High Dose of Amiodarone in a Short-Term Period Reduces The Incidence of Postoperative Atrial Fibrillation and Atrial Flutter

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Objective

To investigate wheter oral amiodarone administered before surgery for a short period in high dose would reduce the incidence of postoperative atrial fibrillation or atrial flutter and reduces the lenght of hospital stay.

Methods

In the double-blind, randomized study, 93 patients were given either oral amiodarone (46 patients) or placebo (47 patients). Therapy consisted of 600mg of amiodarone three times a day, started at mininum 30 hours and at maximum 56 hours before surgery.

Results

Postoperative atrial fibrillation or atrial flutter occurred in 8 of 46 patients in the amiodarone group (17.4%) and 19 of the 47 patients in the placebo group (40.4%) ($p=0.027$). The mean dose of amiodarone was 2.8g. Patients in the amiodarone group were hospitalized for 8.9±3.1 days and patients in the placebo group were hospitalized for 11.4± 8.7 days ($p=0.07$). The hospital lenght were significantly prolonged in patients who developed atrial arrhythmias after surgery, despite the treatment received.($p<0.001$).

Conclusion

This new alternative way of using amiodarone in high dose and in a short-term period before surgery reduce the incidence of postoperative atrial fibrillation or atrial flutter in coronary artery bypass graft surgery.

Key words

Amiodarone, Atrial fibrillation, Atrial flutter and Coronary Artery Bypass Graft Surgery.

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The incidence of supraventricular arrhythmias (atrial fibrillation or atrial flutter) in the postoperative period is high, reaching 53% of the cases[1] after myocardial revascularization surgery (MRS). Patients who develop atrial fibrillation (AF) or atrial flutter (AFLU) generally develop comorbidities in addition to symptoms, which increase the duration of hospital stay and costs[2]. Many prophylactic methods for the reduction of supraventricular arrhythmias, especially AF, have been investigated with promising results[3]. The prophylactic use of amiodarone has shown to be effective in minimizing the incidence of AF[1, 4-10]. However, the lack of a consensus regarding the homogenous dose, period of treatment and administration route observed among the clinical studies makes it difficult to utilize amiodarone as a prophylactic method. Studies utilizing oral amiodarone show a long period of preoperative administration, which hinders its use in our country. Therefore, the aims of this study are to analyze whether the oral use of 1,800 mg of amiodarone/day, started at least 30 hrs and at most 56 hrs before surgery can reduce the incidence of atrial fibrillation or atrial flutter, and to compare the duration of hospital stay between the groups.

Methods

Patient population - Ninety-three patients in sinusal rhythm, who had been electively assigned to myocardial revascularization surgery (MRS), were randomly selected to receive 1,800 mg/day of oral amiodarone or placebo. All patients underwent conventional MRS.

Exclusion criteria included a history of antiarrhythmic drug use class I or III in the previous 6 months; history of atrial fibrillation or atrial flutter, history of toxicity with amiodarone use; participation in another clinical study protocol; untreated thyroidopathy; four-fold increase in the hepatic transaminases reference values; presence of second or third-degree atrioventricular block; cardiac frequency below 50 bpm or systolic blood pressure below 100 mmHg; decompensated heart failure; use of pacemaker; valve substitution concomitant with MRS and ejection fraction < 40%.

Study Design - We carried out a randomized, double-blind, placebo-controlled study. All patients signed the informed consent form. The study protocol was approved by the Review Board of the local Institution. The patients who consented to study were randomized to receive the study medication on the same day. Amiodarone was prescribed at a dose of 600 mg three times a day, starting at least 30 hrs and at most 56 hrs before surgery.

The placebo was identical, in appearance, to amiodarone. Other conventional drug therapies were not modified by the study protocol.

All patients underwent MRS with extracorporeal circulation and the anesthetic procedure was similar for all of them. The choice of using the internal thoracic artery was left to the clinical and surgical team's discretion. After surgery, all patients were admitted the Intensive Care Unit (ICU) and all procedures followed the Service routine. Patients were kept under continuous electrocardiographic monitoring until they were released from the ICU and transferred to the Infirmary, where they were monitored through daily clinical exams and electrocardiograms.

Additional electrocardiograms were performed when the patient presented symptoms, such as palpitations and/or suspected arrhythmia. Patients did not undergo telemetry until hospital release.

Myocardial infarction, heart failure, bleeding, brain ischemia, atrial fibrillation and atrial flutter were the outcomes analyzed in the postoperative period.

The study primary outcome was the development of atrial fibrillation or atrial flutter, registered through electrocardiogram and analyzed by two cardiologists, in the postoperative period until hospital release. The secondary outcome was the duration of hospital stay.

In order to be considered a primary outcome, the episode should have lasted at least 10 minutes, or if it lasted less than that, it should have caused hemodynamic instability. Atrial fibrillation was characterized at the electrocardiogram by the absence of P waves before each QRS complex and an irregular ventricular frequency. Atrial flutter was characterized at the electrocardiogram by the absence of P waves, presence of biphasic F waves, with either fixed or variable atrioventricular block. Treatment for supraventricular tachyarrhythmia was not controlled by the study. All patients were followed during hospital stay.

Statistical Analysis - The data were analyzed based on the intention to treat. Continuous variables were expressed as means and standard deviations and compared by student's t test, whereas categorical variables were expressed as proportions and compared by chi-square test and Fisher's exact test. A p value < 0.05 was considered statistically significant. Tests were performed with the SPSS software, version 11.0.1 (SPSS Inc. Chicago, Illinois).

Results

A total of 93 patients were randomized in this study. Twenty-eight basal characteristics were collected. The most representative basal characteristics are shown in Table 1, reflecting similarity between the two groups. Age, ventricular function and comorbidities were identical in both groups. Approximately 75% of the study population was being treated with beta-blockers before surgery. Surgical characteristics are shown in Table 2, with no difference between the groups. Complete revascularization was carried out in 90 patients (96.7%), with no difference between the amiodarone and placebo groups.

Amiodarone mean dose was 2.8±0.7g. The study group was withdrawn shortly in two patients, one from the amiodarone group and the other from the placebo group, due to adverse gastrointestinal effects, i.e., epigastralgia and diarrhea. There were no further adverse effects related to the

Table 1 - Baseline features

	Amiodarone (n=46)	Placebo (n=47)	p
Age (yrs)	61.0 ± 10.1	61.1 ± 10.5	0.76
Males (%)	63.0	70.2	0.61
Unstable angina (%)	32.6	38.3	0.72
AMI History (%)	32.6	51.1	0.11
Diabetes mellitus (%)	23.9	21.3	0.95
Hypertension (%)	87.0	78.7	0.41
HF III or IV (%)	6.5	10.6	0.73
Beta-blocker (%)	73.9	74.5	1.00
Calcium Blocker, (%)	19.6	10.6	0.36
LCT lesion (%)	15.2	12.8	0.97
VF (bpm)	63.8 ± 8.2	63.7 ± 8.2	0.98
Ejection Fraction (%)	54.2 ± 10.1	52.1 ± 10.1	0.37

AMI – acute myocardial infarction; HF - heart failure; LCT – left coronary trunk; VF – ventricular frequency; bpm – beats per minute.

study medication. Mean amiodarone dose in patients who developed atrial fibrillation or atrial flutter in the postoperative period was de 2.6±0.7g vs. 2.9±0.7g, compared to those patients who maintained the sinusal rhythm (p=0.37).

Atrial fibrillation or atrial flutter occurred in 8 patients (17.4%) who had been randomized for the amiodarone group and in 19 patients (40.4%) of those randomly assigned to the placebo group (p=0.027), which represents a relative risk reduction of 56%. All 27 patients who developed atrial fibrillation or atrial flutter in the postoperative period presented sinusal rhythm at hospital release.

Duration of hospital stay tended to be shorter for the amiodarone group, 8.9±3.1 vs. 11.5±8.7 days for the placebo group (p=0,07). The occurrence of atrial fibrillation or atrial flutter was associated to an increase in the duration of hospital stay, regardless of the randomization, being 14.5±10.4 days for patients who developed arrhythmias and 8.3±2.3 days for those who kept the sinusal rhythm (p<0.001).

Table 2 - Operative features

	Amiodarone (n=46)	Placebo (n=47)	p
Extra-corporeal circulation (min)	81.2 ± 28.2	81.6 ± 29.2	0.94
Aortic clamping (min)	48.0 ± 16.2	49.1 ± 18.6	0.76
Bypass graft surgery (#/patient)	2.9 ± 1.1	2.65 ± 1.1	0.89
Internal thoracic artery (%)	87.0	72.3	0.14

Non-fatal complications in the postoperative period were similar in the amiodarone and placebo groups (Table 3). There was a significantly higher number of postoperative complications in those patients who developed atrial fibrillation or atrial flutter, regardless of the randomization, especially regarding the development of heart failure. Perioperative myocardial infarction showed a tendency to be more frequent in the group that developed atrial fibrillation or atrial flutter (Table 4).

Table 3 - Postoperative complications

	Amiodarone (n=46)	Placebo (n=47)	p
Heart failure (%)	21.7	31.9	0.38
Brain ischemia (%)	2.3	2.2	1.00
Bleeding (%)	19.6	25.5	0.66
Myocardial infarction (%)	17.4	19.1	0.89

Table 4 - Postoperative complications

	Atrial fibrillation or flutter (n=27)	Sinusal (n=66)	p
Heart failure (%)	52.0	20.6	<0.01
Brain ischemia (%)	3.8	1.6	0.72
Bleeding (%)	25.9	21.2	0.83
Myocardial infarction (%)	29.6	13.6	0.13

Discussion

In this study, a dose of 600 mg of oral amiodarone, administered every eight hours, with the total dose varying from 1,800 mg/day to 4,200 mg/day was proposed. The study drug, i.e., amiodarone, was administered neither during the transoperative nor in the postoperative periods. The prophylactic use of oral amiodarone, at a dose of 1,800 mg/day, with a mean total dose of 2,800 mg administered within a short-term period preoperatively - a maximum of 56 hrs before the surgery – showed this drug to be effective and safe in reducing the incidence of atrial fibrillation or atrial flutter, with a risk reduction decrease of approximately 56%.

The distinguishing feature of this study when compared to the others described in literature is the short-term period of treatment, associated to the absence of drug use during and after surgery. Another difference is the elevated dose, the highest found in literature, with no significant adverse effects.

Dauod et al[1] showed a reduction in the incidence of atrial fibrillation of 54% with the use of oral amiodarone with a mean dose of 4.8 g. Maras et al[7] utilized a single oral dose of 1,200 mg one day before surgery and maintenance dose of 200 mg/day until the seventh postoperative day, showing a significant reduction in the incidence of atrial fibrillation only among elderly patients (26.7% vs. 43.1%). The amiodarone dose utilized by Katariya et al[8] was 600 mg/day, started on the first postoperative day and kept until hospital release, showing a reduction in the incidence of atrial fibrillation of 19.7% in the control group to 4.7% in the amiodarone group.

The AFIST Study[11] shows two different treatment regimens with amiodarone. One group received a rapid loading – 1,600 mg one day before surgery, 1,200 mg on the day of the surgery and 800 mg on the first postoperative day for four days. The other group started receiving amiodarone five days before surgery, at a dose of 600 mg/day that was increased to 800 mg on the day of the surgery, and kept at 800 mg/day until the fourth postoperative day. At the analysis, the two types of treatment were grouped, showing a decrease in the

incidence of atrial fibrillation in the amiodarone group, resulting in a risk reduction of 61%.

White et al[10] compared two strategies of the prophylactic use of oral amiodarone. The first group received oral amiodarone, which was started five days before the surgery, and kept until it totaled 7g; the other group received a rapid loading of amiodarone from the day before the surgery, at a dose of 1,600 mg, and was kept with 800 mg until it totaled 6 g, and the third group received placebo. Patients who received 7 g presented a significant risk reduction of 48.4% for the occurrence of atrial fibrillation, when compared to the placebo group, whereas the patients who received 6 g of amiodarone presented a risk reduction of 34% (p=0.054).

Indeed, the fact that only two days are necessary in the pre-operative period to start the prophylaxis of atrial fibrillation or atrial flutter helps to make this method more applicable, as one of the main impediments for not using amiodarone as a prophylactic method is the long-term drug use in the preoperative period, or having its use started in the immediate postoperative period, which many times is accompanied by significant hemodynamic instability, limiting its use under these circumstances.

No significant difference was observed regarding duration of hospital stay. The studies on amiodarone are consistent concerning the reduction of atrial fibrillation; however, regarding duration of hospital stay, the results are quite diverse. Duration of hospital stay in the study by White et al[10] was similar in the three groups of patients, with a mean of 9.4, 9.3 and 9.0 days for the placebo, slow loading amiodarone and rapid loading amiodarone groups, respectively. Daoud et al[1], however, showed a significant reduction of 7.9 days in the placebo group, to 6.5 days in the amiodarone group. Other authors such as Dorge et al[5], Guarnieri et al[6], Maras et al[7] and Solomon et al[9] did not find a significant decrease in duration of hospital stay, whereas authors such as Katariya et al[8] and Lee et al[4] demonstrated a favorable effect of amiodarone in reducing duration of hospital stay.

When these studies are analyzed as a whole, a significant reduction in duration of hospital stay is observed, with a difference of –0.91 days with CI of 95% (-1.59 to –0.23)[3] in favor of amiodarone use.

When the patients who developed atrial fibrillation or atrial flutter were analyzed, regardless of the treatment group they were assigned to, it was observed that the patients who presented, at any time, an episode of atrial fibrillation or atrial flutter showed a longer duration of ICU stay, as well as a longer hospital stay. These findings are in accordance with several studies in the literature that showed an increase of 3 to 4 days in the hospital stay in those patients who developed AF in the postoperative period of myocardial revascularization surgery[12].

Study limitations - Firstly, the sample size was small to demonstrate a statistical difference regarding duration of hospital stay. Secondly, Holter monitoring was not carried out to detect asymptomatic supraventricular arrhythmia, therefore underestimating the incidence of atrial fibrillation or atrial flutter. However, it is known that the occurrence of asymptomatic and transient atrial fibrillation or atrial flutter in the postoperative period does not represent significant clinical implications, with no influence on the routine care given to the patients. Thirdly, the study protocol did not include the treatment of atrial fibrillation or atrial flutter; therefore, the increase of duration of hospital stay might have been due more to a reflex of the strategy of atrial fibrillation or atrial flutter treatment in the postoperative period than the effect of the study drug.

Conclusions

The results of this study on atrial fibrillation or atrial flutter prevention in the postoperative period of myocardial revascularization surgery, with the administration of oral Amiodarone, 600 mg three times a day, initiated at least 30 hrs and at most 56 hrs before surgery, showed a decrease in the incidence of atrial fibrillation or atrial flutter, although duration of hospital stay was not significantly reduced. Therefore, we believe the use of this new strategy, with the administration of oral Amiodarone at a dose of 1,800 mg/day in the preoperative period of myocardial revascularization surgery, is well tolerated and presents a desirable alternative for the prevention of supraventricular tachyarrhythmia in patients who are candidates to myocardial revascularization surgery.

Potencial Conflict of Interest

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

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