

# Comparison of magnesium sulphate with placebo for prevention of atrial fibrillation in post Coronary Artery Bypass Grafting (CABG) patients

## Abstract

**Background:** Postoperative Atrial Fibrillation (AF) is the most common complication that develops after cardiovascular surgery and is associated with adverse outcomes. Magnesium is an essential element in the body, which is required as a cofactor for over 300 enzymatic reactions and reduced levels of magnesium in the blood have been found related with an increased risk of AF, both in ambulatory setting and after cardiac surgeries. Our study was aimed at determining the role of prophylactic magnesium sulphate in preventing postoperative AF in subjects undergoing Coronary Artery Bypass Graft (CABG).

**Objective:** To compare efficacy of magnesium sulphate with placebo for prevention of atrial fibrillation after coronary artery bypass surgery.

**Duration:** 6 months (07-03-2018 to 06-09-2018).

**Setting:** Department of Cardiac surgery, Cardiac Center PIMS Islamabad.

**Subjects and methods:** In the present study, we enrolled a total of one hundred and twenty-eight (n=128) patients of both gender between ages 50-70 years who were planned for coronary artery bypass surgery. All the patients were randomized by lottery method into group A, who were given intravenous injection of 200 mEq MgSO<sub>4</sub> in 100 ml of normal saline/day for 03 days and group B, who were given intravenous injection of 100 ml of normal saline only for 03 days. All the patients had continuous cardiac monitoring performed for 72 hours to observe for occurrence of AF. Occurrence of postoperative AF was compared in both groups by applying chi-square test, a p-value of <0.05 was considered as significant.

**Results:** Postoperative AF was observed in 12.5% (n=8/64) patients in group A while it was observed in 45.3% (n=29/64) patients in group B (p=0.001). When stratified for age and gender magnesium sulphate was found more effective in preventing postoperative AF in younger males (p=0.001).

**Conclusion:** In the present study, postoperative AF was developed in significantly lesser number of patients who received prophylactic magnesium sulphate as compared to placebo group. Magnesium sulphate was found more effective in preventing postoperative AF among younger males.

**Keywords:** Atrial fibrillation • CABG • Magnesium sulphate

## Introduction

Atrial Fibrillation (AF) may occur in early postoperative period after cardiac surgery, and it may be manifested as a late complication [1]. It occurs in about 15%-40% of patients undergoing CABG [2,3]. The incidence is higher (approximately up to

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60%) in patients who experience CABG combined with valve replacement [4]. Atrial fibrillation after CABG is related to certain perioperative factors, which include prior degenerative changes in atrial myocardium and perioperative factors like an increase in phase-3 depolarization, dispersion of refractoriness of atria, enhancement in automaticity, shorter inter-atrial conduction time, reduced conduction velocity and fluid and electrolyte shifts. These electrophysiologic factors lead to and promote the development of AF [5,6]. Postoperative AF is associated with several adverse outcomes, which include increased cardiovascular, renal, and cerebral complications; increased cost of care and resource utilization; and reduced long-term survival [7-10].

Magnesium is an essential element in the body, which is required as a cofactor for over 300 enzymatic reactions and reduced levels of magnesium in the blood have been found related with an increased risk of AF, both in ambulatory setting and after cardiac surgeries [11]. Several mechanisms are involved by which hypomagnesemia promotes AF [12,13]. These include its effect on duration of action potential, atrioventricular conduction and on effective refractory period of atria. Administration of Magnesium prophylaxis for the prevention of POAF in the context of cardiac surgery appeared to confirm these beneficial results [14].

In a study conducted in 1996, Nurözler, et al. aimed to assess the efficacy of prophylactic use of magnesium sulfate in reducing the occurrence of postoperative AF in patients undergoing CABG. Two groups of 25 patients each were included in study. In one group (Study) magnesium was administered in a dose of 200 mEq during first five days after the surgery, while in the other group (Placebo) normal saline was given. Their results demonstrated that 4% of patients in the MgSO<sub>4</sub> group experienced AF as compared to 20% of patients who experienced AF in the placebo group (p<0.05) [15].

Post-operative AF is associated with significant complications. Our study is aimed at determining role of magnesium sulphate in preventing atrial fibrillation in patients after coronary artery bypass surgery [1].

## Materials and Methods

A randomized controlled trial was conducted between March 2018 and September 2018 at the Cardiac Center at Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan. A total of 128 patients (n=128) included in the study. The patients were randomly divided into two equal groups where group A was to receive MgSO<sub>4</sub> (Mg), and group B would be administered placebo in the form of normal saline (Saline). Each group comprised of 64 patients (n=64). The sample size was calculated by using WHO sample size calculator taking the level of significance as 5%,

power of test at 80% and anticipated populations (P1 and P2) as 20% and 4% respectively. The sampling technique employed was nonprobability consecutive sampling.

The inclusion criteria for the study were patients between the age of 50 to 70 years of either gender with ejection fractions greater than 35. Patients with previous history of CABG or angioplasty were excluded. Additionally, exclusion criteria also comprised of patients with previous history of AF or history of any chronic disease like diabetes mellitus and chronic renal disease.

The study was started after taking approval from hospital ethics committee. Patients admitted to cardiac surgery ward fulfilling the inclusion criteria were included in the study. Informed written consent was taken from each patient. Initial data about age, contact number and date of admission was recorded on predesigned proforma. Pre-operative Electrocardiography (ECG) was performed by senior cardiologist to rule out pre-existing AF and preoperative findings including patient demographics were recorded. All patients underwent CABG under general anesthesia which was performed by a team of cardiac surgeons. Perioperative cardiac monitoring was performed. Post operatively patients were kept in ITC for 72 hours. Patients in group A were given intravenous injection of 200 mEq MgSO<sub>4</sub> in 100 ml of normal saline per day for 03 days and group B subjects were given intravenous injection of 100 ml of normal saline per day for 03 days. All the patients had continuous cardiac monitoring performed for 72 hours and findings were noted in the proforma.

## Data analysis

The data were entered in SPSS version 20. Descriptive statistics was used to calculate means  $\pm$  SD for quantitative variables i.e., age. Frequencies with percentage were calculated for qualitative variables i.e., gender and occurrence of AF. Chi square test was applied for comparison of efficacy between both groups. Effect modifiers like age and gender were controlled by stratification. Post stratification chi-square test was applied. p value<0.05 was considered significant.

## Results

All the patients in both groups had continuous cardiac monitoring performed for 72 hours post operatively to observe for occurrence of AF. Table 1 shows the preoperative patient demographic data. There were 93.8% (n=60/64) males and 6.3% (n=4/64) females in group A and 90.6% (n=58/64) males and 9.4% (n=6/64) females in group B. Mean age of subjects in group A was 59.9 years  $\pm$  6.7 SD while it was 58.6 years  $\pm$  6.3 SD in group B. Mean baseline LVEF for both groups are also given in Table 1. Different age groups are shown in Table 2.

Postoperative AF was observed in 12.5% (n=8/64) patients in group A while it was observed in 45.3% (n=29/64) patients in group B. P-value estimated was 0.001, implying postoperative AF was developed in significantly lesser number of patients who received prophylactic magnesium sulphate as compared to placebo

group (Table 3).

When stratified for age (Table 4) and gender (Table 5) magnesium sulphate was found more effective in preventing postoperative AF in younger age group(p=0.001) and males (p=0.001).

**Table 1: Preoperative patient demographics of the study groups.**

Variable	Group A, Mg (n=64)	Group B, Saline (n=64)
Male sex	93.80%	90.60%
Age (y)	59.9 ± 6.7	58.6 ± 6.3
Baseline LVEF	0.527 ± 0.081	0.534 ± 0.059

**Note:** Values are expressed as mean ± SD or as number (percentage)

**Table 2: Different age groups in the study sample.**

Age group	Group A, Mg	Group B, Saline	Total
50-60 years	53.1%	57.8%	55.5%
61-70 years	46.9%	42.2%	44.5%
Total	100%	100%	100%

**Note:** Values are expressed as a number (percentage)

**Table 3: Postoperative AF in both groups.**

Postoperative AF	Group A, Mg (n=64)	Group B, Saline (n=64)	Total (n=128)	p-value chi-square
Present	12.50%	45.30%	28.90%	0.001
Absent	87.50%	54.70%	71.10%	

**Note:** Values are expressed as percentages

**Table 4: Postoperative AF in both groups (stratification with reference to age).**

Age Group (y)	Postoperative AF	Group A, Mg (n=64)	Group B, Saline (n=64)	Total (n=128)	p-value chi-square
50-60	Present	11.8%	64.9%	39.4%	0.001
	Absent	88.2%	35.1%	60.6%	
61-70	Present	4 13.3%	18.5%	15.8%	0.592
	Absent	26 86.7%	81.5%	84.2%	

**Note:** Values are expressed as numbers and percentages

**Table 5: Postoperative AF in both groups (stratification with reference to gender).**

Age Group (y)	Postoperative AF	Group A, Mg (n=64)	Group B, Saline (n=64)	Total (n=128)	p-value chi-square
50-60	Present	13.3%	46.6%	29.7%	0.001
	Absent	86.7%	53.4%	70.3%	
61-70	Present	0.0%	33.3%	20.0%	0.197
	Absent	100.0%	66.7%	80.0%	

**Note:** Values are expressed as numbers and percentages

## Discussion

Postoperative atrial fibrillation is the most common complication that develops after cardiovascular surgery and is associated with adverse outcomes [7,16-18]. Magnesium is an essential element in the body, which is required as a cofactor for over 300 enzymatic reactions and reduced levels of magnesium in the blood have been found related with an increased risk of AF, both in ambulatory setting and after cardiac surgeries [11]. Our study was aimed at determining role of prophylactic magnesium sulphate in preventing atrial fibrillation in subjects after coronary artery bypass surgery. In the present study, we enrolled a total of one hundred and twenty-eight (n=128) patients of both gender between age 50-70 year who were planned for coronary artery bypass surgery. Our results showed that postoperative AF was observed in 12.5% (n=8/64) patients in group A while it was observed in 45.3% (n=29/64) patients in group B (p=0.001). When stratified for age and gender magnesium sulphate was found more effective in preventing postoperative AF in younger males (p=0.001).

Magnesium is an essential element in the body, which is required as a cofactor for over 300 enzymatic reactions. Magnesium supplementation may reduce the incidence of postoperative ventricular arrhythmias [19]. In a comprehensive systematic review Shepherd, et al. assessed the clinical efficacy and cost-effectiveness of magnesium sulfate in comparison with placebo and sotalol for the prevention of postoperative AF in subjects who underwent CABG [20]. They selected 22 papers, which met their criteria of inclusion. All the selected trials reported comparison of magnesium sulfate with placebo or control. They did not find any trial comparing magnesium with sotalol. The pooled data of more than one thousand patients comprised of magnesium group showed 21% had developed postoperative AF compared with 30% patients in the placebo/control group. They also reported AF was less likely to develop when a longer duration of prophylaxis was used, and the earlier that prophylaxis is started. No clear relationship between dose and AF was observed, although a lower constant dose rate was associated with the lowest odds of AF.

In another meta-analysis including 10 trials, 1195 patients were identified that evaluated the use of magnesium for this purpose [21]. Ventricular arrhythmias occurred significantly less often in patients treated with magnesium compared to controls (6 vs. 13 percent; relative risk 0.52). There was no effect on length of hospital stay, frequency of perioperative MI or mortality.

Salaminia S, in another pooled analysis evaluated the effects of magnesium sulfate on the incidence of cardiac arrhythmias after cardiac revascularization [22]. They selected 22 studies for the

final analysis they reported that the cumulative rate of ventricular arrhythmia was lower in the group receiving magnesium sulfate than placebo (11.88% vs. 24.24%).

In another meta-analysis, Gu, et al. aimed to evaluate the effectiveness of IV magnesium in preventing postoperative AF after CABG [23]. They identified 7 randomized controlled trials comprising of more than 1000 patients. The pooled results showed that IV magnesium reduced the incidence of postoperative AF by 36% as compared to control group.

Our study results are also in alignment with other similar studies on the subject. In a study conducted at Japan, Naito Y assessed effect of magnesium infusion as a prophylactic therapy on postoperative AF [24]. They assigned 62 patients either to IV magnesium or placebo (saline) group. Their results showed that postoperative AF developed in 10.0% patients in magnesium group compared to 43.8% patients in the control group (p<0.01). Some authors have compared oral versus intravenous administration of magnesium sulfate as a prophylactic therapy for controlling postoperative AF. Jannati, et al. enrolled 82 patients and randomized them into two groups, one group received oral magnesium in a dose of 1600 mg by naso-gastric tube whereas the second group was administered with an IV dose of 2 g of magnesium during anesthesia induction phase [25]. Their results demonstrated no significant difference in the occurrence of postoperative AF among IV and oral groups (13.9% and 6.5% respectively, p>0.05). Naghipour, et al. studied the effects of prophylactic administration of magnesium sulfate in preventing postoperative arrhythmia after cardiac surgery [26]. They assigned 80 patients each to two groups, Group 1 (magnesium) and Group 2 (control). The development of arrhythmias was compared in both groups. Their results demonstrated that there was a significant difference in the incidence of arrhythmia between two groups (p=0.037). Magnesium remarkably reduced the incidence of all type of arrhythmia including postoperative AF after cardiac surgery. In a study conducted in 1996, Nurözler, et al. aimed to assess the efficacy of prophylactic use of magnesium sulfate in reducing the occurrence of postoperative AF in patients undergoing CABG [15]. Two groups of 25 patients each were included in study. In one group (Study), magnesium was administered in a dose of 200 mEq during first five days after the surgery, while in the other group (Placebo) normal saline was given. Their results demonstrated that 4% of patients in the MgSO<sub>4</sub> group experienced AF as compared to 20% of patients who experienced AF in the placebo group (p<0.05) [15]. In another study, Kohno, et al. administered magnesium sulfate for first three days in the postoperative period and assessed the effects on postoperative AF [27]. Their study was retrospective in nature and they studied

200 subjects who underwent CABG and divided them into two equal groups (treated with magnesium and untreated) of 100 cases each. They found that incidence of postoperative AF was significantly lower in patients who preoperatively treated with magnesium as compare to those who were untreated (16% vs. 35% respectively,  $p=0.002$ ). Toraman in their study assessed the effect of intermittent magnesium infusion on postoperative AF after cardiac surgery [14]. A total of 200 consecutive subjects were prospectively randomized to two groups, IV magnesium and saline group. Their results showed that postoperative AF developed in 2% of patients in the magnesium group compared to 21% subjects in the control group ( $p<0.001$ ).

There are some contrasting results reported as well. Kaplan, et al. investigated the efficacy of magnesium sulfate in preventing postoperative AF in subjects undergoing CABG [28]. They assigned 100 patients to each of the treatment (magnesium sulfate) and placebo (normal saline) groups. Their results showed that atrial fibrillation developed in 15 subjects from the treatment group and in 16 subjects from the control group, the difference was not significant. They further demonstrated that there was also no remarkable difference found between operations with cardiopulmonary bypass and beating-heart operations in terms of atrial fibrillation incidence. Wu, et al. in their pooled analysis selected five randomized controlled trials enrolling more than 1200 patients [29]. They compared efficacy of beta blockers combined with magnesium versus beta blockers alone for the prevention of postoperative AF. They found that the combination of magnesium and beta-blocker did not significantly decrease the incidence of postoperative AF after CABG versus beta-blocker alone.

### Conclusion

In summary, based on the present study results and comprehensive review of literature on the subject, the available evidence strongly suggests that prophylactic use of magnesium sulphate results in significantly lower incidence of postoperative AF after cardiac revascularization surgery. The therapy is safe with no reported adverse events. In the present study, we did not compare the length of hospital stay associated with administration of magnesium and control group. We suggest future research in this regard. Further areas of research that should be investigated are relationship between dose rate, dose and timing of initiation of therapy, duration of prophylaxis and subject characteristics, such as degree of risk for AF. Economic analysis comparing magnesium with other therapies for being in use for prevention is another area for future research.

In the present study, the incidence of postoperative AF was significantly lower in coronary artery bypass graft patients who received prophylactic magnesium sulphate as compared to placebo group. Magnesium sulphate was found more effective in preventing postoperative AF among younger males.

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