RESEARCH

Cardiovascular Therapeutics

Ability of Amiodarone and Propranolol Alone or in Combination to Prevent Post-coronary Bypass Atrial Fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia in coronary artery bypass grafting (CABG) patients. The purpose of this study was to determine the best prophylaxis for AF prior to CABG. In this double-blind randomized study, 240 consecutive patients underwent elective CABG. They were then divided randomly into three groups to receive propranolol (n = 80), amiodarone (n = 80), or both drugs (n = 80). All groups received their medications from preoperative day 7 to post-CABG day 5. The patients were well matched for age, sex, risk factors, comorbidities, ejection fraction, and cardioplegic technique. Post-CABG AF developed in 22 patients (9.2%) of whom 13 (16.3%) had received propranolol, 5 (6.3%) had received amiodarone, and 4 (5%) had received both drugs. The difference between the propranolol group and the other two groups was statistically significant ($P = 0.02$), but that between the amiodarone and amiodarone + propranolol group was not significant. Age was a significant predictor of post-CABG AF ($P = 0.034$). Other factors such as diabetes, sex, hyperlipidemia, smoking, hypertension, family history, cerebrovascular accidents, left atrial size, and ejection fraction were not significant predictors of post-CABG AF. Preoperative amiodarone or amiodarone with propranolol were more effective than propranolol in reducing the frequency of AF. There was a strong relationship between age and the development of AF. (Clinicaltrial.gov registration NCT00654290.)

Introduction

Atrial fibrillation (AF) is a common complication of postoperative cardiac surgery. New-onset AF, atrial flutter and other atrial tachyarrhythmias occur in 15–50% of patients after cardiac surgery [1–10]. The incidence of AF and atrial flutter were reported to be as high as 40–60% after coronary artery bypass grafting (CABG) or cardiac valve surgery [11,2]. These arrhythmias most often developed between the second and fifth postoperation days [13], with a peak incidence in the first 2–3 days [14]. Although many surgeons hold the view that post-CABG AF has a benign course, several reports have shown a definite increase in the incidence of stroke, heart failure and poor hemodynamic performance due to impaired left ventricular function, primarily caused by shortened filling time [14–20]. In addition, several reports have indicated increased morbidity, length of hospitalization, and total cost [21–31]. Postoperative AF has also been shown to independently predict postoperative delirium and neurocognitive decline [32,33]. Although most reports have documented a significant effect of beta-blockers in preventing the occurrence of AF, there is no general agreement on the issue [33–36]. However, joint ACC/AHA/ESC guidelines published in 2006 mentioned beta-blockers as a class IA indication for the prevention of perioperative AF in patients undergoing cardiac surgery.

Many clinical trials have evaluated the effectiveness of a variety of pharmacological and nonpharmacological interventions to decrease the incidence of AF [34], but the results of trials that compared the ability of amiodarone versus propranolol to prevent perioperative AF are

unconvincing [35]. Higher doses of amiodarone were shown to be effective in AF prevention in CABG and valvular surgeries [39]. Various *meta*-analyses have been carried out to determine the efficiency of beta-blockers and amiodarone in preventing the occurrence of AF [40]. Although their efficacy was different, the difference was not significant.

This article reports one of a few studies that have compared the prophylactic effect of amiodarone and propranolol alone and in combination for post-CABG AF.

Patients and Methods

The participants in this double-blind randomized prospective study were 400 patients who underwent elective CABG in the Shiraz University of Medical Sciences-affiliated hospitals, during a 6-month period from October 2007 to March 2008. Of these participants, 240 consecutive patients who were referred for CABG and who met the inclusion criteria were randomly allocated to one of three groups in a blinded fashion (Fig. 1). This study was approved by our local ethical committee (February 2007), and all patients completed a written consent form before enrollment.

All risk factors for coronary diseases were recorded. Hypertension was defined as a history of blood pressure (BP) more than 140/90, and diabetes mellitus was defined as fasting blood sugar >126 mg/dL or nonfasting concentration >200 mg/dL. Smoking status was recorded as current smoker of even one cigarette per day, and the family history of coronary disease was recorded if there was a history of coronary disease presentation before the age of 50 years. All echocardiographic and laboratory studies were performed by personnel who were blinded to the enrollment protocol.

We enrolled those patients who were candidates for elective CABG and who were referred for CABG 7 days prior to the operation, and excluded anyone with emergency surgery who did not meet these criteria. We excluded patients with chronic obstructive lung airway disease, renal failure, asthma, preoperative ejection fraction less than 35%, preoperative AF or other contraindications for beta-blocker therapy, and those who refused to enter the study.

Propranolol replaced all other beta-blockers in participants who were receiving beta-blockers before surgery, and in the amiodarone group, amiodarone replaced beta-blockers. Patients who used any other antiarrhythmic medication were also excluded. The amiodarone group consisted of 80 patients receiving amiodarone 200 mg p.o. twice a day from 7 days before surgery to 5 days post-CABG. The total preoperative dose was 1.4 g, which is far above the loading dose for amiodarone (800–1000 mg), and the total cumulative (pre- and postoperative) dose was 2.4 g. The propranolol group consisted of 80 patients receiving propranolol 20 mg p.o. twice a day from 7 days

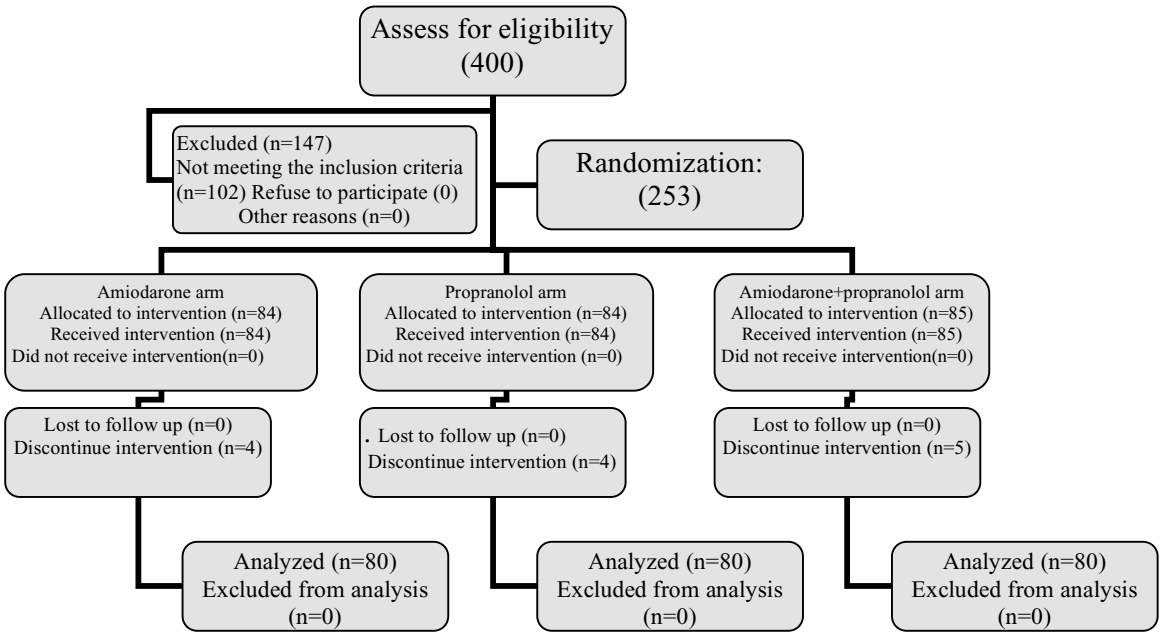

Figure 1 Patient enrollment of 240 patients in Iran who underwent coronary artery bypass graft and received prophylaxis for atrial fibrillation with propanolol, amidarone, or both drugs.

before surgery to 5 days post-CABG, for a total dose of 280 mg before the operation and a cumulative dose of 480 mg. The amiodarone + propranolol group consisted of 80 patients receiving amiodarone 200 mg p.o. twice a day and propranolol 20 mg p.o. twice a day from 7 days before surgery to 5 days post-CABG. Each patient in the first two groups received a placebo which was like propranolol in the amiodarone group and like amiodarone in the propranolol group. The patients who did not receive the medications, that is those who died, developed low BP or heart rate, or complications of any other cause were excluded from the study and replaced with new patients who were randomly selected based on the same protocol as for the allocation of new patients.

All surgical procedures were performed with cold blood cardioplegia intermittently after the body was cooled to 32°C. Intraoperative hemodynamic monitoring was routinely done in all patients for heart rate, systemic BP, pulmonary artery pressure, and cardiac output. All patients had continuous ECG monitoring for 5 days post-CABG (monitoring with memory and supervision by ICU nurses), and ECG recording was performed if any irregularity or supraventricular or ventricular tachyarrhythmia was detected. Any drug reaction and adverse outcome was recorded during the ICU stay. All nurses and cardiologists were blind to therapeutic strategies in different groups, and were specially trained in AF detection and the appropriate response. Significant AF was defined as any AF which last at least 30 seconds; all paroxysmal or continuous AF rhythms were included. Based on the new American Heart Association criteria, the use of preoperative prophylaxis for AF is mandatory (class I), so we did not use a true placebo group; rather, each patient was assigned to at least one prophylaxis protocol.

The data were reported as the mean ± standard deviation (SD). We used *t*-tests to analyze the variance and significance of the differences between mean values, and chi-squared tests to determine the significance of differences in incidence. All statistical tests were done at core lab, by personnel who were unaware of the study design or results. *P*-values <0.05 were considered statistically significant.

Results

A total of 240 patients were enrolled and assigned randomly as shown in Figure 1. There were no significant differences between patients in all three groups regarding their clinical and surgical data (Table 1). Patients were well matched for medications and generally received oral nitroglycerine, angiotensin-converting enzyme inhibitors and statin therapies.

Post-CABG AF developed in 22 patients (9.2%) of whom 13 (16.3%) were in the propranolol group, 5 (6.3%) in the amiodarone group, and 4 (5%) in the amiodarone + propranolol group. The difference in AF between the propranolol and the amiodarone group was statistically significant, with a *P*-value of 0.02 (likelihood ratio [LR]: 8.91), but was not significant between the propranolol and amiodarone + propranolol group ($P = 0.6$) or between the amiodarone and propranolol +

Table 1 Clinical and surgical data for 240 patients in Iran who underwent coronary artery bypass graft and received prophylaxis for atrial fibrillation with propanolol, amidarone, or both drugs

Variable	A group (n = 80)	P group (n = 80)	AP group (n = 80)	*P*-value
Age (years)	59.9 ± 10.2	59.6 ± 10.7	59.7 ± 10.5	0.6 (LR: 0.273)
Sex (M:F)	42:38	44:36	52:28	0.281 (LR: 2.543)
Ejection fraction (EF)	50.3 ± 9.1	51.8 ± 9.6	51.5 ± 8.1	0.670 (confidence interval: 48.5–52.62)
Left atrial size	35.4 ± 5.7	35.5 ± 5.6	35.3 ± 5.2	0.627 (confidence interval: 34.1–36.7)
Smoker (P:N)[a]	27:53	22:58	32:46	0.605 (LR: 1.008)
Diabetes mellitus (P:N)[a]	18:62	17:63	23:57	0.617 (LR: 0.954)
Hypertension (P:N)[a]	40:40	42:38	43:37	0.890 (LR: 0.234)
Family history (P:N)[a]	15:65	17:63	8:72	0.089 (LR: 5.2)
Hyperlipidemia (P:N)[a]	34:46	36:44	38:42	0.889 (LR: 0.235)
History of cerebrovascular accident (P:N)[a]	1:79	1:79	1:79	0.9 (LR: 1.001)
Extent of coronary artery disease	Single vessel: 8	5	0	0.604 (LR: 1.4)
	Two vessel: 14	14	15	
	Three vessel or left main: 58	61	65	

[a]P: positive, N: negative.

A: amiodarone, P: propranolol, AP: amiodarone and propranolol, LR: likelihood ratio.

amiodarone group ($P = 0.76$). The patients who developed AF were treated with a loading dose of intravenous amiodarone; acute heart rate was controlled with intravenous verapamil if needed. Sinus rhythm recovered spontaneously without cardioversion. The duration of these AF episodes was less than 24 h in four patients (80%) in the amiodarone group, in nine patients (69.2%) in the propranolol group, and in four patients (100%) in the amiodarone + propranolol group.

We also searched for correlations between the incidence of AF and patients' age and sex, presence of diabetes mellitus (DM), hyperlipidemia, hypertension, cerebrovascular accidents (CVA), cigarette smoking, coronary artery disease, left atrial size, ejection fraction, and family history. Of these factors, age was the only significant predictor of post-CABG AF ($P = 0.034$, LR: 9.1). Age distribution in the three groups did not differ significantly (Table 1). Of the patients who developed post-CABG AF, 80% in the amiodarone, 53.8% in the propranolol, and 75% in the amiodarone + propranolol group were older than 60 years. Of the 22 patients who developed AF in all three groups, 15 (68.2%) were men and 7 (31.8%) were women ($P = 0.28$). Nine patients (40.9%) had hyperlipidemia and 13 (59.1%) did not ($P = 0.68$); 4 patients (18.2%) were smokers and 18 (81.8%) were nonsmokers ($P = 0.10$); 15 patients (68.2%) had hypertension and 7 (31.8%) had no hypertension ($P = 0.11$); 4 patients (18.4%) had a family history of myocardial infarction or ischemic heart disease and 18 (81.8%) had no such history ($P = 0.84$); 7 patients (31.8%) had DM and 15 did not ($P = 0.37$). Left atrial size ($P = 0.10$) and ejection fraction ($P = 0.29$) were also not significant predictors of post-CABG AF. The incidence of cerebrovascular accidents was not significantly higher in patients with AF ($P = 0.58$).

In the amiodarone group, one patient died on the second post-CABG day and three patients did not receive medication due to low BP (persistent systolic BP <90 mmHg for more than 12 h) and heart rate (persistently <50/min). In the propranolol group 4, patients did not receive medication due to low BP and heart rate. In the amiodarone + propranolol group, one patient died on the third post-CABG day and four patients did not receive medication due to low BP or low heart rate. The intervention was discontinued in these patients and all of them were replaced with new patients chosen randomly from patients scheduled for CABG. However, for the intention-to-treat sample excluding the substituted patients, there was still a significant difference ($P = 0.01$, LR: 11.3) between the rate of AF in the three groups: 4 AF in the amiodarone (5%), 13 AF in the propranolol (16.2%), and 4 AF in the amiodarone + propranolol group (5%).

Thirty-day mortality was the same in all three groups: one patient (2.5%) in each group. The deaths were due to pump failure, resistant ventricular arrhythmia, and respiratory arrest. Mortality was not related to arrhythmia or bradycardia.

Discussion

AF in the postoperative period develops most commonly on the second and third days [14]. There is significant variation in the incidence of postoperative AF [23,24,34,40]. For example a *meta*-analysis [40] reported incidences of AF as high as 40–60%; in another study [39], the incidence of postoperative AF was reported to be 25–40%; and still another study [23] found the incidence of postoperative AF to be 26% (ranging from 17% to 35%). The reason for the relatively low frequency of AF in our study (9.2%) may be because we excluded any patients with significant comorbidities and low EF. A strong independent predictor of postoperative AF is the patient's age. The older myocardium probably makes the atrial muscle more vulnerable to multiple reentrant circuits and variable refractory periods [40]. Postoperative AF also increases the risk of various hemodynamic and neurological problems. The slow recovery and the long hospital stay can increase the incidence of ventricular tachycardia and fibrillations as well as increasing the need for permanent pacemaker implantation [23,37]. The prevention of hemodynamic and neurological problems is essential, and various medications such as beta-blockers, sotalol, amiodarone, magnesium, and digoxin have been tested to this end [38].

However, despite the large number of studies, no prophylactic or therapeutic interventions have yet been established to be universally and optimally effective. Amiodarone is a unique antiarrhythmic agent that inhibits multiple ion channels (i.e., potassium and calcium) and adrenergic receptors (α and β). The use of beta-blockers has been recommended as a the first line medication for the prevention of postoperative AF, although no marked differences between beta-blockers and amiodarone were found in reducing the risk of postoperative AF (odds ratio for beta-blockers 0.39 [95% CI, 0.28–0.52]; odds ratio for amiodarone, 0.48 [95% CI, 0.37–0.61]) [38]. Our results showed a clearly significant effect, with a decrease in the incidence of post-CABG AF in all the three groups compared to the overall rate of post-CABG AF with no prophylaxis (40%) based on prior studies [40].

We found a significant difference between the amiodarone and amiodarone + propranolol groups in comparison to the propranolol group regarding the incidence

of post-CABG AF: this complication was less frequent in the first two groups ($P = 0.02$). The difference in the development of post-CABG AF between the amiodarone and amiodarone + propranolol groups was not statistically significant. The results also confirmed that older age was a strong risk factor for post-CABG AF.

The number of patients who died or for whom medication was withdrawn post-CABG was low in the present study. The low figures support the safety of these medications, particularly amiodarone, for the prevention of post-CABG AF without prominent complications. It should nonetheless be recalled that other studies reported a 15% increase in the incidence of stroke in AF patients, and an increase in the length of hospitalization, rate of heart failure, and frequency of various hemodynamic and neurological problems, and hence in morbidity and mortality [14,21,25].

In our study the incidence of post-CABG AF in the amiodarone group was 2.5-fold (10%) lower than in the propranolol group. If we consider the average incidence of post-CABG AF to be 40% based on prior studies [11,12], the absolute risk reduction (ARR) for amiodarone would be 33.7% and the ARR for propranolol would be 23.7%. The number needed to treat (NNT) for amiodarone versus propranolol would be 2.96 versus 4.2 for 12 days—a considerable advantage for amiodarone.

We believe, therefore, that starting preoperative amiodarone or amiodarone + propranolol from day 7 pre-CABG is more effective than using propranolol to prevent AF. Prophylactic amiodarone alone was the most effective way to prevent the occurrence of post-CABG AF in our patients; moreover, it decreased complications from this common arrhythmia. Regarding the choice between amiodarone and amiodarone + propranolol, we suggest that amiodarone alone is preferable because the incidence of post-CABG AF did not differ between these two groups. In addition, a single medication was favored by the patients, and may result in fewer complications.

Conclusion

Age was a strong predictor of post-CABG AF. Amiodarone (200 mg orally twice per day from 7 days pre-CABG) was better than propranolol (20 mg orally twice per day from 7 days pre-CABG) in preventing perioperative AF.

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Conflict of Interest

The authors declare no conflict of interest.

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