Amiodarone reduces the incidence of atrial fibrillation after coronary artery bypass grafting

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Objective: The purpose of this study was to evaluate the safety and efficacy of postoperative administration of prophylactic amiodarone in the prevention of new-onset postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting.

Methods: In this prospective study 157 patients were randomly divided into two groups: 77 patients (amiodarone group) received intravenous amiodarone in a dose of 10 mg/kg/d for postoperative 48 hours. On postoperative day 2 oral amiodarone was started with a dose of 600 mg/d for 5 days, 400 mg/d for the following 5 days, and 200 mg/d for 20 days, and 80 patients received placebo (control group).

Results: Preoperative patient characteristics and operative variables were similar in the two groups. Postoperative atrial fibrillation occurred in 8 patients (10.4%) receiving amiodarone and in 20 (25.0%) patients receiving placebo ($P = .017$). Duration of atrial fibrillation was 12.8 ± 4.8 hours for the amiodarone group compared with 34.7 ± 28.7 hours for the control group ($P = .003$). The maximum ventricular rate during atrial fibrillation was slower in the amiodarone group than in the control group (105.9 ± 19.1 beats per minute and 126.0 ± 18.5 beats per minute, respectively, $P = .016$). The two groups had a similar incidence of complication other than rhythm disturbances (20.8% vs 20.0%, $P = .904$). Amiodarone group patients had shorter hospital stays than that of control group patients (6.8 ± 1.7 days vs 7.8 ± 2.9 days, $P = .014$). The in-hospital mortality was not different between two groups (1.3% vs 3.8, $P = .620$).

Conclusions: Postoperative intravenous amiodarone, followed by oral amiodarone, appears to be effective in the prevention of new-onset postoperative atrial fibrillation. It also reduces ventricular rate and duration of atrial fibrillation after coronary artery bypass grafting. It is well tolerated and decreases the length of hospital stay.

New-onset atrial fibrillation (AF) is a frequent clinical problem and occurs in up to one third of patients undergoing coronary artery bypass grafting (CABG), with a peak incidence on postoperative days 2 to 3.¹⁻⁴ Advanced age and withdrawal of preoperative β -blockers, together with postoperative sympathetic activation and a history of preoperative paroxysmal supraventricular arrhythmia, seem to play a major role in the development of AF.⁵ Although postoperative AF usually does not result in long-term sequelae, it often increases length and cost of hospital stay due to hemodynamic compromise or thromboembolic

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complications.⁶ The loss of contribution of normal atrial contraction on cardiac performance may result in hemodynamic deterioration during the postoperative period.

Over the years, different regimens have been proposed to prevent postoperative AF. Several pharmacologic agents such as digoxin, β -blockers, calcium channel blockers, quinidine, magnesium, and sotalol have been used to prevent the occurrence of AF after CABG.⁷⁻¹² Many of these agents have been disappointing and none of them has been uniformly accepted as a drug of choice.

Amiodarone, a class III antiarrhythmic drug with antiadrenergic properties, has been reported to be effective in converting AF to sinus rhythm and in the treatment of refractory AF.^{13,14} Although considered to be a class III antiarrhythmic, amiodarone also has class I, II, and IV actions, which give it a unique pharmacologic and antiarrhythmic profile.¹⁵ It can be taken orally after a high-dose preloading.¹⁶ Preoperative oral amiodarone has been shown to decrease the occurrence of AF after cardiac surgery.¹⁷ In this prospective study, we aimed to assess the efficacy of short-course intravenous amiodarone followed by oral therapy in the prevention of new-onset AF after CABG.

Patients and Methods

Patient Selection

This prospective trial evaluated 157 patients (mean age 60.2 ± 9.3 , range 36-78 years) who underwent elective CABG at Ege University Hospital from October 2000 to November 2001. There were 121 men and 36 women. All of the patients were in sinus rhythm and had a baseline corrected QT interval of 440 ms or less. Exclusion criteria were refusal of consent; the presence of preoperative chronic AF; history of paroxysmal AF; myocardial infarction less than 3 weeks before surgery; second- or third-degree atrioventricular block; sick sinus syndrome; need for temporary or permanent pacemaker; preoperative use of certain interacting drugs (phenytoin, cyclosporine, cholestyramine, cimetidine, or class I and class III antiarrhythmic drugs); history of amiodarone side effects; use of amiodarone in the year preceding the operation; heart rate less than 60 beats/min at rest; an initial systolic blood pressure of less than 100 mm Hg; redo coronary artery bypass surgery; concomitant operations such as valve replacement and aneurysmectomy; thyroid disease; asthma; chronic obstructive pulmonary disease; chronic renal failure (serum creatinine greater than 1.9 mg/dL); or liver function test results greater than 2 times normal. The Institutional Review Board approved the study, and all patients gave written informed consent for participation in the study the day before surgery.

Study Protocol

The patients were randomly assigned in a double-blind fashion to treatment with amiodarone or placebo. In the amiodarone group, intravenous amiodarone was begun postoperatively, within 2 hours of entering the cardiovascular surgical intensive care unit (ICU). An intravenous infusion without a loading dose was given for 48 hours at a dose of 10 mg/kg per day. On postoperative day 2 the patients started to receive oral amiodarone 600 mg per day three

times a day for 5 days, 400 mg per day twice a day for the following 5 day-period, and 200 mg per day in a single dose for the last 20 days for a total of 30 days. For patients randomized to the control arm, a 5% glucose infusion was given intravenously for the first 48 hours. The patients were then switched to oral placebo in the same manner as the amiodarone group. To avoid an increased incidence of AF as a result of β -blocker withdrawal, β -blockers were continued in patients who were receiving β -blockers at the time of the surgery, if possible.

Operative Techniques

All operations were performed through a median sternotomy. Cardiopulmonary bypass (CPB) was established via standard aortocaval cannulation with a roller pump and hollow-fiber membrane oxygenator at moderate hypothermia (28°C to 30°C), with pump flow rates of 2.0 to 2.5 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ to maintain a perfusion pressure of about 65 mm Hg. During bypass the hematocrit value was maintained between 20% and 25%. After aortic crossclamping, all patients received intermittent cold blood cardioplegia. Cardioplegic solution was delivered either in an antegrade fashion via the aortic root or in a retrograde fashion via the coronary sinus. Topical hypothermia with cold saline solution was used in all operations. Distal anastomoses were performed during a period of aortic crossclamping and proximal anastomoses were performed with partial aortic clamping during rewarming. Conduits for bypass included saphenous veins or internal thoracic arteries or a combination of the two.

Postoperative Monitoring

After surgery, all patients were admitted to the cardiovascular surgical ICU and monitored continuously with electrocardiography, three-channel pressure, and cardiac output via pulmonary artery catheter. When the patients were transferred to wards, continuous electrocardiographic tracings were recorded until hospital discharge. Twelve-lead electrocardiograms were done routinely every day and additionally when an arrhythmia was detected during the hospital stay to confirm and document any rhythm disturbances. QTC intervals were measured by the use of the Bazett formula. Postoperative AF was defined as atrial activity that was either not discernible or completely unorganized, accompanied by an irregular ventricular rate lasting more than 5 minutes or requiring therapy as a result of hemodynamic compromise. Management of AF was directed by the cardiac surgery team. We began oral anticoagulation with warfarin when the arrhythmia was persistent for more than 24 hours. At the end of the prophylactic oral amiodarone therapy (postoperative day 30), all patients were clinically examined and a 12-lead electrocardiogram was obtained. Intraoperative and postoperative data, including complications and adverse events, were assessed through a medical record review.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill). Where appropriate, data are expressed as mean values $\pm$ standard deviation or as percentages. Once the homogeneity was confirmed with the Levene test, independent-samples *t* test was used to compare the noncategorical or continuous variables. Comparison between groups for categorical variables was made by the χ^2 test and Fisher exact test was

TABLE 1. Patients demographics and preoperative variables (mean $\pm$ SD)

	Amiodarone group, n (%)	Control group, n (%)	Statistical significance
Patient number	77	80	
Sex			.313*
Male	62 (80.5)	59 (73.7)	
Female	15 (19.5)	21 (26.3)	
Age (years)	59.3 $\pm$ 8.9	61.1 $\pm$ 9.6	.212†
BSA (m ²)	1.83 $\pm$ 0.19	1.81 $\pm$ 0.16	.388†
LVEF (%)	47.0 $\pm$ 9.9	47.9 $\pm$ 10.4	.554†
LVEF <30 (%)	8 (10.4)	7 (8.8)	.727*
AST level (IU/L)	22.7 $\pm$ 9.9	24.6 $\pm$ 13.0	.318†
ALT level (IU/L)	25.9 $\pm$ 14.7	29.9 $\pm$ 18.6	.133†
Preoperative medication			
β -blockers	23 (29.9)	17 (21.3)	.215*
Ca ⁺⁺ -channel blockers	24 (31.2)	24 (30.0)	.874†
Digitalis	5 (6.5)	4 (5.0)	.743‡

BSA, body surface area; LVEF, left ventricular ejection fraction; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

*Chi-square test.

†Independent samples Student *t* test.

‡Fisher's exact test.

used if expected contingency table cell frequencies were less than 5.

Results

Baseline Characteristics

Of the 157 patients enrolled in this study, 77 were randomized to receive amiodarone, whereas 80 were randomized to receive placebo. The mean age of the patients was 59.3 $\pm$ 8.9 years in the amiodarone group and 61.1 $\pm$ 9.6 years in the control group ($P = .212$). The patient demographics and preoperative variables are summarized in Table 1 and were not significantly different. Prevalence of coexisting disorders and coronary risk factors such as hypertension, diabetes mellitus, and hyperlipidemia in both groups of patients was similar (Table 2).

Operative Variables

Operative variables are summarized in Table 3. There were no significant differences in CPB time, crossclamp time, number of grafts, and intraoperative hemodynamic variables.

Postoperative AF

The incidence of new-onset AF occurring during hospitalization was 10.4% (8 patients) in the amiodarone group and 25.0% (20 patients) in the control group ($P = .017$). AF occurred at a mean of 1.9 $\pm$ 0.6 days after surgery in the amiodarone group and 2.5 $\pm$ 1.3 days after surgery in the control group ($P = .239$). The maximum ventricular rate

TABLE 2. Associated coexisting disorders and coronary risk factors

	Amiodarone group, n (%)	Control group, n (%)	Statistical significance
Hypertension	39 (50.6)	52 (65.0)	.069*
Smoking	45 (61.9)	15 (65.2)	.820*
DM	20 (26.0)	25 (31.3)	.465*
Hyperlipidemia	39 (50.6)	45 (56.3)	.482*
History of CHF	14 (18.2)	13 (16.3)	.748*
Prior MI	32 (41.6)	41 (51.3)	.224*
PVD	4 (5.2)	9 (11.3)	.169*
CVD	2 (2.6)	2 (2.5)	1.0†
NYHA class	2.40 $\pm$ 0.65	2.44 $\pm$ 0.55	.717‡
Unstable angina pectoris	12 (15.6)	14 (17.5)	.747*
Coronary artery lesion			
No. of vessels	2.71 $\pm$ 0.51	2.79 $\pm$ 0.47	.350‡
3-vessel disease	57 (74.0)	65 (81.3)	.272*
LMC disease	7 (9.1)	9 (11.3)	.655*

DM, diabetes mellitus; CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; CVD, cerebrovascular disease; NYHA, New York Heart Association; LMC, left main coronary artery.

*Chi-square test.

†Fisher's exact test.

‡Independent samples Student *t* test.

during AF was significantly lower in the amiodarone group than in the control group (105.9 $\pm$ 19.1 vs 126.0 $\pm$ 18.5 beats/min, $P = .016$). There was significant difference between the groups in the duration of AF (12.8 $\pm$ 4.8 hours vs 34.7 $\pm$ 28.7 hours, $P = .003$). In the amiodarone group, AF converted to sinus rhythm spontaneously in 4 patients. In the remaining patients, 2 treated successfully with β -blocker, 1 with digoxin, and the last 1 with electrical cardioversion. In the control group, AF converted to sinus rhythm spontaneously in 1 patient. Among the other 19 patients, 7 patients were managed with amiodarone, 5 with digoxin, 2 with calcium-channel blockers, 1 with β -blocker, and 4 with electrical cardioversion. One patient in the amiodarone group had symptomatic AF within 3 weeks of discharge, whereas 4 patients (5.0%) in the control group had symptomatic AF in the same period ($P = .367$).

Postoperative Complications

Postoperative complications other than rhythm disturbances occurred in 32 patients (16 in the amiodarone group and 16 in the control group, $P = .904$). Postoperative complications and results are shown in Table 4. There was no significant difference in the incidence of low cardiac output, cerebrovascular accident, respiratory complication, or renal dysfunction. More rhythm disturbances such as ventricular fibrillation or ventricular arrhythmia were detected in the control group (18.8% vs 7.8%, $P = .044$).

Amiodarone had to be discontinued in 4 patients (5.2%) because of sinus bradycardia (heart rate less than 60 beats/min) or excessive corrected QT interval prolongation (>440

TABLE 3. Operative variables (mean $\pm$ SD)

	Amiodarone group, n (%)	Control group, n (%)	Statistical significance
CPB (min)	65.1 $\pm$ 18.3	69.7 $\pm$ 21.7	.156*
Crossclamp time (min)	41.0 $\pm$ 13.4	44.0 $\pm$ 14.8	.192*
Graft number	2.99 $\pm$ 0.75	3.02 $\pm$ 0.71	.745*
Use of LITA	75 (97.4)	77 (96.3)	1.0†
Mediastinal drainage (mL)	619 $\pm$ 233	564 $\pm$ 305	.098*
Post-CPB			
Pacing	3 (3.9)	2 (2.5)	.677‡
Electrolyte imbalance	23 (29.9)	25 (31.3)	.851*
Heart rate (bpm)	102.2 $\pm$ 16.9	99.4 $\pm$ 15.1	.281*
CI (L/min.m ²)	2.99 $\pm$ 0.7	2.95 $\pm$ 0.72	.744*
Body temperature (°C)	35.0 $\pm$ 0.8	34.8 $\pm$ 0.9	.129*
Use of IABP	0	1 (1.3)	1.0†
Perioperative MI	2 (2.6)	3 (3.8)	1.0†
Perioperative hypotension	13 (16.9)	11 (13.8)	.586‡

CPB, cardiopulmonary bypass; LITA, left internal thoracic artery; CI, cardiac index; IABP, intraaortic balloon pump; MI, myocardial infarction.

*Independent samples Student *t* test.

†Fisher's exact test.

‡Chi-square test.

ms). In these patients bradycardia resolved after discontinuation of amiodarone, and AF did not occur in any of them. In comparison, 2 patients (2.5%) in control group had significant bradycardia ($P = .437$). Additionally, a higher incidence of postoperative hypotension was observed in patients receiving amiodarone (10.4% vs 5.0%), but this did not reach statistical significance. No patients in the amiodarone group had other significant side effects or adverse reactions included pulmonary toxicity during the study. Nausea was the most frequent side effect in the amiodarone group, which did not require the discontinuation of the amiodarone. β -Blockers were discontinued in 3 (3.9%) of the amiodarone group patients and in 2 (2.5%) of control group patients ($P = .677$). In all patients the reason of discontinuation was low cardiac output.

The average length of in-hospital stay for patients in amiodarone group was 6.8 ± 1.7 days, whereas it was 7.8 ± 2.9 days for patients in control group ($P = .014$). There was one postoperative death (1.3%) in amiodarone group. The cause of death was cerebrovascular accident in a patient who did not have AF. There were 3 postoperative deaths in control group. AF occurred in 2 of them. The causes of deaths in control group patients were ventricular tachyarrhythmia in 2 patients and low cardiac output in 1 patient.

Discussion

Despite the advances in surgical technique and myocardial protection, the incidence of AF has not been decreased after cardiac surgery, especially in elderly patients.^{17,18} Advances in continuous monitoring technology have led to more frequent diagnosis of AF. Our results confirm the high incidence of AF in patients who had CABG. AF has been

TABLE 4. Postoperative complications and results

	Amiodarone group, n (%)	Control group, n (%)	Statistical significance
In-hospital morbidity	16 (20.8)	16 (20.0)	.904*
Acute renal failure	3 (3.9)	1 (1.3)	.361†
Low cardiac output	9 (11.7)	9 (11.3)	.931*
Pulmonary complications	2 (2.6)	2 (2.5)	1.0†
Wound infection	4 (5.2)	3 (3.8)	.716†
Sepsis and MOF	1 (1.3)	1 (1.3)	1.0†
Gastrointestinal bleeding	1 (1.3)	1 (1.3)	1.0†
Stroke	1 (1.3)	0	.490†
Transient neurologic deficit	1 (1.3)	4 (5.0)	.367†
Reexploration for bleeding	1 (1.3)	3 (3.8)	.620†
Ventricular tachyarrhythmia	6 (7.8)	15 (18.8)	.044*
Postoperative continuation of			
β -blockers	31 (40.3)	30 (37.5)	.723*
Ca ⁺⁺ -channel blockers	14 (18.2)	20 (25.0)	.300*
Digitalis	7 (9.1)	12 (15.0)	.256*
Entubation (hours)	13.6 $\pm$ 3.4	15.3 $\pm$ 15.1	.330‡
ICU stay (days)	1.25 $\pm$ 0.65	1.20 $\pm$ 0.77	.682‡
In-hospital stay (days)	6.8 $\pm$ 1.7	7.8 $\pm$ 2.9	.014‡
In-hospital mortality	1 (1.3)	3 (3.8)	.620†

MOF, multiple organ failure; ICU, intensive care unit.

*Chi-square test.

†Fisher's exact test.

‡Independent sample Student *t* test.

thought of as transient and benign, but it can lead to hemodynamic instability or peripheral embolization. Postoperative AF is a widely known risk factor for postoperative stroke.¹⁹

It appears that there are multiple underlying pathophysiologic mechanisms responsible for the high incidence of postoperative AF. Preoperative factors such as an increased age, hypertension, chronic obstructive pulmonary disease, greater number of grafts, poor left ventricular function, preoperative β -blocker withdrawal, and history of AF were identified as predictors of AF.^{5,20,21} Previous studies have indicated that AF after CABG is associated with sympathetic activity.²² Pericardial inflammation or effusion has been detected after cardiac surgery before AF develops.²³ The incidence of postoperative atrial arrhythmia was found to be higher in patients with a history of paroxysmal AF.²⁴ A combination of the factors outlined above might be important in the occurrence of AF.

Although long-term sequelae of postoperative AF are unusual, the frequent consequence is prolonged hospitalization and increased medical costs. Therefore, any intervention that would reduce the incidence of postoperative AF would result in an economic benefit. A variety of pharmacologic strategies are available to prevent AF after cardiac surgery. However, controversies still continue about the risks and benefits of these strategies.

The principles of treatment for postoperative AF are the control of the ventricular rate, anticoagulation, and conver-

sion to sinus rhythm. Amiodarone increases the refractory period of atrial and ventricular muscle as well as the atrio-ventricular node. It has mild β -blocker and calcium channel blocker activity in addition to its class III antiarrhythmic activity. It has been effective in acute as well as chronic AF.²⁵ As a result of these properties, amiodarone has been studied in the prevention of AF after cardiac operations.²⁶⁻³⁰ Use of oral amiodarone preoperatively and/or postoperatively was investigated in some of these studies.^{17,25,29,31} Others have used postoperative intravenous amiodarone.^{10,32,33} In most of these studies, amiodarone administration ranged from 2 to 15 days. After short-term low-dose intravenous administration, AF tended to occur after termination of the infusion.^{21,33} There is no consensus about the optimal dose of amiodarone. In most of the studies, intravenous amiodarone doses ranged from 10 to 20 mg/kg per day over 2 to 8 days.^{10,16,21,26,28,32,33} Oral amiodarone doses ranged from 2.8 to 7.0 g over 7 to 20 days.^{17,25,27,29-31} A limited number of trials used a combination of intravenous and oral amiodarone.^{16,28} The variability in dosing strategy and the inconsistency in results have led us to adopt a new regimen. We used a combination of postoperative intravenous amiodarone after oral administration for two reasons: first, to take the advantage of accelerated loading time with the intravenous amiodarone, and second, to obtain the incremental benefits of the oral amiodarone over the short-term intravenous administration. To prevent the possible adverse effects such as hypotension or bradycardia, we have used relatively short-term low-dose (10 mg/kg per day for 48 hours) intravenous administration followed by oral tapered doses at a total of 9.0 g over 30 days. We have used a dosing strategy that gives higher total dose by increasing the length of oral administration instead of giving it at a relatively high dose in a short hospitalization period.

Our study showed that in CABG patients amiodarone in the immediate postoperative period effectively reduced the incidence of postoperative AF by more than 50%. Among the patients who did have AF, amiodarone reduced the ventricular rate significantly. The duration of AF was also longer in control group patients. Postoperative AF is often a transient phenomenon. AF persisted in only 2 patients despite repetitive attempts at restoring sinus rhythm even with electrical cardioversion.

We also investigated the effect of amiodarone prophylaxis on the length of ICU and in-hospital stay. The length of hospitalization was significantly reduced from 7.8 to 6.8 days. This can be explained by increased duration of AF in control group patients. We found that amiodarone prophylaxis is cost-effective even it only reduces the length of stay by 1 day. In our protocol, total cost of amiodarone is only one third that of the cost of 1-day hospitalization.

In the present study, development of AF did not produce significant increases in the length of ICU stay. AF occurred

mostly after postoperative day 2, when the patients have already left the ICU. In our practice, new-onset AF without hemodynamic compromise is not an indication for readmission to ICU. In addition to the lower incidence of postoperative AF, the amiodarone group patients had significantly less postoperative ventricular arrhythmias than the control group. Fatal ventricular tachyarrhythmia was not seen in the amiodarone group, whereas 2 deaths in the control group related to ventricular tachyarrhythmia. These results may be due to its effectiveness against a broad range of arrhythmias. Accordingly, large randomized trials indicate that amiodarone is a potent suppressor of ventricular arrhythmia and reduces arrhythmic death after myocardial infarction.^{34,35} Patients whose β -blocker therapy is discontinued postoperatively have a higher incidence of postoperative atrial tachyarrhythmias.³⁶ In the present study, patients who had been receiving β -blockers before surgery continued to receive them, if possible, postoperatively. One of the drawbacks of our study is that the number of study patients (approximately 26.0%) who received preoperative β -blocking drugs is limited. In our hospital, preoperative management was directed by the patients' cardiologist rather than by a standardized protocol. We think that possible negative impact of this nonstandardized treatment have been compensated by the randomization of patients. There is no difference in the percentage of patients who were receiving β -blockers between the groups in either the preoperative or the postoperative period.

Our homogenous patient population demonstrates the efficacy and safety of a combination of intravenous and oral amiodarone after CABG. The combined intravenous and oral amiodarone regimen used in this study appears to be well tolerated. Amiodarone was discontinued approximately 5% of our patients because of sinus bradycardia and excessive QT prolongation. Additionally, a higher incidence of postoperative hypotension that was observed in patients receiving amiodarone (10.4% vs 5.0%) did not reach to statistical significance. No proarrhythmic effect was observed among the patients who received amiodarone. The direct negative inotropic effect of the drug is minimal and transient, may be partially caused by its antisymphathetic effect, and usually does not lead to a decreased cardiac output.³⁷ Amiodarone is well tolerated in patients with poor left ventricular function and can be used for patients who are not candidates for β -blockade. The group of patients with left ventricular ejection fraction less than 30% represents a small percentage (10%) in our study population. Our primary aim was not to investigate the effect of amiodarone in patients with poor left ventricular function. Our results may not be applicable to the cohort of patients with a lower ejection fraction.

In conclusion, we showed that postoperative intravenous amiodarone followed by oral administration significantly

reduced the incidence of new-onset postoperative AF without an increase in adverse effects. It also reduced the ventricular rate and the duration of AF, as well as the length of hospital stay.

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