

Prevention of Atrial Fibrillation with Moderate Doses of Amiodarone in the Postoperative Period of Cardiac Surgery is Safe and Effective in Patients with High Risk for Developing this Arrhythmia

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Summary

Objective: To assess if prophylaxis with moderate doses of amiodarone in the postoperative period of cardiac surgery (coronary artery bypass grafting and/or valve surgery), reduces the incidence of atrial fibrillation in patients with high risk for developing this arrhythmia.

Methods: A randomized and prospective clinical study involving 68 patients who underwent elective cardiac surgery. Mean age was 64 years and 59% of participants were males. Patients with three or more risk factors for atrial fibrillation, according to the literature, were randomized into two groups to receive or not prophylaxis with amiodarone in the first postoperative day. The dose administered ranged from 600 mg/day to 900 mg/day, intravenously, on the first postoperative day, followed by 400 mg/day orally until hospital discharge or until completing seven days. The other patients, who presented two or fewer risk factors, were followed up until hospital discharge. All patients were evaluated by means of cardiac and/or electrocardiographic monitoring.

Results: In the group treated with amiodarone, 7% of patients presented atrial fibrillation, whereas in the control group 70% of patients developed arrhythmia. Among the non-randomized individuals (with two or fewer risk factors), only 24% presented atrial fibrillation.

Conclusion: The prophylactic use of amiodarone was effective in the prevention of atrial fibrillation in patients with three or more risk factors for this arrhythmia. This treatment can be useful to reduce stay at the Intensive Care Unit and, consequently, the complications originating from longer hospitalization. (*Arq Bras Cardiol* 2007; 89(1) : 20-24)

Key words: Atrial fibrillation/therapy; amiodarone; thoracic surgery; postoperative care.

Introduction

Atrial fibrillation is the most common arrhythmia in the postoperative period of cardiac surgery. It can occur due to multiple mechanisms¹.

The prevalence of this arrhythmia is approximately of 11% to 40% after coronary artery bypass grafting, but it can reach 50% of cases after valve surgery²⁻⁴. It generally occurs between the first and fifth postoperative days, and it is more prevalent in patients over 65 years⁵⁻⁸ of age.

Although spontaneous recovery of sinus rhythm may occur after 6 to 8 weeks⁹, this arrhythmia increases the time spent at the Intensive Care Unit (ICU), thus increasing the risk of nosocomial infections and hemodynamic instability¹⁰.

Among the main risk factors contributing to the onset of this arrhythmia are: old age, male gender, valve disease, increased atrial size, previous arrhythmias, chronic

obstructive pulmonary disease, previous cardiac surgery, discontinuation of betablockers, use of digoxin, ventricular dysfunction and anemia¹¹.

It is known that the more risk factors, the greater the likelihood of atrial fibrillation in the postoperative period of cardiac surgery^{12,13}.

Prophylaxis of atrial fibrillation can be effectively performed using betablockers or amiodarone. On the other hand, the use of verapamil, digoxin and/or procainamide has not brought any benefits^{12,14-17}.

The efficacy of amiodarone is generally equivalent or greater than that of other drugs with the same indications, and there is no consensus regarding an optimum dose. It must be administered at the lowest possible dosage for the best intended effect, in order to avoid side effects that are generally dose-dependent. These are the reasons that made the authors of this study choose amiodarone, a class-III- antiarrhythmic drug. This drug is able to relax the smooth muscles and decrease both coronary and peripheral vascular resistance. Its effect prolongs the action potential and refractoriness of all cardiac fibers, without affecting the resting potential. It also reduces the sinus and atrioventricular (AV) rates and prolongs the AV conduction time. Additionally, it may trigger

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widening of QT interval and appearance of the U-wave. It can be indicated to treat ventricular arrhythmias, supraventricular paroxysmal tachycardia, fibrillation and atrial flutter. Moreover, it has also shown to be safe and effective in the prevention of atrial fibrillation in cardiac surgery postoperative period¹⁸.

Contrary to previous studies carried out with prophylactic treatment as early as in the preoperative period, there are no scientific studies demonstrating the benefits for high risk patients - who are therefore more susceptible to this arrhythmia - of pharmacological intervention started only in the postoperative period.

Methods

A prospective clinical study carried out between August 2004 and February 2005 in 68 patients, with 59% males and a mean age of 64 years. The patients underwent elective cardiac surgery (coronary artery bypass graft and/or valve surgery) with cardiopulmonary bypass.

The inclusion criteria were defined for patients presenting three or more risk factors for atrial fibrillation according to the literature (Table 1). This criterion was adopted from a statistical method (a multivariate analysis known as CART – Classification and Regression Tree) used in a previous study performed but not yet published, which stated that the presence of three or more risk factors among those listed in the literature would increase the incidence of this arrhythmia in the postoperative

period of cardiac surgery.

After inclusion, patients were selected for a second randomization and were divided into two groups: Amiodarone (Group 1) and Control (Group 2). The exclusion criteria and the stratification model used to select patients are described in Tables 2 and 3, respectively.

On the first postoperative day, Group 1 patients received intravenous amiodarone at a dose between 600 mg and 900 mg, in 24 hours, followed by 400 mg/day, orally, until completion of seven-day treatment or hospital discharge. Group 2 patients followed the conventional treatment. Those with two or fewer risk factors and who would not be randomized for prophylaxis with the study medication were followed up until hospital discharge.

All patients were evaluated by means of electrocardiography and/or cardiac monitoring.

Statistical analysis - To evaluate the association between the occurrence of atrial fibrillation and risk factors we used the Fisher's exact test. Student's *t* test was used to compare the mean age of patients. The evaluation of amiodarone efficacy in the prevention of atrial fibrillation was carried out using Fisher's exact test. To compare the mean age between the groups (groups with up to two, groups with three or more risk factors, and groups with and without amiodarone), we used the variance analysis (ANOVA). The significance level in this study was 5% ($p < 0.05$).

Table 1 – Study inclusion criteria

Age \geq 65 years
Valve disease
Left atrium overload
Ventricular dysfunction
Cardiac reoperation
Electrolyte disorder
Previous atrial arrhythmia
Hypoxemia
Chronic obstructive pulmonary disease
Discontinuation of betablocker 24 hours before surgery
Previous use of digitalis

Table 2 – Study exclusion criteria

Persistent atrial fibrillation
Thyroid disease
Pulmonary fibrosis
Atrioventricular block
Decompensated heart failure (ejection fraction $<$ 25%)
Previous use of amiodarone
Pacemaker use

Results

Of the 68 patients analyzed, 33 (49%) presented two or fewer risk factors and were followed up until hospital discharge.

Table 3 – Stratification model used to select patients in the search of risk factors for atrial fibrillation

Risk factors	Yes	No
Age \geq 65 years		
Left atrium overload		
Valve disease		
Cardiac reoperation		
Previous atrial arrhythmia		
Hypoxemia		
Ventricular dysfunction		
Chronic obstructive pulmonary disease		
Electrolytic disorder (Hb $<$ 10 g/dl; K $<$ 3.5 mmol/l or $>$ 5.0 mmol/l)		
Previous use of betablocker; discontinued before surgery		
Previous use of digitalis		
Number of risk factors of the patient		

Hb - hemoglobin; K - potassium.

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The remaining 35 (51%) patients who had three or more risk factors were randomized to receive or not amiodarone (Figure 1). In the group treated with amiodarone (n = 15), only one patient (7%) developed atrial fibrillation, whereas in the control group (n = 20), without prophylaxis, 14 patients (70%) developed arrhythmia (Table 4). Hence, it was observed that the group treated with amiodarone presented lower incidence of atrial fibrillation (significance level of 5%).

Among those patients not randomized to receive amiodarone for presenting two or fewer risk factors, only 8 patients (24%) presented atrial fibrillation, while 25 (76%) did not develop this condition. The age factor, already established in the literature as a relevant risk factor for the occurrence of atrial fibrillation in the postoperative period of cardiac surgery, was high in this case series, but there was no statistically significant difference between the groups (Tables 5 and 6). This finding probably occurred due to the advanced age of this population. Coronary artery bypass grafting was the most prevalent type of surgery, occurring in 79.7% of the cases analyzed (Table 7).

Discussion

Atrial fibrillation remains the most frequent complication in the postoperative period of cardiac surgery. According to

the literature, its incidence ranges from 20% to 50% of cases, depending on the type of surgery (more frequent in valve surgeries)¹⁻⁴. This comorbidity prolongs hospital stay, which can lead to several clinical complications.

Patients with advanced age and the association of risk factors contribute to higher rate of atrial fibrillation in the postoperative period^{15,19}. In this study, the number of risk factors (three) was the determining factor in the selection of individuals for the prophylaxis - or not - with amiodarone.

Several clinical trials have evaluated the effectiveness of pharmacological interventions in reducing the incidence of this arrhythmia¹⁸⁻²². However, these trials are generally not much statistically significant when the effects of these treatments on shorter hospital stay or on the occurrence of stroke are estimated to estimate. The main indication in the prophylaxis of atrial fibrillation in the postoperative period of cardiac surgery is still a reduced hospital stay and less complications, such as strokes^{16,17}.

Some randomized studies assessed the prophylaxis of this arrhythmia with drugs such as amiodarone, betablocker, sotalol and a biatrial pacemaker. The effectiveness of these

Table 4 – Distribution of atrial fibrillation according to the use of amiodarone

Use of amiodarone	Atrial fibrillation			Total
	No	Yes		
No	n	6	14	20
	%	30	70	100
Yes	n	14	1	15
	%	93	7	100
Total	n	20	15	35
	%	57	43	100

Fisher's exact test, p value = 0.011. n - number of patients.

Table 5 – Distribution of atrial fibrillation according to the use of amiodarone in each age group

Use of amiodarone	Frequency	< 65 years of age		≥ 65 years of age	
		No	Yes	No	Yes
No	n	2	5	4	9
	%	28	72	31	69
Yes	n	6	0	8	1
	%	100	0	89	11
Total	n	8	5	12	10
	%	61	39	53	47
Fisher's exact test (p value)		0.4000		0.066	

n - number of patients.

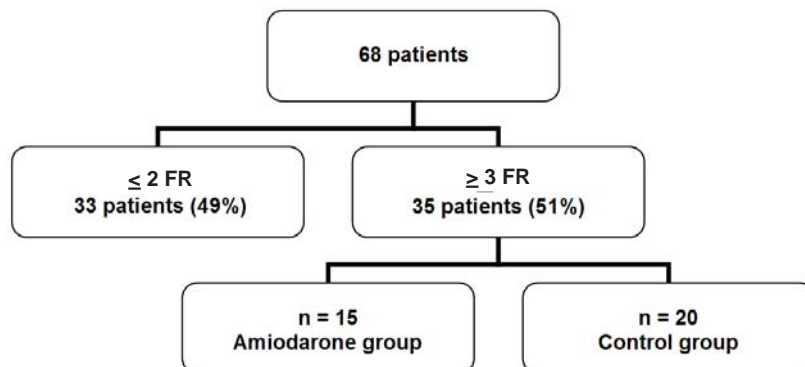


Fig. 1 - Flow chart of patients studied. RF - risk factors; n - number of patients.

Table 6 - Distribution of atrial fibrillation according to the risk factors, use of amiodarone and the summary measures of patients' ages

Risk factors		Atrial fibrillation		Mean age	SD
		No	Yes		
≤ 2 RF	n	25	8	61.9	10.2
	%	75.8	24.2		
≥ 3 RF with amiodarone	n	14	1	65	3,5
	%	91	9		
≥ 3 RF without amiodarone	n	6	14	61.1	14.6
	%	30	70		

SD - standard deviation; RF - risk factors.

The comparison between antiarrhythmic drugs, such as betablockers, sotalol and amiodarone, either as combination therapy or not, has also shown significant reduction in atrial fibrillation in the cardiac surgery postoperative period. In studies where the antiarrhythmic agent used was amiodarone, there was a reduction in hospital stay^{21,22}.

In this study we also observed a shorter hospital stay in the group receiving prophylaxis with amiodarone, as compared to the control group (two and five days, respectively).

The intravenous administration of amiodarone to prevent atrial fibrillation in patients selected according to risk factors (such as advanced age, valve surgery, patients with chronic obstructive pulmonary disease and other risk factors analyzed) showed a good cost-effectiveness ratio favoring prophylaxis^{23,24}.

The efficacy of prophylactic amiodarone against atrial

Table 7 – Percentile distribution of groups according to surgery performed

Surgery	Up to 2 risk factors	Three or more risk factors		Total
		With amiodarone	Without amiodarone	
Mitral commissurotomy	0.0	0.0	9.1	2.0
Mitral valveplasty	0.0	0.0	9.1	2.0
Coronary bypass grafting	89.7	90.1	45.5	79.7
Coronary bypass grafting + mitral valveplasty	3.4	0.0	0.0	2.0
Coronary bypass grafting + mitral valve replacement	0.0	0.0	9.1	2.0
Aortic valve replacement	2.0	8.9	0.0	4.1
Mitral valve replacement	4.9	1.0	27.2	8.2
Total	100	100	100	100

drugs in the reduction of atrial fibrillation in the postoperative period of cardiac surgery was confirmed. However, a decreased incidence of strokes is still inconclusive¹⁵.

A study with intravenous administration of amiodarone up to 1 g/day compared with placebo has already shown safety and effectiveness of this drug in reducing atrial fibrillation in the postoperative period of cardiac surgery¹⁹. The efficacy of oral administration has also been analyzed in a placebo-controlled study at a dose of 2 g/day, from one to four days before surgery, and 400 mg/day up to seven days after surgery²⁰.

This study did not require previous admission of patients to show the effectiveness of amiodarone in the prevention of atrial fibrillation. The drug was initiated only on the first postoperative day in selected patients (high risk). Additionally, what differentiates this study from other previous studies is the fact that the dose of amiodarone used, both the loading dose (600 mg/24 hours to 900 mg/24 hours, intravenously) and the maintenance dose (400 mg/day orally until hospital discharge or completion of seven days), was lower; therefore, with fewer risks of adverse events to the patients.

fibrillation in the postoperative period of cardiac surgery was confirmed in this study. The drug regimen used protected 93% of patients with three or more risk factors, whereas in the control group, 70% of individuals presented atrial fibrillation.

In addition to confirming the need of a more strict selection including patients at a higher risk (with three or more of the above-mentioned risk factors), this study showed the benefit of this drug treatment at a moderate dose, initiated only in the postoperative period.

Conclusion

It was demonstrated that amiodarone is safe and effective in prevention of atrial fibrillation in the postoperative period of cardiac surgery in patients with three or more risk factors for arrhythmia. This prophylaxis proved to be safe and it may reduce hospitalization periods as well as the clinical complications resulting from prolonged stay at ICU.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association with Graduate Work

This study is not associated with any graduation program.

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