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Original Article

Comparing the Effect of Perioperative Amiodarone and Magnesium Sulphate Combination with Magnesium Sulphate for Prevention of Cardiac Dysrhythmias in Open Heart Surgeries: A Quasi-Experimental Study

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ABSTRACT

Objective: To compare the effectiveness of combining Magnesium Sulphate with Amiodarone vs Magnesium Sulphate to prevent cardiac arrhythmias in Coronary Artery Bypass Grafting (CABG) patients.

Study Design: Quasi-Experimental Study.

Place and Duration of Study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases Rawalpindi Pakistan, from Jul 2022 to Mar 2023.

Methodology: Two hundred and sixty-two (n=262) Coronary Artery Bypass Graft patients, eligible for the study, were enrolled through consecutive sampling and divided into group A - experiment group (3 mg/kg amiodarone+30 mg/kg magnesium sulphate was given, n_1=131) and group B- control group (30 mg/kg magnesium sulphate was given, n_2=131) by non-random allocation lottery method at the removal of the aortic cross-clamp. The statistical package for social science, SPSS version 26:00 was used to analyse the data. Mean±SD was calculated for continuous variables whereas for categorical variables, percentages and frequencies were calculated. Chi-square test was utilized to find the association and student t-test was applied to find the mean difference between the study groups.

Results: Study participants consisted of 194(74.1%) males and 68(26.0%) females. The patients' mean age was 57.29±9.88 years and 58.30±10.69 years respectively, in group-A and group-B. The frequency of pre and post-operative cardiac dysrhythmias was considerably different in both groups. In group-A, 22(16.7%) patients developed dysrhythmias, while in control group, dysrhythmias occurred in 49 (37.4%) patients (*p*-value <0.001).

Conclusion: Combined prophylactic therapy with amiodarone and magnesium sulphate significantly reduced the per and post-operative dysrhythmias in CABG surgeries.

Keywords: Amiodarone, Coronary artery bypass grafting, Dysrhythmias, Magnesium sulphate.

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INTRODUCTION

The most frequent complication of open-heart surgery is cardiac dysrhythmias. It is an autonomous risk factor which leads to higher postoperative morbidity and mortality.[1] Dysrhythmias occur in around 40% to 60% of Coronary Artery Bypass Graft surgeries, which not only increases hospital stay but also affects economic outlays.[2] Among post CABG cardiac dysrhythmias (premature ventricular contractions, premature atrial contraction, conduction blocks, paroxysmal supraventricular tachycardia, ventricular tachycardia and ventricular fibrillation), atrial fibrillation is the most common.[3] Besides beta-blockers, calcium channel blockers, amiodarone, magnesium, sotalol, and digoxin have been in use controlling dysrhythmias, Electrical cardio version has also been very effective and useful in treating critically ill patients.[4]

Dysrhythmias in cardiac surgery patients lead to life threatening complications such as hemodynamic instability, thromboembolic events, stroke, renal injury, extended ICU stay, which require need for intra-aortic balloon pump/inotropic support, and ultimately increased mortality.[5]

Magnesium deficiency was evident in 71% of Cardiopulmonary Bypass (CPB) patients.[1] Hypomagnesaemia has shown to be proarrhythmic, demonstrating an increased risk of atrial and ventricular dysrhythmias. Myocardial magnesium exhaustion in the postoperative period due to decreased dietary intake, neuro-hormonal activation, use of diuretics promote magnesium excretion, circulating volume dilution from extracorporeal support, and norepinephrine-induced redistribution of magnesium from intracellular to extracellular compartment.[6]

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Magnesium (Mg) is an essential cofactor for cellular respiration and ATP synthesis in mitochondria. It slows the pace at which Sino Atrial (SA) node originates the impulses, prolongs conduction time, encourages the passage of sodium, potassium and calcium into and out of cells, modulates cardiac contraction and stabilizes excitable membranes. Mg decreases platelet aggregation, reduces sympathetic activity, and decreases coronary artery spasm.[7]

Amiodarone is categorized as, class III antiarrhythmic agent (Vaughn-Williams classification) having anti–beta-adrenergic effects, combining with sodium, potassium, and calcium channel-blocking properties. Furthermore, amiodarone also plays role in prolongation of action potential, repolarization and decreases sinus node action and AV conduction time.[8] The combination of amiodarone and magnesium significantly decreases cardiac dysrhythmias.[9]

Limted data is available on effectiveness of Amiodarone and Magnesium Sulphate in prevention of dysrhythmias in our population. This study was focused to compare the effectiveness of combined magnesium sulphate and amiodarone vs magnesium sulphate to prevent cardiac arrhythmias in CABG patients.

METHODOLOGY

This Quasi-experimental study was conducted at Armed Forces Institute of Cardiology/National Institute of Heart Diseases Rawalpindi Pakistan, from July, 2022 to March, 2023 after ethical approval from Institutional Ethical Review Board (IERB letter number: 9/2/R&D/2022/198). Non-probability consecutive sampling technique with non-random treatment allocation was adopted to gather data.

The sample size (n=262) was calculated by using WHO sample size calculator at level of significance 5%, confidence level 90%, and 40% prevalence of dysrhythmias in CABG patients.[2]

Inclusion Criteria: Patients of both gender, hemodynamically stable with ASA class I-IV, having sinus rhythm and age ranging between 18-80 years undergoing CABG surgeries were included in the Experimental and Control group.

Exclusion Criteria: Predefined exclusion standards included patients with a history of hypersensitivity to any of the study drugs, thyroid disease, baseline eGFR <30 mL/min/1.73 m^2, serum creatinine >2 mg/dl, elevated liver enzymes, heart rate <50/min, EF <30%, arrhythmias on admission, moderate or severe valvular disease, cardiopulmonary bypass time >180 seconds, recent MI <2 weeks, emergency CABG surgeries, atheroma bridging, endarterectomy, incomplete revascularization or high inotropic support.

Study participants were divided into two equal groups; group-A (experimental group; n=131) and group-B (control group; n=131).

Patients were interviewed, explained and counseled about the purpose of the study, procedure and risk-benefit ratio of administering amiodarone and magnesium sulphate. Informed written consent was obtained in pre-anesthesia clinic.

Oral beta-blockers were prescribed continuously pre-operatively and post-operatively. Premedication with dexamethasone 4mg and metoclopramide 10mg was done. Induction was started with titrated doses of Propofol, Midazolam 0.02mg/kg, Morphine 0.15mg/kg or Fentanyl 3-5ug/kg, Cisatracurium 0.2mg/kg. Dexmetedomidine 1ug/kg loading dose and 0.5ug/kg/hr maintenance dose plus 1-1.5% Isoflurane was done. Target of hemodynamics was ±20% of baseline in pre-bypass period, and MAP of 55–65 mmHg. 350 IU/kg Heparin was injected before going for bypass. A 20ml/kg of tepid modified Del Nido cardioplegia solution was given through antegrade approach to arrest the heart. Subsequent doses (10ml/kg) were repeated every 45 minutes. During non-pulsatile CPB, 2.4 L/min/m^2 body surface area (BSA) of blood flow was maintained. Inotropic support, vasopressor and vasodilator were given as per requirement.

Patients who met the study's eligibility criteria were split into group A and B by non-random treatment allocation. Post de-clamping factors like reperfusion injury, myocardial ischemia, mechanical factors, CPB induced inflammation, electrolyte imbalance and inotropic support, can potentially trigger abnormal electrical activity more frequently, so after rewarming, at removal of aortic cross clamp, and before weaning from cardiopulmonary bypass, group-A was given 3mg/kg injection of Amiodarone in 20 mL saline plus 30mg/kg MgSO4 in 20 ml saline through CPB machine and group-B received 30 mg/kg Magnesium Sulphate in 40 ml of normal saline. Thereafter, dysrhythmias were diagnosed by continuous 5 leads ECG recording through cardiac monitor intra-operatively and within first 72 hours post-operatively in intensive care unit, high dependency unit. Normal serum magnesium levels were maintained in both groups post-operatively.

After collection and recording of all data, analysis was done by using Statistical Package for Social Sciences (SPSS version-26.00). Mean±SD was calculated for numerical values like age, height, weight, preoperative EF, pre-operative serum creatinine levels, bypass time and post-operative CK-MB. For categorical variables like gender, ASA class, left ventricular function, IABP, comorbidity and incidence of dysrhythmias, percentages and frequencies were calculated. Chi-square test was used for comparison of study groups. Student t-test was applied to find mean differences. A *p*-value of 0.05 or less was considered significant.

RESULTS

Each study group consisted of n=131 respondents. Male participants in study were 194(74.1%) and females were 68(26.0%) collectively, with age ranging between 36-80 years. 57.29±9.88 years was the mean age of group-A, mean weight was 73.89±10.85 kg and the mean height was 166.08±7.64 cm whereas the mean age of group-B was found to be 58.30±10.69 years with an average weight of 72.92±13.35 kg, and the average height of 165.98±8.39 cm. Majority of patients were males in both groups; 96(73.3%) and 98(74.8%) in group-A and B respectively. No significant difference was found between the two groups in terms of gender distribution, mean age, height and weight (p>0.05). Hypertension and Diabetes Mellitus were the major preoperative co-morbidities (p>0.05) (Table-I).

Table-I: Comparison of baseline characteristics between group A and B (n=262)

Characteristics		Group-A (Experimental) (n=131)	Group-B (Control) (n=131)	*p*-value
Gender	Male	96(73.3%)	98(74.8%)	0.88
	Female	35(26.7%)	33(25.2%)	
Age (years) (Mean±SD)		57.29±9.88	58.30±10.69	0.42
Height (cm) (Mean±SD)		166.08±7.64	165.98±8.39	0.92
Weight (kg) (Mean±SD)		73.89±10.85	72.92±13.35	0.52
Diabetes Mellitus		72(55.0%)	64(48.9%)	0.38
Hypertension		69(52.7%)	78(59.5%)	0.31

Pre-surgery physical status classification according to American Society of Anesthesiologists (ASA), left Ventricular Function, pre-operative Ejection Fraction and pre-operative serum creatinine levels were also quite similar in both groups with insignificant results (p>0.05) (Table-II).

Table-II: Comparison of pre-operative indices between group A and group B (n=262)

Pre-operative Indices		Group-A (Experimental) (n=131)	Group-B (Control) (n=131)	*p*-value
American Society of Anesthesiologists Class	I	-	-	0.56
	II	8 (6.1%)	11(8.4%)	
	III	119(90.8%)	118(90.1%)	
	IV	4(3.1%)	2(1.5%)	
Left Ventricular Function	Good	28(21.4%)	34(26.0%)	0.46
	Fair	41(31.3%)	33(25.2%)	
	Moderate	50(38.2%)	56(42.7%)	
	Poor	12(9.2%)	8 (6.1%)	
Pre-operative Ejection Fraction (%) Mean±SD)		48.59±8.85	49.23±8.23	0.54
Pre-operative Creatinine (mg/dL) (Mean±SD)		1.02±0.26	1.03±0.28	0.65

Cardiopulmonary bypass time was 137.04±30.58 minutes in experimental group and 122.94±34.45 minutes in control group (p=0.005). In the Experimental group, 14(10.68%) patients had requirement of Intra-Aortic Balloon Pump (IABP) insertion, compared to 18(13.7%) patients in the control group. Postoperative CK-MB was almost identical in both groups (Table-III).

Table-III: Intra-operative and post-operative indices of patients in group A and B (n=262)

Characteristics	Total (n=262)	Group-A (Experimental) Frequency (%) (n=131)	Group-B (Control) Frequency (%) (n=131)	*p*-value
IABP	32(12.2%)	14(10.7%)	18(13.7%)	0.57
CPB Time (min) (Mean±SD)	137.04± 30.58	137.04±30.58	122.94±34.45	0.005
Post-operative CK MB (IU/L) (Mean±SD)	56.69± 49.79	58.44±56.42	54.95±42.30	0.57

CPB=Cardiopulmonary Bypass Time; IABP= Intra-Aortic Balloon Pump; CK MB= Creatinine Kinase-Myoglobin Binding

The frequency of dysrhythmias in the experimental group was 22(16.7%) whereas, in the control group, dysrhythmias occurred in 49(37.4%) patients i.e. 21% less incidence of dysrhythmias due to the use of amiodarone and Magnesium Sulphate combination (p-value<0.001) (Figure).

DISCUSSION

Although the precise etiology of dysrhythmias following cardiac surgery is unknown but pre-operative variables such as advanced age, enlarged left atrium, left ventricular dysfunction, hypertension, chronic kidney disease, COPD, obesity, multiple vessels disease, previous history of dysrhythmias, recent myocardial infarction, hyperthyroidism, electrolyte imbalance including imbalanced potassium and

deficiency of magnesium are the main causes of dysrhythmias.[12] Intraoperative and postoperative factors like cardiopulmonary bypass time, cross-clamp time, atrial injury, inadequate cardiac protection, exogenous and endogenous catecholamine, electrolytes imbalance, beta-blockers withdrawal, reopening due to bleed, poor grafts or targets, post-operative pain, hypoxemia and sepsis also introduced dysrhythmias.[13]

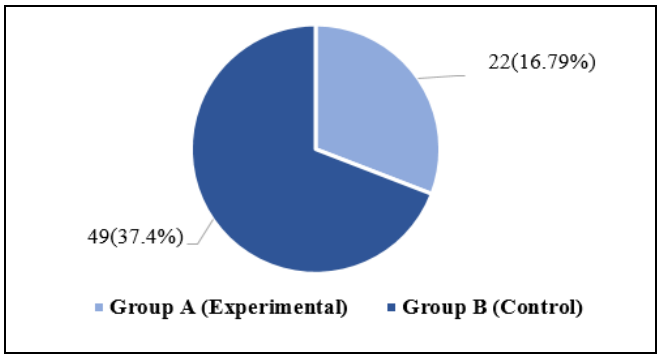

Figure: Comparison of frequency of Dysrhythmias between study groups (n=262)

In our study, remarkable decrease in the incidence of arrhythmias was due to the combined usage of magnesium sulphate and amiodarone 22(16.7%) vs 49(37.4%) p<0.001, whereas Sharma S. *et al*. reported that they used either magnesium or amiodarone as prophylaxis. The mechanism behind the beneficial effect of the conjoint use of magnesium sulphate and amiodarone could only be speculative. Action potentials and the refractory period both are prolonged when amiodarone is used. The synergistic effect with amiodarone may be explained by the well-established relationship between the homeostasis of potassium and magnesium.[11]

Salaminia *et al*. compared magnesium with placebo in a meta-analysis and discovered that it reduced supraventricular and ventricular arrhythmias.[1] Sarhan *et al*. and Naghipour *et al*. found that magnesium sulphate was more effective in preventing arrhythmia in all types of post-cardiac surgery.[14,15] Heidaranlu *et al*. showed that magnesium sulphate administration appeared to be effective in avoiding new occurrences of atrial fibrillation and ventricular ectopic prior to, during, and after open heart surgery.[12]

In patients with rheumatic valvular heart disease, Rehman *at el*. investigated the effects of intraoperative loading doses of amiodarone for prophylaxis against atrial fibrillation. In the amiodarone group, ventricular tachycardia manifested in 6.7% of patients and atrial fibrillation was identified in 26.7% of patients.[13] Sasa *et al*. explained that in patients who received amiodarone in the post-operative period the incidence of AF was reduced.[16] According to Atreya *et al*. and Thanavero *et al*., patients receiving peri-operative amiodarone had reduced risk of atrial arrhythmias and AF than those without prophylactic treatment.[17,18]

The current study's findings are close to those of Cagli *et al*. which showed that the prevalence rate of AF in the group receiving magnesium sulphate with amiodarone was 9%, while 36% in amiodarone group and 33% in control group respectively.[19] Another study discovered that a single preventive intraoperative dosage of combined amiodarone and magnesium sulphate reduces post-bypass arrhythmia in Mitral Valve Replacement (MVR) surgery patients as compared to the placebo group (26.7% vs 71.7% respectively).[11] Kashani S *et al*. and Smith H. reported that the use of amiodarone+magnesium sulfate decreased the frequency of postoperative atrial and ventricular fibrillation and also showed a drop in the number of defibrillations after the removal of the aortic cross-clamp.[9,20] Burrage *at el*. in a meta-analysis, found a significant reduction in AF after cardiac surgeries in patients receiving prophylactic amiodarone and magnesium as compared to controls.[21]

LIMITATION OF STUDY

The main limitation of this study was the long-term use of beta blockers by the patients.

CONCLUSION

There was significant reduction in dysrhythmias from 37.4% in the control group to 16.7% in the experimental group. Amiodarone and magnesium sulphate com-bination proved to be the most ideal choice for pre-venting intra and post-operative cardiac dysrhythmias in CABG patients.

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Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MUF: IB & FY: Study concept, Manuscript writing, Critical review, Data analysis, Editing, approval of the final version to be published.

SMHK: WA & SARAS: Data collection, Critical review, Study concept, Data analysis, approval of the final version to be published.

AS: & JK: Data analysis, Critical review, Study concept, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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