AMIODARONE PROPHYLAXIS FOR ATRIAL FIBRILLATION AFTER CORONARY ARTERY BYPASS GRAFTING

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ABSTRACT

Objective: This study was planned to evaluate the preventive role of Amiodarone against atrial fibrillation after coronary artery bypass grafting.

Design: A comparative and interventional study.

Place and Duration of Study: The study was done at Armed Institute of Cardiology/National Institute of Heart Diseases AFIC/NIHD Rawalpindi.

Patients and Methods: In this study, 100 patients admitted three days before coronary artery bypass grafting were divided into Control and Amiodarone groups of 50 patients each. Patients in Control group did not receive any prophylaxis against atrial fibrillation before and after the coronary artery bypass grafting. While the patients in Amiodarone group received 200 mg oral Amiodarone thrice daily for three days, then 200 mg once daily on operative day and continued so until discharge.

Results: Postoperative atrial fibrillation occurred in 8 of 50 patients in the Control group (16%) and 2 of 50 patients in the Amiodarone group (4%) (p=0.045). Maximum ventricular rate during atrial fibrillation episode in Control group was 122 ± 5.83 beats per minute and 108 ± 2.89 beats per minute in amiodarone group.

Conclusion: Preoperative amiodarone was found to be significantly useful prophylactic agent to prevent atrial fibrillation after coronary artery bypass grafting and this drug can be used safely.

Keywords: Atrial fibrillation, prophylaxis, amiodarone, coronary artery bypass grafting

INTRODUCTION

Atrial tachydysrthmias are common in early recovery period after cardiothoracic surgery. These develop in 11 to 40 percent of patients after coronary artery bypass grafting (CABG) [1,2]. Technical advances in surgery and anesthesia, as well as changing methods of myocardial protection, have not decreased the incidence of postoperative atrial tachydysrthmias [1,2].

Postoperative atrial fibrillation (AF) most often occurs during the first five days with a peak incidence on the second and third day postoperatively [3].

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Classically, atrial fibrillation is attributed to enhanced automaticity in one or several rapidly depolarizing foci and re-entry involving one or more circuits. The pathogenesis in postoperative coronary artery bypass grafting (CABG) patients is not clear and is likely multifactorial [4]. The most frequently identified risk factors include increased age, valvular heart disease, atrial enlargement, preoperative atrial dysrhythmias and chronic lung disease [3]. Some of other responsible mechanisms include ß-blocker withdrawal, the use of cardiopulmonary bypass, inadequate atrial protection, and overmanipulation of the right atrium [5]. However, increasing age has been a consistent independent predictor for AF after CABG [2]. The high catecholamine state seen postoperatively also plays a key role [6].

Post-CABG atrial fibrillation is unique in that it has a high rate of spontaneous conversion. This spontaneous conversion rate is much higher than atrial fibrillation unrelated to open heart surgery [7].

Many drugs have been tried to prevent this common postoperative complication. As sympathetic activation may be important in the pathogenesis of atrial fibrillation after coronary artery bypass grafting, ß-adrenoceptor blockade is considered good choice for prophylaxis. Propranolol, Metoprolol, Atenolol and Acebutolol have been found to be successful in this regard.

The preoperative use of intravenous Magnesium Sulfate dramatically reduces the incidence of atrial fibrillation after cardiac surgery [8]. Patients who are prophylactically digitallized priors to coronary artery bypass grafting have relatively low incidence of atrial fibrillation afterwards [9].

Amiodarone is a unique drug belonging to class III anti dysrhythmic agents. It is being used for the treatment of supra ventricular, ventricular and acute myocardial infarction related dysrhythmias. The use of low dose intravenous as well as oral amiodarone for 3-5 days before and then after the coronary artery bypass grafting has significantly reduced the development of atrial fibrillation [10,11].

Very little research work has been done in Pakistan on postoperative AF and prophylaxis against it. This study was designed to find out a useful agent to be used routinely in order to prevent AF after coronary artery bypass grafting along with its associated potentially life-threatening complications. Amiodarone is being widely prescribed in clinical practice for various conditions. Inspite of its being an excellent anti dysrhythmic agent its use as a prophylactic agent against postoperative AF is still uncommon. This study is likely to be helpful in encouraging the use of amiodarone in this regard.

The hypothesis at the onset of the study was that amiodarone is a useful agent in preventing the post CABG atrial fibrillation.

PATIENTS AND METHODS

This study was carried out from 15 January 2003 to 15 March 2004, at Armed Forces Institute of Cardiology/National Institute of Heart Diseases, a tertiary care hospital, established for the management of heart diseases.

It was a prospective, comparative and interventional study. Our inclusion criterion was all 30-65 years of age patients, from either sex, undergoing elective coronary artery bypass grafting and having sinus rhythm. While patients having the conditions (table-1) were excluded from the study.

One hundred patients fulfilling our criteria were studied and were divided into two groups based on convenience. Informed written consent was taken from the patients before enrollment. Both groups were comparable in respect of all variables ($p > 0.05$) as depicted (table-2).

In control group, patients did not receive any prophylaxis for postoperative AF (a routine practice). While all the patients in the Amiodarone group were given tablet amiodarone 200 mg thrice a day for three days before operation, then 200 mg once daily on first postoperative day and were continued so, until discharge.

To create uniformity all the patients received the same anaesthetic technique. Pre medication was offered in the form of oral Lorazepam 2 mg at night and intra muscular Morphine sulphate 10 mg and Promethazine 25 mg, two hours before the surgery. Induction of general anaesthesia was done with intravenous Midazolam and Morphine sulphate. Intubation and muscle relaxation was facilitated by the use of Pancuronium bromide. Anaesthesia was maintaied with oxygen, air and isoflurane. Repeated arterial blood samples were taken during surgery and post operatively for blood gases and potassium level and these were kept within normal limits.

All surgeries were performed under hypothermic cardiopulmonary bypass

(cooling to 28 0C), using ante grade warm blood cardioplegia, non-magnesium containing prime and a membrane oxygenator. All surgeries were performed during a single period of aortic clamping.

Peri-operatively, continuous electro-cardiogram, invasive blood pressure, central venous pressure, pulse oximetry, central and peripheral temperature monitoring was done. In ICU and post operative ward continuous bedside ECG monitoring was done for five days. Until discharge, patients included in the study were not permitted to receive any other antidysrhythmics. If a patient developed atrial fibrillation postoperatively, the primary study endpoint was reached. An episode of atrial fibrillation was counted if it persisted for more than five minutes. Management of atrial fibrillation was directed as under:-

- In haemodynamically stable patients Metoprolol was given in 5 mg increments, up to a total dose of 15 mg.
- Synchronized cardio version with 50-100 joules in unstable patients.
- Anticoagulation: Heparin was given after 24 hours of atrial fibrillation and patients in atrial fibrillation were discharged to home on Warfarin.

Intra operative data like number of grafts applied, cross clamping time and cardiopulmonary bypass time were noted (table-3).

There was no statistically significant difference noted between two groups in respect of all intra operative variables.

Statistical program for social sciences version 10.0 was used for data entry and analysis. Dichotomous variables were analyzed by χ^2 Chi square test and continuous variables were analyzed by student "t" test. "P" value of < 0.05 was considered statistically significant.

RESULTS

The incidence of postoperative AF among patients in Control group was 16% (8 of 50 patients), and 4% (2 of 50 patients) in Amiodarone group and this was statistically significant (p=0.045).

Maximum ventricular rate during episodes of postoperative AF in control group was 122 ± 5.83 beats per minute and was lower in Amiodarone grouping i.e. 108 ± 12.11 beats per minute.

Five patients in Control group and both the patients from Amiodarone group developing postoperative AF were successfully converted to sinus rhythm with the treatment as per study protocol (p=0.24).

One patient in control group died; a 72 years old man with a preoperative left ventricular ejection fraction of 40%, who underwent a 3-vessels bypass, suffered a peri-operative myocardial infarction due to incomplete revascularisation and died of cardiogenic shock with terminal ventricular fibrillation on postoperative day 2.

Table-1: Exclusion criteria.

Severe left ventricular dysfunction (left ventricular ejection fraction < 30%)
History of acute myocardial infarction during the prior 6 months
Previous history of cardiac dysrhythmias
History of amiodarone allergy or toxicity
Abnormal liver function tests
Severe congestive heart failure
Thyroid disease
Marked bradycardia (heart rate <50
Marked renal dysfunction (creatinine clearance ≤ 70 ml/min)

DISCUSSION

In our study the use of prophylactic oral amiodarone for three days before elective CABG reduced the incidence of postoperative AF by 75% as compared with the control group. This prophylactic short term, low-dose, oral amiodarone is sufficient to suppress cardiac dysrrhythmias and does not depress left ventricular ejection fraction. It circumvents some of the limitations of

Table-2: Patient demographics.

Variable	Control group	Amiodarone group	P-value
Age	56.22 ± 8.73	56.68 ± 9.22	0.802
Sex	Male: 42 Female: 08	43 07	0.77
Ejection fraction	45.90 ± 11.01	46.14 ± 10.09	0.914
COPD	04	06	0.504
Hypertension	25	22	0.547
Diabetes Mellitus	15	17	0.668
Previous MI	17	15	0.668
Smoking	20	14	0.205

Table-3: Intra operative data.

Variable	Control Group	Amiodarone Group	P-value
Grafts (no)	3.42 ± 0.64	3.38 ± 0.63	0.755
Cardiopulmonary bypass time (min)	100.20 ± 29.18	101.20 ± 30.55	0.876
Cross Clamp time (min)	58.32 ± 18.25	58.30 ± 18.30	0.996

intravenous administration and can also be used in patients who are not candidates for beta-blockers. In our study only 4% (2 of 50 patients) developed postoperative AF as compared control group 16% (8 of 50 patients). The likely reason for relatively low incidence of postoperative AF as compared with other studies is that this study included only the patients undergoing CABG. The incidence is higher in patients undergoing valve surgery or combined CABG-valve surgery [3]. The other reason for lower incidence of postoperative AF in our study may be relatively younger age group.

Amiodarone was well tolerated and did not increase the risk of intraoperative or postoperative complications. Amiodarone therapy was not associated with proarrhythmia or serious adverse reactions. Among the patients who did have atrial fibrillation, amiodarone reduced the ventricular rate more significantly than the patients in control group.

Noncardiac toxic effects of amiodarone include dose-related and non–dose-related effects [12]. The low-dose amiodarone regimen used in this study did not result in important side effects. Also, there were no acute pulmonary toxic effects after surgery. However, one patient in Amiodarone group had raised levels of alanine aminotransferase.

Cardiac toxicity due to amiodarone is uncommon. The incidence of amiodarone-induced ventricular proarrhythmia is also low [13]. Furthermore, amiodarone has little or no negative inotropic effect, rarely exacerbates heart failure, and can reduce congestive symptoms [14]. In this study, the low complication rate in the amiodarone group confirms the results of other studies [15,16].

Numerous studies have been conducted to search for the most effective agent against postoperative atrial fibrillation. Various drugs like digoxin, magnesium sulphate, verapamil, quinidine, procainamide, beta-blockers were used but the results have been disappointing.

Beta- blockers have been shown to reduce the incidence of AF in a number of studies. The benefit of beta-blockade is greatest in patients who have received beta-blockers previously, although a reduction in atrial fibrillation is seen also in patients not previously on beta-blockers. Various agents like propranolol, metoprolol, atenolol and sotalol have been used in different studies. Unfortunately, in some of these trials, patients assigned to placebo that had previously been on beta-blockers suffered from bet-blocker withdrawal, thus biasing the results against placebo. Also, beta-blockers may not be well tolerated in many patients, including those with severe LV dysfunction and chronic lung disease [17].

A literature search and meta-analysis of the randomized control studies published since 1996 was done by Miller et al [18]. They identified 20 randomized trials and concluded that Magnesium administration decreased the proportion of patients developing postoperative AF from 28% in the control group to 18% in the treatment group.

The small pilot trial done by Laub et al [19] using IV procainamide followed by oral procainamide administered postoperatively was shown to have reduced the incidence of postoperative AF. However, the study was relatively small (22 patients) and the discontinuation rate was high (68%).

Two trials using quinidine [20] and propafenone [21] have not shown significant beneficial effects. A recent trial by Gomes et al [22] suggested that the use of sotalol in the periopertave period appeared promising. However, due to the fact that torsades pointes is a potential side effect of sotalol and its use is limited in patients with asthma or renal insufficiency its use as standard therapy in CABG patients is limited.

Due to clear evidence of a strong supraventricular antiarrhythmic potential, there have been various studies attempting to use short term amiodarone to suppress postoperative AF.

Amiodarone has been used intravenously, orally and in combination in different studies. In the largest study using oral amiodarone, Daoud et al [17] conducted a study using oral amiodarone as prophylactic agent for both coronary artery bypass grafting and valvular surgery. Postoperative AF occurred in 25% of amiodarone group and 53% of placebo group. In this study 46% patients on amiodarone prophylaxis were also taking beta blockers. So it was unclear that whether the reduced incidence of postoperative AF was due to the amiodarone alone or a combined effect of amiodarone and beta blockers.

Due to the fact that most patients require CABG on an urgent basis, IV amiodarone has been used in other studies. Hohnloser et al [23] performed a placebo-controlled study of intravenous amiodarone as prophylaxis against atrial fibrillation after heart surgery in 77 patients. The total intravenous dose of 4.5 grams was given and infusion began after completion of the surgical procedure and significantly reduced the incidence of atrial fibrillation. However, amiodarone was discontinued in 18% of patients because of side effects. In the second study done by Butler et al [24], 60 patients received IV amiodarone; there was reduction in postoperative AF from 20 to 8%. In a recent study, Amiodarone Reduction in Coronary Heart (ARCH) trial, Guarneiri et al [10] randomized 300 patients to receive low-dose IV amiodarone vs placebo. Two grams of amiodarone were administered starting slowly after completion of cardiac surgery. The study confirmed the significant reduction in postoperative AF in amiodarone treated patients.

Kerstein et al [25] used both intravenous and oral amiodarone perioperatively and noted the significant reduction in postoperative AF.

A limitation of this study is that Holter monitoring was not performed to screen for postoperative atrial fibrillation or other arrhythmias during outpatient therapy. The primary goal of the study, however, was to address the clinical utility of prophylactic oral amiodarone. Failure to detect brief, asymptomatic episodes of atrial fibrillation or asymptomatic arrhythmias was unlikely to influence patient care or affect it adversely and does not detract from the clinical implications of this study.

CONCLUSION

Prophylactic short term, low-dose, oral amiodarone started three days before coronary artery bypass grafting helps in decreasing the incidence of postoperative atrial fibrillation. This regimen is well tolerated by most of the patients.

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