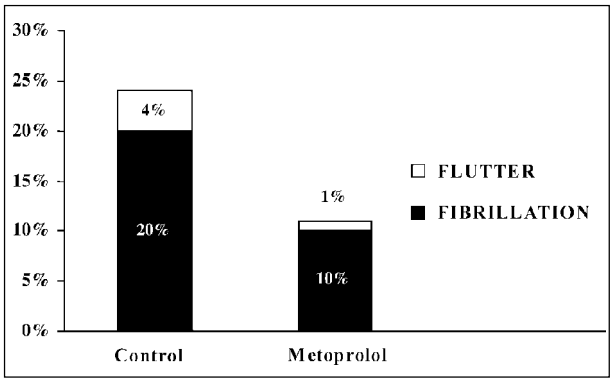

Fig. 2 - Incidence and type of arrhythmias observed.

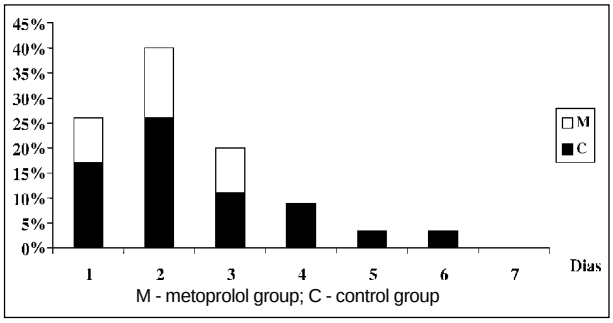

Fig. 3 - Moment of occurrence of atrial fibrillation and flutter in the postoperative period.

The dosages of metoprolol ranged from 100 to 300 mg/day, the mean dosage being 184 ± 5 mg. Most patients received 150 mg/day (n=47), followed by 200 mg/day (n=40), 300 mg/day (n=10), and, finally, 100 mg/day (n=3). The 89 patients in the metoprolol group who had no arrhythmias received a greater dosage than did the 11 patients who had that outcome (186.5 ± 48.1 versus 159.1 ± 30.2 mg), but with no significant difference (P=0.07).

In 8 patients, metoprolol was suspended due to the presence of the following undesired symptoms: arterial hypotension in 4 patients; bronchospasm and heart failure in 3 patients; and sinus bradycardia in 2. Of these 8 patients, 4 received 150 mg/day, 3 received 100 mg/day, and 1 received 200 mg/day.

The most frequent complications observed in the study were myocardial infarction in 8 patients, and stroke in 5 patients. No embolic events attributed to the presence of arrhythmias were observed. Three patients died during the study, 2 of whom were in the intervention group.

Discussion

The incidence of atrial fibrillation and flutter in the postoperative period of myocardial revascularization varies depending on the criteria used for qualifying arrhythmia as

an outcome, and on the intensity and type of monitoring used. In the present study, the incidence of these arrhythmias was 24% in the control group, which was slightly greater than that found by Leitch et al [4], who used basically the same type of monitoring. Considering that these arrhythmias may be transient and even fugacious, passing unnoticed with no clinical importance, in this study, we tried to emphasize the value of the sustained or symptomatic ones, considered as outcomes.

Atrial fibrillation and flutter were most frequently found between the first and third postoperative days, which is in accordance with reports in the literature [1,19]. Their less frequent occurrence after a patient's discharge from the intensive care unit may also be attributed to the purely clinical method of outcome detection used in that situation.

In the present study, the use of metoprolol caused a 54% reduction in the risk of arrhythmias, a slightly greater reduction than that reported by Janssen et al [20], who also used that medication in fixed dosages and almost the same type of monitoring. The meta-analyses by Andrews et al [9] and Kowey et al [16] reported reductions in the risk of arrhythmias of 74% and 51%, respectively, with the use of beta-blockers. It is worth emphasizing that most of these meta-analyses included analyzes with more prolonged monitoring with electrocardiography or Holter, and, therefore, with a greater power to detect the outcomes.

The lower heart rate observed in patients receiving metoprolol as compared with that in the control group during arrhythmic episodes confirms another beneficial effect of that drug in the present study. On the other hand, no relation has been observed between the use of greater dosages of this beta-blocker and the prevention of arrhythmias. A previous study with metoprolol could not demonstrate the beneficial prophylactic effect of this medication against atrial fibrillation and flutter after myocardial revascularization surgery using variable dosages to promote beta-blockade [21].

Unlike some studies that showed a reduced effectiveness of beta-blockers in the elderly [1,19], our study showed that metoprolol significantly reduced the incidence of atrial fibrillation and flutter in this high-risk group. On the other hand, in the group of patients aged less than 70 years, this beneficial result was not confirmed, leading to the conclusion that the protective effect of the medication observed in the group aged 70 years or more was the major determinant of the positivity of the study. This conclusion is important because more and more elderly patients undergo cardiac surgery, and the systematic use of beta-blockers in this age group may attenuate the impact of age as a risk factor for the appearance of those arrhythmias.

The discontinuation of beta-blockers in the postoperative period has long been a point of discussion, because it would leave the patient more exposed to the action of circulating catecholamines, increasing the risk of arrhythmias [22,23]. A more recent open study showed that the mere maintenance of those agents at the same preoperative dosages could reduce the risk of atrial fibrillation by 55% [24]. Our study showed no significant difference in the incidence of arrhythmias in the control group between the patients who discontinued the drug and those who continued to use metoprolol after the surgery. Maybe with a greater number of patients and with an adequate study design, we could assess the real impact of the suspension of metoprolol.

Metoprolol was discontinued in 8 patients due to the appearance of side effects, which were initially attributed to the drug. However, rather than representing the noxious effects of metoprolol itself, this pseudo-intolerance may be attributed to the borderline cardiovascular condition of certain patients in the postoperative period.

The limitations of the present study result from the fact that it was an open nonplacebo-controlled study, and, therefore, subject to potential bias of assessment. Transient, or even persistent and asymptomatic, arrhythmias may have passed unnoticed due to the lack of continuous monitoring, mainly after a patient's discharge from the intensive care unit. Metoprolol may also have masked or attenuated symptoms in patients with arrhythmias. In this situation, the study design itself considered the outcomes of clinical impact certainly prevented by the drug.

In conclusion, we believe that the use of beta-blockers should be routinely implemented in the postoperative protocols of myocardial revascularization for patients with no contraindication to their use. In particular, the elderly subgroup seems to benefit even more due to the significant results obtained in this study.

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