COMPARISON OF AMIODARONE VS MAGNESIUM SULPHATE IN THE PREVENTION OF ATRIAL FIBRILLATION AFTER CORONARY ARTERY BYPASS GRAFTING SURGERY

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ABSTRACT

Background: Atrial fibrillation (AF) is common in patients after coronary artery bypass grafting (CABG) and can result in increased morbidity and mortality, increased length of hospital stay, and increased cost. In this study we compared the efficacy of amiodarone versus magnesium sulphate in the prophylaxis of post-CABG atrial fibrillation.

Objective: This study was carried out to assess the efficacy of amiodarone in comparison to magnesium sulphate in the prevention of atrial fibrillation after coronary artery bypass grafting.

Study Design: Randomized controlled trials.

Place and duration of study: The study was carried out at Armed Forces Institute of Cardiology and National Institute of Heart Diseases, Rawalpindi from July 2010 to December 2011

Patients and Methods: Total 240 patients were included in the study and randomly divided in two groups of 120 each using random number table. Patients in Group A (Amiodarone group) were given a loading dose of amiodarone 5 mg/Kg after induction of anesthesia which was then continued as infusion at 5 µgm/Kg/minute on first postoperative day. This was followed by an oral dose of 600 mg/day postoperatively for 5 days. Those in Group B (Magnesium Sulphate group) received 2 g of magnesium sulphate in 100 ml of isotonic 0.9% solution intravenously over 1 hour at following times: preoperatively, immediately following the operation, and on postoperative days 1, 2, and 3.

Results: Thirteen patients (10.8%) developed AF in Amiodarone group, compared to 31 patients (25.8%) in magnesium sulphate group. The results proved amiodarone to be more effective than magnesium sulphate in preventing post-CABG AF (p<0.001). Thirty one patients who developed AF postoperatively in the magnesium group were treated with amiodarone, and all patients recovered normal sinus rhythm. In the amiodarone prophylaxis group, 9 patients regained sinus rhythm in 6 – 8 hours, while for 4 remaining patients cardioversion was attempted out of which 2 responded.

Conclusion: Prophylactic use of amiodarone is significantly better in preventing post-CABG AF in comparison to magnesium sulphate and its use is recommended as prophylactic treatment for post-CABG AF.

Keywords: Atrial Fibrillation, Coronary Artery Bypass Grafting (CABG), Amiodarone, Magnesium Sulphate.

INTRODUCTION

Postoperative rhythm disorders are a serious complication of open heart surgery. The incidence of postoperative supraventricular arrhythmias has been reported to be 11 – 54%, and the incidence of ventricular arrhythmia to be 1.8 – 13%[1-3]. Although atrial fibrillation (AF) occurs frequently, the mechanism behind its development has not yet been clearly understood. The arrhythmia contributes to increased morbidity and expenditure after CABG[4]. AF may cause hemodynamic compromise, postoperative stroke, and prolongation of hospital stay independent of other factors such as age.[5,6]

Post operative AF has been extensively studied and risk factors for its development include increased age, male gender, history of AF, discontinuation of preoperative β-blocker therapy, congestive heart failure, electrolyte depletion (low potassium and magnesium), cardiopulmonary bypass, left atrial expansion and dysfunction, severity of coronary artery disease, respiratory disease, and pulmonary disease.[7-13]

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Perioperative factors, such as atrial extrasystoles, change in autonomic tone, electrolyte shifts, inadequate myocardial protection, β blocker withdrawal, or the response to cardiopulmonary bypass, can trigger AF in these at-risk patients[14].

Many clinical trials have evaluated the effectiveness of a variety of pharmacological and nonpharmacological interventions to decrease the incidence of AF[15-25]. Amiodarone and magnesium sulphate are commonly used for this purpose[16-19,21-23]. In this study we will compare the relative effectiveness of these two drugs in preventing post-CABG atrial fibrillation.

PATIENTS AND METHODS

Patient selection

These randomized controlled trials were carried out from July 2010 to December 2011 at Armed Forces Institute of Cardiology and National Institute of Heart Disease. Two hundred and forty patients who presented for CABG and fulfilled the inclusion criteria were enrolled. Patients were then randomly assigned to one of two groups (Group A and B) of 120 each using random number table. Permission was taken from hospital ethics committee. Written informed consent was obtained from the patients.

Inclusion criteria consisted of

- Informed consent.
- Age > 50 years.
- elective heart surgery requiring cardio pulmonary bypass.
- Normal sinus rhythm with heart rate > 50 bpm,
- Creatinine clearance >60 ml/min

Exclusion criteria included

- Participation in another investigational protocol,
- Heart rate < 55 bpm (while patient was awake)
- A second degree or a higher degree heart block
- Presence of a permanent pacemaker
- Pre-existing class I or III antiarrhythmic therapy or on digoxin
- History of supraventricular (including atrial flutter or AF) or ventricular tachyarrhythmias.
- Redo-operation.
- Known hyperthyroid or hypothyroid patients.
- Patients with liver disease or renal derangement.
- Patients with valvular heart surgery in addition to CABG.
- Cardiogenic shock.

Patients in Group A (Amiodarone group) were given a loading dose of amiodarone 5 mg/Kg after induction of anesthesia which was then continued as infusion at 5 µgm/Kg/minute on first postoperative day. This was followed by an oral dose of 600 mg/day postoperatively for 5 days. Those in Group B (Magnesium Sulphate group) received 2 g of magnesium sulphate in 100 ml of isotonic 0.9% solution intravenously over 1 hour at following times: preoperatively, immediately following the operation, and on postoperative days 1, 2, and 3.

Anesthetic management

All medications were continued until surgery. Premedication constituted oral lorazepam and famotidine alongwith their routine medication the night before surgery. General anesthesia was induced with midazolam (0.05 mg/kg), fentanyl (25 µg/kg) and sevoflurane, and muscle paralysis was obtained with atracurium (0.5 mg/kg). Anesthesia was maintained with isoflurane and a continuous infusion of fentany[1] (5ug kg-1 h-1). At the end of the surgical procedure, patients were transferred to the intensive care unit (ICU). Weaning from mechanical ventilation and tracheal extubation were done once patients were stable. Patients were discharged from the ICU to the ward as soon as their hemodynamic and respiratory condition was stable.

Perioperative Measurements

ECGs, core and peripheral temperature, and hemodynamic variables, including non-invasive and invasive arterial blood pressure, heart rate, and central venous pressure, were monitored continuously throughout the operation and during the stay in ICU. A 12-lead ECG was obtained before surgery and on first 5 postoperative days. Serum magnesium concentration was measured before surgery, immediately after surgery, and every morning for 5 days postoperatively and maintained at a level 1.7-2.1 mEq/L. Serum potassium and calcium concentrations were also measured perioperatively and adjusted to maintain potassium levels at 4.0-5.5 mEq/L and calcium levels at 2.1-2.6 mmol/L. AF was considered significant if it persisted for >30 minutes.

Statistical Analysis

Data was analyzed using SPSS version 11. Descriptive statistics were used to describe the data. Between the two groups, quantitative variables were compared through independent samples t-test, while qualitative variables were compared through chi-square test. *p*-value <0.05 was considered as significant.

RESULTS

Groups A and B did not show significant differences in their demographic profile or preoperative variables like age, left ventricular ejection fraction, diabetes mellitus, hypertension, chronic obstructive airway disease (COAD), or previous myocardial infarction (MI)(Table 1). The mean number of grafts used was 3.3±0.8 in Group A and 3.1±0.7 in Group B. No significant difference was observed between bypass time, aortic cross clamp time, use of inotropes or duration of intubation (Table 2).

Pre-operative magnesium levels did not differ statistically between two groups. Later, however, all the measured levels of magnesium sulphate showed significant increase in group B due to magnesium sulphate prophylactic treatment (p<0.005)(Table 3).

A total of 13 (10.8%) patients developed AF in group A, compared to 31 (25.8%) patients in group B (p<0.001). If AF was not converted spontaneously to sinus rhythm (SR), either pharmacological means or electrical cardioversion was used to restore SR. AF that occurred postoperatively in the magnesium group was treated with amiodarone infusion (5 mg/Kg loading, 5 µgm/Kg/min for 24 hours, and then 600 mg/day oral continuation for 5 days), and all the patients recovered normal sinus rhythm. For AF patients in amiodarone group, amiodarone infusion was increased to 15 µgm/Kg/min. At this dose, 9 patients regained

Table-1: Preoperative characteristics

Characteristics	Group A (Amiodarone Group)	Group B (Magnesium Sulphate Group)	*p*-value
Age (years)	57±9	58±6	>0.05
Male: Female	74/46	69/51	>0.05
Heart rate (bpm)	71.4±12.5	73.1±11.3	>0.05
Hypertension, n (%)	44 (36%)	39 (32.5%)	>0.05
Diabetes mellitus, n (%)	47 (39%)	51 (42.5%)	>0.05
Smoking, n (%)	31 (25.8%)	34 (28.3%)	>0.05
COAD, n (%)	9 (7.5%)	11 (9.1%)	>0.05
BMI (Kg/m2)	27.2±4.5	28±3.1	>0.05
Previous MI, n (%)	27 (22.5%)	24 (20%)	>0.05
LVEF	53.4±7.9	51.8±8.1	>0.05
Preoperative medication			
• ACE inhibitor, n (%)	67 (55.8%)	71 (59.1%)	>0.05
• Ca-channel blockers, n (%)	21 (17.5%)	19 (15.8%)	>0.05
• Statins, n (%)	91 (75.8%)	97 (80.8%)	>0.05

*COAD: chronic obstructive airway disease, BMI: body-mass index, MI: myocardial infarction, LVEF: left ventricular ejection fraction, ACE: angiotensin converting enzyme inhibitors, Ca: Calcium

sinus rhythm in 6–8 hours, while for remaining 4 patients cardioversion was attempted, which proved useful in 2 patients. However, 2 patients did not respond to these measures and remained in AF. These latter patients continued to receive amiodarone treatment, and no additional treatment was given. These patients recovered normal sinus rhythm by 7th postoperative day.

DISCUSSION

Supraventricular tachyarrhythmias, particularly AF, is the most common dysrhythmia developed after CABG[2,3]. It prolongs patient's ICU and hospital stay, and delays recovery after CABG[1-3]. Despite the major advances in cardiac surgery and anesthesia practices, the frequency of post-CABG AF remains distressingly high. AF is often short-lived, but is associated with significant morbidity in critical care.

Several factors may contribute to the development of AF after cardiac surgery through alterations in atrial refractoriness and/or local reentry: operative trauma, rise in atrial pressure, increased atrial electrical susceptibility from rapid rewarming, atrial distention, chemical stimulation due to inotrope use, reflex sympathetic activation, and pericardial or respiratory complications.[9–11,13] Altered load changes myocardial segment length that, acutely, can result in decreased resting potential and the occurrence of after-depolarizations that cause extrasystoles in the region of greatest stretch.[12] Recent clinical studies have also suggested the possible role of inflammatory mechanisms in the pathogenesis of AF after cardiac surgery.[15,26]

Table- 2: Comparison of variables between both the groups

Characteristic	Group A (n=120)	Group B (n=120)	*p*-value
Average number of grafts	3.3±0.8	3.1±0.7	<0.05
Aortic cross clamp time (min)	53±17.1	52±18.4	>0.05
Duration of operation (min)	197±51.4	203±47.9	>0.05
Duration of intubation (hours)	13.8±3.2	14.1±3.9	>0.05
Intra aortic balloon pump (n, %)	13(10.8%)	15 (12.5%)	>0.05
Inotropic support (n)	39 (32.5%)	43 (35.8%)	>0.05

Table-3: Comparison of magnesium sulphate levels between both the groups

Serum magnesium (mg/dl)	Group A (n=120)	Group B (n=120)	*p*-value
Preoperative	1.8±0.9	1.9±0.7	>0.05
After coming off heart lung machine	1.9±0.7	1.6±0.6	<0.05
In ICU (Operation day)	1.6±0.3	2.9±0.8	<0.05
1st postoperative day	1.7±0.4	3.0±0.6	<0.05
2nd postoperative day	1.7±0.5	3.1±0.5	<0.05
3rd postoperative day	1.6±0.7	2.8±0.7	<0.05

Table- 4: Postoperative dysrhythmias

	Group A (n=120)	Group B (n=120)	*p*-value
Number of patients developing dysrhythmias	23 (19.1%)	46 (38.3%)	<0.001
Supraventricular dysrhythmias	16 (13.3%)	36 (30%)	<0.001
Premature atrial contractions	3 (2.5%)	5 (4.1%)	>0.05
AF	13 (10.8%)	31 (25.8%)	<0.001
Ventricular dysrhythmias	7 (5.8%)	10 (8.3%)	>0.05
Premature ventricular contractions	5 (4.1%)	7 (5.8%)	>0.05
VT/ VF	2 (1.6%)	3 (2.5%)	>0.05

Several studies have demonstrated the efficacy of amiodarone in decreasing the incidence of postoperative AF[16–19]. There have been different studies for prevention of post-CABG AF with digoxin, β-blockers, magnesium, or a combination of these drugs[20-22]. Aerra et al[23] confirmed that combination of sotalol and magnesium can significantly reduce the incidence of postoperative AF. Recent data have suggested a possible protective role of statins,[27] steroids[28,29] and sodium nitroprusside.[24] Other strategies, such as continuous overdrive atrial pacing through temporary epicardial electrodes, is currently under investigation.[30]

In our study we compared the efficacy of amiodarone and magnesium sulphate for the prophylaxis of post-CABG AF. Amiodarone is a class III anti-arrhythmic drug that acts on Phase III of myocardial action potential. It decreases delayed rectifier current (K efflux) and slows phase 3 (repolarization) of action potential thus increasing action potential duration and effective refractory period-especially in Purkinje and ventricular tissues. It mimics all anti-arrhythmic drug classes (I,II,III,IV) as it blocks Na, Ca, K channels and adrenoceptors and is effective in a wide range of atrial and ventricular arrhythmias.

Magnesium is a cation that functions by lengthening the refractory period at the atrioventricular node. Thus, magnesium likely has an important role in preventing and treating atrial fibrillation, especially considering that serum magnesium levels below 0.8 mmol/L trigger atrial fibrillation.

In our study the frequency of post-CABG AF was comparable to other studies[1-3]. Our results indicated that prophylactic amiodarone therapy reduced significantly the frequency of post-CABG AF when compared to magnesium sulphate (10.8% vs 25.8%). The results of our study are comparable to similar studies.[16-19] Many comparative studies and meta-analyses have been published on this topic. Some have good results with β-blockers and ACE inhibitors[8], others have used amiodarone and magnesium sulphate in combination in high risk patients with better results than either of these used alone[31]. The same study and some other researchers are of the opinion that amiodarone is effective for post CABG AF, where as magnesium prophylaxis is ineffective.[8,19,31]

CONCLUSION

The results of our study suggest that the frequency of post CABG AF is reduced significantly by amiodarone compared to magnesium sulphate. Also the patients who developed AF in magnesium sulphate group responded to therapy by amiodarone. Thus prophylactic treatment with amiodarone should be considered for patients undergoing CABG for avoiding AF and its associated morbidity.

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