AMIODARONE VERSUS PROPANOLOL ATRIAL FIBRILLATION PREVENTION AFTER CABG IN PATIENTS WITH LOW EJECTION FRACTION

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Abstract

BACKGROUND: Atrial fibrillation (AF) occurs often in patients after coronary artery bypass grafting (CABG) and can result in increased morbidity and mortality. The purpose of this study is to compare the prophylactic effect of Amiodarone versus Propranolol in patients with various levels of ejection fraction.

METHODS: In a randomized double-blinded clinical trial, 110 patients received either Amiodarone (*n*=65) or propanolol (*n*=65). Adult patients of either sex and age of 40-75 years were considered for participation when listed for nonemergent CABG surgery and bypass without other concomitant procedures. Amiodarone was given as 150 mg single dose 30 min after procedure through 48 hours. In addition, Amiodarone was also administered intravenously during surgery in a 300-mg bolus for 1 h and as a total maintenance dose of 20 mg/kg weight over 24 h on the first day following surgery. Propanolol was given as 10 mg oral single dose immediately after surgery and continued for long term operation.

RESULTS: The primary endpoint was the occurrence of AF after CABG. The secondary endpoint was the hospitalization length of stay after CABG. The baseline characteristics were similar in both treatment groups. The incidence of post-operative AF was significantly higher in the Propranolol group compared with the Amiodarone group (4 vs 12.2 % of patients with low EF, *P*<0.0001). The durations of postoperative intensive care unit stays were the same in the Amiodarone and Propranolol groups (2±0.7 vs. 3.5±0. 5 days, *P*<0.001).

CONCLUSION: This study demonstrates that postoperative course of Amiodarone administration is an effective, possibly safe, well-tolerated, and widely applicable therapy for the prevention of postoperative atrial tachyarrhythmia after cardiac surgery. This benefit was associated with a reduction in the probability of preoperative sustained ventricular tachyarrhythmia and a trend toward a reduction in postoperative hospital stay.

Keywords: Atrial Fibrillation, Coronary Artery Bypass Grafting, Amiodarone, Propranolol.

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Introduction

Atrial fibrillation (AF) has been shown to increase morbidity and mortality after coronary artery bypass grafting (CABG). It also results in prolonged stays in the intensive care unit (ICU) and in the hospital.[1] Atrial tachyarrhythmia, frequently known as AF or atrial flutter, is facilitated by atrial trauma, atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances, and electrophysiological changes that convoy sympathetic nervous system discharge.[2] As these factors are typical immediately after cardiac surgery, atrial tachyarrhythmia is the most common postoperative complication occurrence [2-6] of sustained atrial tachyarrhythmia after coronary artery bypass graft (CABG) surgery is approximately 30%.[7] The consequences of CABG atrial tachyarrhythmia include discomfort or anxiety, hemodynamic deterioration, stroke, exposure to the risks of tachyarrhythmia treatments, prolongation of hospital stay, and increased health care costs. AF has recently been reported to increase hospital stay after cardiac surgery by 1.4 days at an additional cost of $6356 per patient in the USA.[8-10] Accordingly, considerable at-

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tempt has been invested in finding a practical, safe, and widely appropriate prophylactic treatment for atrial tachyarrhythmia occurring after cardiac surgery.[11] The most extensively studied prophylactic therapy is blockade.[1] However, the applicability of Propranolol therapy is limited by the frequency of contraindications to its use[11] and its modest efficacy in contemporary cardiac surgery populations.[12] Furthermore, clinical trials have not demonstrated that prevention of postoperative atrial tachyarrhythmia with Propranolol therapy reduces hospital stay or resource use.[12-13] The purpose of this study is to compare the prophylactic effect of Amiodarone versus Propranolol in patients with various levels of ejection fraction.

Materials and Methods

Study Population

Adult patients of either sex and age of 40-75 years were considered for participation when listed for nonemergent CABG surgery and bypass without other concomitant procedures. All patients had a baseline 24-hour ambulatory electrocardiogram. Exclusion criteria included myocardial infarction within 2 weeks, any rhythm other than sinus, congestive heart failure despite treatment, persistent hypotension (systolic blood pressure <80 mm Hg), requirement for antiarrhythmic drug therapy, history of sustained atrial tachyarrhythmia, treatment with Amiodarone within 3 months, sinus bradycardia while awake (<50/min-1), PR interval greater than 220 milliseconds, second- or third-degree AV block, corrected QT interval of 480 milliseconds or higher, peripheral neuropathy, aspartate aminotransferase twice the upper limit of normal, interstitial pulmonary disease, clinical hypothyroidism or hyperthyroidism, bleeding diathesis, and women of child-bearing potential. Eligible patients participated after a full-disclosure, written, informed consent process. The study was approved by the research Council of the Isfahan University of Medical Sciences.

Study Protocol

Participants, who have been under surgical procedures (CABG surgery alone vs valve replacement/repair surgery with or without CABG surgery), were randomized to receive either Amiodarone or proponalol in a double-blind trial. The random allocation sequences were computer-generated and were implemented by a hospital pharmacist who was not otherwise involved in the trial. After randomization into main groups, Amiodarone Vs. Propranolol, patients were divided into two subgroups according to their EF. Treatment with Amiodarone or Proponalol was administered 30 min after surgery (primary boluse was 150 mg/min until 48 after operation and the oral consumption of 400mg/12 hours was continued for 6 days). The other group was treated by Propranolol 10 mg/8 hour for six days. Electrocardiographic monitoring began intraoperatively and was continued for the subsequent 6 days. Trough serum Amiodarone and diethyl Amiodarone levels were determined preoperatively on the day of surgery but were not provided to study personnel until after the study closure. Patients receiving digoxin had its dosage halved.

Outcome Events

The primary outcome was an atrial tachyarrhythmia during the first 6 days after surgery that lasted for 5 minutes or longer and prompted treatment by the attending physician. Prespecified secondary outcomes included the primary outcome in each subgroup defined by the stratified randomization scheme, the ventricular response rate of atrial tachyarrhythmia that did happen, the postoperative day of an atrial tachyarrhythmia occurrence, the number of atrial tachyarrhythmia episodes, the duration of the longest episode, the tachyarrhythmia "burden" (number of hours of atrial tachyarrhythmia during the first 6 postoperative days), and length of postoperative hospital stay. Adverse events potentially attributable to Amiodarone were also prospectively recorded. Since the optimal treatment for atrial tachyarrhythmia after cardiac surgery is unknown, it was not prescribed by the protocol.

Sample Size Determination and Data Analyses

Analyses were based on the intention-to-treat principle in all patients as randomized. Patient characteristics were summarized by standard descriptive statistics and were compared between groups using paired or unpaired t tests or the Fisher exact test as appropriate. ANOVA test was used between groups. Adjustment for differences between groups with respect to baseline characteristics was accom-

plished using the Cox proportional hazards model. Analyses were performed using SPSS (Version 12).

Results

Between December 1st, 1999, and June 1st, 2002, a total number of 130 patients were randomized in this trial.

Of the whole 130 patients who have had surgery, 65 were assigned to the Amiodarone group and 65 were assigned to the B propranolol group. Patients in the 2 groups were matched. The mean (SD) age of the patients was 55 (2.2) years; 112 (85%) were male. The mean age, sex, type of heart disease, mean systolic and diastolic blood pressure values were similar in patients who agreed to participate compared and those who declined to participate. No patients were lost to follow-up. The preoperative characteristics of the patients are shown in the table 1.

Preoprative drugs and duration: Mean ± SD in both groups should be equivalent. On the day of surgery and immediately after the operation, patients received 150 mg of intravenous Amiodarone during 30 minutes. The treatment continued with 150 mg/6 hour of Amiodarone for 48 hours and was followed by oral administration of Amiodarone 400 mg/12 hour until the patients were discharged (ordinarily after 6 days).The second group received Propranolol immediately after surgery as 10 mg 10 mg oral single dose immediately after surgery and continued for long term operation.

Table 1: Baseline Characteristics of patients and operative procedure.

	Amiodarone	**β blocker**	**P value**
Age, mean (SD) y			>0.05
female	(14) 21%	(11) 18%	>0.05
Left ventricular ejection frac-	(13)20%	(11)18%	>0.05
tion			
History			
Congestive heart disease	(13)20%	(11)18%	>0.05
myocardial infarction	(13)20%	(11)18%	>0.05
Hypertension			
Diabetes mellitus	(9)15%	(11)18%	>0.05
Chronic obstructive pulmonary	(1) 1.5%	(2) 3%	>0.05
disease	(0)0%	(1)1.5%	>0.05
Cerbervascular accident/TIA			
PREOPRATIVE USE			
Beta blocker	(15)23%	(35)53%	>0.05
Ace inhibitors	(10)15%	(12)18%	<0.05
Postoperative use of β blocker	(0)0%	(65) 100%	<0.05
Operative procedure			
CABG surgery			
1	3	4	>0.05
2	15	10	>0.05
3	35	40	>0.05
4>	2	11	>0.05
Type /No. Multiple			
Type of surgery or CABG	64	64	>0.05
Valve replacement	1	1	>0.05
Time, mean Process			
Pump			
Cross-clamp	92 ±10 min	98±8 min	<0.05

Table 2: Preoperative data in two groups of patients.

	Amiodarone (n=65)	Propanolol (n=65)	P Value
Preoperative AF	3	5	>0.05
Age (40-70)	86.15%	89%	>0.05
Age >70	13.84%	11%	>0.05
Sex (female)	21%	18%	>0.05
Left ventricular EF<35%	20%(18)	22%(21)	>0.05
Diabetics	(15)	(18)	>0.05
Preoperative Use of β-blocker	20	(15)	>0.05
Preoperative COPD	1	2	>0.05
Preoperative CRF	1	2	>0.05
Perfusion time (min)	115±18	121±12	>0.05

Occurrence of postoperative atrial fibrillation in Amiodarone group (6.15%) was less than proponalol group (12.3%;P<.001;table 2). Recurrent AF after treatment was 3.2% mean period to control AF was 72[10] min and in the amiodaron was 55[15] min. One patient in each group had already had an atrial tachyarrhythmia. When atrial tachyarrhythmia happened, the ventricular response rate was slower in Amiodarone receiving patients than in propanolol receiving patients, however there were no differences in the postoperative day of atrial tachyarrhythmia onset, the duration of the longest atrial tachyarrhythmia episode, the mean number of atrial tachyarrhythmia episodes per patient, or the burden of atrial tachyarrhythmia per patient (Table 1).

The durations of postoperative intensive care unit stays were the same in the Amiodarone and Propranolol groups. Although the total mean (SD) length of postsurgical hospital stay was shorter for Amiodarone receiving patients (8.2 [7.4] days) than for propranolol receiving patients (7days), this difference did not reach statistical significance (P=0.11) or this difference is statistical significant (P<0.011).

Discussion

The present study showed that postoperative treatment with oral Amiodarone prevented paroxysmal atrial fibrillation after CABG. Our results showed that Amiodarone is more effective in elderly patients with very low AF. AF is the most common complication occurring after cardiac surgery [1-5,10] and despite advances in CPB, cardioplegic arrest, and surgical techniques, its incidence has paradoxically increased in recent years [2] as the result of surgical patients being older and sicker and advances in continuous ECG monitoring technology.[3] AF is frequently not well tolerated and may cause some symptoms including temporary hemodynamic instability, thromboembolic events, and shortness of breath or chest discomfort, and therefore has been shown to increase the hospital costs and to lengthen the hospital stay.[3, 11]

Table 3: Unsaturated AF in low EF Patients.

Groupe	AF	Without AF	P Value
Amiodarone	12.2(5)	57(67.7)	P<0.05*
Propanolol	4(6.15)	61(93.55)	P<0.05*

Table 4: Other postoperative outcome in two groups.

	Amiodarone With AF	Amiodarone Without AF	Propanolol With AF	Propanolol Withouth AF	P Value
ICU stay	1.5	2	1.8	3.5	0.065*
High dose Inotropic (h)	6	10.1	1	15	P<0.05*
Ventricular Arrhythmia	1	2	1	5	P<0.05*

Many preoperative and postoperative factors, such as higher age [3], hypertension [3], withdrawal of β-blocker drug [12], right coronary artery stenosis [1], respiratory complications [4], and bleeding [13], have been recommended to be in charge of increased incidence of postoperative AF after conventional CABG. Strategies, directed toward reduction of postoperative AF and focusing on several prophylactic drugs, such as β-adrenoceptor antagonists [11-12], calcium antagonists [15], Amiodarone [16], and propafenone [16], showed conflicting results. In the same way, Amiodarone has brilliant effect in prevention of all types of aritimia especially ventricular arrhythmia.[17] In contrast in some cases Propranolol may be demonstrate respiratory effects.[17] However, little is known about intraoperative mechanisms through which the incidence of postoperative AF could be reduced.[17] The results of other studies showed that β-blocker drugs, such as Propranolol, are most effective in patient with normal EF.[18] However, in patients with low and very low EF, β-blocker drugs are not appropriate alternatives and based on our results Amiodarone is more effective in these patients. It seems that higher incidence of AF is related to very low EF, entropic support and also longer mechanical ventilation. In addition, Amiodarone has several benefits that decreased ICU stay. Although several investigators have reported that postoperative β blockers prevent postoperative paroxysmal atrial fibrillation.[18] Because in this study we had two subgroups according to the amount or Level Of EF our results showed that the incidence of paroxysmal atrial fibrillation significantly in the same condition by EF had equal effects, but lower in the Amiodarone group than in the Propranolol group. Other studies revealed that Propranolol decrease cardiac output and increase some risk factors as negative inotropic in elderly patients. On the other hand our results showed that β blockers could raise the AF rate in the patient with low EF.

Postoperative treatment with Amiodarone can prevent paroxysmal trial fibrillation after CABG in patients with low and very low EF. This study demonstrates that postoperative course of oral Amiodarone is an effective, possibly safe, well-tolerated, and widely applicable therapy for the prevention of postoperative atrial tachyarrhythmia after cardiac surgery. This benefit was associated with a reduction in the probability of preoperative sustained ventricular tachyarrhythmia and a trend toward a reduction in postoperative hospital stay.

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