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M Hamid

*Aga Khan University*

RS Kamal

*Aga Khan University*

SA Sami

*Aga Khan University*

F Atiq

*Aga Khan University*

A Shafquat

*Aga Khan University*

*See next page for additional authors*

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**Authors**

M Hamid, RS Kamal, SA Sami, F Atiq, A Shafquat, HI Naqvi, and Fazal Hameed Khan

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## Original Article

# Effect of single dose magnesium on arrhythmias in patients undergoing coronary artery bypass surgery

Mohammad Hamid<sup>1</sup>, Rehana Shafi Kamal<sup>2</sup>, Shahid Ahmed Sami<sup>3</sup>, Farouk Atiq<sup>4</sup>, Azam Shafquat<sup>5</sup>, Hamid Iqbal Naqvi<sup>6</sup>, Fazal Hameed Khan<sup>7</sup>

Department of Anaesthesia<sup>1,2,6,7</sup>, Department of Cardiothoracic Surgery<sup>3</sup>, Department of Cardiology<sup>5</sup>, Aga Khan University, Karachi, Department of Anaesthesia<sup>4</sup>, FMH College of Medicine and Dentistry, Lahore.

## Abstract

**Objective:** To evaluate the safety and role of prophylactic administration of magnesium in preventing arrhythmias.

**Method:** This double blind randomized placebo controlled clinical trial was conducted at Aga Khan University Hospital on coronary artery bypass surgery patients. All patients were connected to holter monitor before induction of anaesthesia and this monitoring continued for 24 hours. Study drug containing either 2-grams of magnesium or normal saline was given after intubation. Levels of serum magnesium was checked preoperatively and then in ICU at 0, 6, 12, and 24 hours. Independent t-test and chi square test were used for analysis. Statistical significance was defined as p-value < 0.05.

**Results:** A total of 104 patients consented to participate in the study, 53 patients were randomly allocated in magnesium (Mg) group and 51 in placebo group. Two (3.77%) patients in magnesium group and five patients (9.8%) in placebo group developed atrial fibrillation. Incidence of ventricular and supraventricular tachycardia was also slightly higher in placebo. Mg level after arrival in CICU (Cardiac Intensive Care Unit) showed mean of 2.1 in magnesium group and 1.6 in placebo group (p = 0.6).

**Conclusion:** Low magnesium levels were noticed in the placebo group after cardiopulmonary bypass and although prophylactic administration of magnesium sulphate was relatively safe but significant benefit on prevention of arrhythmias could not be attained (JPMA 58:22;2008).

## Introduction

Arrhythmias are not uncommon after coronary artery bypass surgery (CABG). The reported incidence of supraventricular arrhythmia ranges from 40-47%<sup>1</sup>, whereas ventricular arrhythmias is 34%.<sup>1</sup> There are reports suggesting that magnesium reduces the incidence of ventricular arrhythmia<sup>1</sup> and supraventricular arrhythmias including atrial fibrillation.<sup>2,3</sup>

Atrial fibrillation (A. Fib), atrial flutter, multifocal atrial tachycardia, supraventricular tachycardia and non sustained ventricular tachycardia (VT) are different forms of arrhythmias but have the same clinical implications in early recovery phase of patients after cardiac surgery.

Potential complications of postoperative arrhythmia include thromboembolic events, haemodynamic compromise, increase length of stay<sup>4</sup> and cost of hospitalisation.<sup>3</sup>

Hypomagnesaemia has been observed after cardiac surgery, and administration of magnesium offers special potential benefit to a patient undergoing CABG. Potential advantages of magnesium include easy availability, less cost, decreased incidence and duration of A. Fib and VT, improved cardiac index and reduction in infarct size. In human and animal models, reperfusion injury due to the release of cross clamp can be attenuated by magnesium administration resulting in better systolic indices of contractility. Furthermore a reduction in infarct size and mortality has been reported.<sup>2</sup>

Despite all the advantages, routine administration of magnesium is still controversial in cardiac surgery patient due to variable results in previous studies<sup>1,4,5</sup> and its potential complications. The purpose of this study was to establish the safety of prophylactic administration of magnesium and to observe the reduction in the incidence of post-operative arrhythmias in patients undergoing coronary artery bypass surgery.

## Patients and Methods

This double blind, randomised placebo controlled clinical trial was undertaken after approval from ethics review committee at Aga Khan University Hospital Karachi. All patients underwent CABG surgery under general anaesthesia with the use of cardiopulmonary bypass, using a centrifugal pump, a membrane oxygenator and cold blood cardioplegia for myocardial protection. One hundred and four patients aged 35-75 years with normal renal function and in normal sinus rhythm were included. Exclusion criteria were, patients with acute or chronic renal failure, serum creatinine >2.0 mg/dl, use of intra aortic balloon pump, left ventricular ejection fraction < 30%, emergency surgery and patients on Group I and III anti arrhythmic drugs.

Parameters monitored included age, gender, height, weight, bypass time and cross clamp time. Preoperative cardiac risk factors were also noted including hypertension, diabetes mellitus, previous myocardial infarction and cerebrovascular accident.

After informed consent, patients were randomly allocated to one of the two study groups. Randomization was done by the hospital pharmacy, using computer software. Pharmacy was also responsible for the preparation of 3 cc syringes containing either two grams of Magnesium sulphate solution or normal saline. The syringes were labelled with a code number and the code stayed in the pharmacy department. Investigators were unaware of the contents of the syringes.

Preoperatively patients were followed for use of  $\beta$  Blockers and calcium channel blockers, presence of arrhythmias, history of myocardial infarction and left ventricular ejection fraction. All patients were premedicated with Lorazepam 2mg per oral (PO), an hour before shifting to the operating room. All the patients were then connected to a holter monitor (Philips zymad holter 2010+) for ECG monitoring. Standard monitoring, including 5-lead ECG, was applied during surgery. After placement of intravenous and arterial line, patients were induced with midazolam, fentanyl and pancuronium bromide. Central line or pulmonary artery catheter was inserted and anaesthesia was maintained using 0.2 to 2% isoflurane in air - oxygen

mixture.

After induction, all patients received the study drug, which was added to 100ml normal saline and administered intravenously over a period of 30 minutes. All patients underwent CABG with blood cardioplegia for myocardial protection after cross clamping. Body temperature was maintained at 28-30°C. Propofol infusion was started at the beginning of cardiopulmonary bypass and continued in the postoperative period.

Weaning from the pump was started upon completion of bypass surgery, complete rewarming to 37.5°C and serum potassium was kept between 4.5-5 mEq/L. Anaesthesia was maintained during post bypass period by using propofol 2mg/kg/hr, while vasodilators and / or inotropes infusion was used for haemodynamic stability.

All postoperative patients were ventilated with synchronized intermittent mandatory ventilation (SIMV) and pressure support, till extubation. Serum magnesium levels were monitored preoperatively, on shifting to ICU, and later at 6 hours, 12 hours and 24 hours postoperatively. Holter monitoring was continued in intraoperative and postoperative period for 24 hours and analysed for supra ventricular tachycardia (SVT), atrial fibrillation, flutter, non sustained VT and bradycardia. Use of defibrillator and pacemaker was also noted.

At the time of termination of the study, the code was broken and the patient data were assembled into placebo and magnesium groups.

Statistical procedures were done by using SPSS 13.0 software. Values are presented as mean  $\pm$  standard deviation or percent of patients. Proportion were compared with Chi square and Fisher's exact test. Student's t-test was used for Quantitative variables. Univariate analysis was used for correlation between A. fib and other variables.

## Results

A total of 104 patients consented to participate in the study, 53 patients were randomly allocated in magnesium group (Mg) and 51 in placebo group.

Both groups were similar in baseline characteristics including age, gender, ejection fraction, serum electrolytes as well as use of  $\beta$  blockers. Preoperative magnesium levels were comparable in both groups.

There was no significant difference in the previous history of myocardial infarction, cross clamp time and cardiopulmonary bypass time. There was a statistically significant difference in patient's magnesium levels, Mg group had a mean of 2.1 compared to the placebo group 1.2 (p-value <0.05). (Table 1).

**Table 1. Preoperative patient characteristics, Intraoperative details related to arrhythmias and postoperative serum electrolyte levels.**

Characteristics	Mg group			Placebo group			P-Value
	Mean	SD	%	Mean	SD	%	
Age (Years)	58.3	7.6		56.3	8.9		0.2
Weight (Kg)	76.6	12.8		74.4	13.3		0.4
Male sex (%)			98			86	0.02
Preop Left ventricular ejection fraction (%)	53.3	11.1		50.4	9.0		0.2
Heart Rate (per min.)	69.1	13.2		68.4	9.2		0.7
Medication	None	8	15.1	5	9.8		0.6
	B blocker	42	79.2	41	80.4		
Myocardial infarction	None	31	58.5	30	58.8		0.9
	<6 weeks	4	7.5	5	9.8		
	>6weeks	18	34.0	16	31.4		
Serum Mg ++ (mmo/L) *...	2.0	0.3		1.9	0.2		0.5
Intra operative factors							
CPB time (min)	90.0	29.5		95.4	24.3		0.3
Cross clamp time (min)	53.7	17.6		59.5	18.7		0.1
After release of cross clamp							
Defibrillation	Yes	26	49.1	22	43.1		0.544
Cardioversion	Yes	5	9.4	3	5.9		0.716
Serum Mg++ (mEq/L) in CICU at arrival	2.1	0.3		1.6	0.2		0.0
Serum Mg++ (mEq/L) in CICU at 6 hours	2.0	0.2		2.0	0.3		0.9
Serum Mg++ (mEq/L) in CICU at 12 hours *...	2.1	0.2		2.1	0.2		0.6
Serum Mg ++ (mEq/L) in CICU at 24 hours *...	2.1	0.2		2.0	0.2		0.9

\*: Missing values in Mg group. ...: Missing values in placebo group. CPB: Cardiopulmonary bypass

**Table 2. Incidence of arrhythmia in the intra and postoperative period - A univariate analysis.**

Characteristics	Magnesium		Placebo		P-Value
	Mean	SD	Mean	SD	
SVT after cross clamp release	0.09	0.40	0.18	0.62	0.43
SVT after bypass in OR	0.02	0.14	0.02	0.14	0.98
SVT in CICU	1.17	4.91	0.80	3.52	0.66
Atrial fibrillation after X clamp	0.06	0.30	0.12	0.47	0.44
Atrial fibrillation after Bypass in OR	0.00	0.00	0.02	0.14	0.32
Atrial fibrillation in CICU	0.00	0.00	0.06	0.42	0.32
VT after cross clamp release	1.04	1.63	0.78	0.99	0.34
VT after Bypass in OR	0.45	1.45	0.33	0.99	0.59
VT in CICU	0.58	1.59	0.14	0.53	0.06
Bradycardia	1.21	0.41	1.12	0.32	0.22
Supra ventricular ectopy	887.2	4818.5	352.8	1435.8	0.45
Bradycardia					
Yes	11	20.75%	06	11.76%	
No	42	79.24%	45	88.23%	0.21

SVT: Supra ventricular tachycardia; VT: Ventricular tachycardia; X clamp: Cross clamp release

Incidence of ventricular tachycardia was comparable in the operating room in both groups but higher in Mg group in the CICU period. Mean episodes of VT were also higher in Mg group in the CICU (p-value 0.06). (Table 2)

Eleven (20.75%) patients in the magnesium group were diagnosed with bradycardia in the first 24 hours after bypass while in placebo group only 6 (11.76%) patients developed bradycardia (p=0.22)(Table 2). Pacemaker

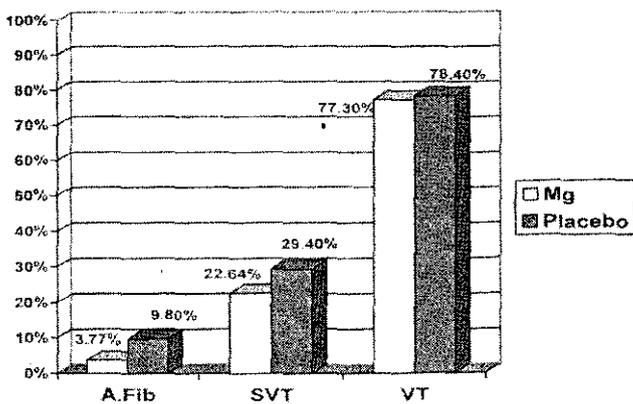


Figure 1: Evaluation of arrhythmia in Magnesium and placebo groups

requirement was also slightly higher in magnesium group (4 vs 3 patients).

Seven patients developed A. Fib in both the groups. Out of these 4 were female and 3 were males. A. Fib developed soon after cross clamp release in 5 patients while one patient developed A. Fib in CICU and one in the OR after bypass period. Mean age of the patients who developed A. Fib was  $58 \pm 10.34$  years.

Only two (3.77%) patients in the magnesium group acquire new onset A. Fib in the first 24 hours (Figure 1). Both of these patients developed A. Fib soon after the release of cross clamp and their Mg levels remained within normal limit during the study period. Five patients (9.8%) in placebo group developed A. Fib with the mean Mg levels of 1.42 mg/dl on arrival in CICU.

## Discussion

Magnesium plays an important role in cardiovascular physiology. It is an essential co-factor in maintaining the intracellular electrolyte balance and membrane potential by acting on Na-K-ATP channels. It also acts like a natural calcium antagonist and its deficiency decreases the threshold for arrhythmia.<sup>2</sup>

Hypomagnesaemia is commonly observed after cardiac surgery which may be related to haemodilution, intra operative and postoperative cellular depletion, intra operative diuretic use, secondary hyper aldosteronism, high levels of epinephrine, increased anabolic activity, extreme stress and increased urinary loss. MgSO<sub>4</sub> reaches its minimum level on first postop day (1<sup>st</sup> POD) and returns to its preop value on 4<sup>th</sup> POD.<sup>6</sup> In this study, significantly low Mg levels in the placebo groups after CABG were also noticed. These low levels of Mg are considered to be responsible for arrhythmias seen after CABG.

Atrial fibrillation is the most commonly observed arrhythmia after cardiac surgery, which might lead to haemodynamic disorders, thromboembolism and increased ICU and hospital stay. Exact cause for A. fib is unknown but aortic cross clamping and inflammatory response during bypass is considered to be a factor in the development of A. Fib. Contrary to this, recent articles mentioned the same incidence of A. Fib in off pump CABG.<sup>7</sup> Most important contributing factor is considered to be the age of the patient due to age related structural changes in the atrium<sup>8</sup>, which is true in the present study as well. Atrial ischaemia due to possible kinking of grafts or poor myocardial protection and rapid re-warming might be other reasons.

Several prophylactic strategies have been used for A. Fib which includes use of magnesium as a single dose, continuous Mg infusion for several days, use of  $\beta$  blockers<sup>9</sup>, amiodarone<sup>10</sup> and diltiazem<sup>11</sup>, but all these drugs have limited success. A meta analysis by Shiga et al. concluded that prophylactic magnesium reduces the incidence of AF after CABG about 23%.<sup>12</sup> Use of prophylactic and continuous infusion is being used in several centres. Using magnesium greater than 4 grams has been associated with occurrence of bradycardia<sup>13</sup> requiring pacing for 24 hours and mild hypotension which is responsive to fluid administration.

In the present study, we gave single infusion of 2 gram of magnesium only in Mg group. In the postoperative period, Mg levels were kept normal in both groups by regular checking of Mg level and boluses accordingly. The incidence of atrial fibrillation in this study treatment and placebo group did not reach statistical significance while other studies have shown higher incidence. The reason might be that these patients were monitored for only 24 hours while in other studies monitoring was continued for four days or more. Stephan et al have monitored these patients for five days and noticed highest incidence of atrial fibrillation on 1<sup>st</sup> postop day<sup>14</sup> and significant benefit of Mg was also noticed on first postop day. Mehmet et al in their study mentioned that more than 75% of patients develop A. Fib on 2<sup>nd</sup> postop day.<sup>4</sup> Another reason for lower incidence in the current study may be that magnesium was replaced in both groups by supplementation in CICU to keep the serum levels within normal limits.

A review of literature showed different dosages and duration of Mg in each study. In some studies infusion was continued for 3 days<sup>15</sup> while in others Mg level was checked regularly and supplemental Mg was given in case of hypomagnesaemia. In the present study, higher Mg level is associated with higher incidence of atrial fibrillation.<sup>16</sup> In our study none of the patients showed higher Mg level, which exceeds physiological range.

Several studies have shown that serum Mg level whether total or ionized, is not a reliable indicator of total body stores of Mg.<sup>14</sup> Low myocardial Mg content may be an indicator of arrhythmia. The value of serum Mg remains questionable and further studies are needed to show the relevance of serum Mg and arrhythmia.

Most of the studies evaluated relationship between Mg and atrial fibrillation in CABG patients but the role of Mg in other arrhythmias like VT and sinus bradycardia has to be evaluated. Hans et al noticed the same incidence of VT in both Mg and non Mg groups.<sup>8</sup> Stephaen et al found a higher incidence of VT in control group on 5th POD.<sup>14</sup> Interestingly the current study found that VT was higher in Mg group in the CICU, although Mg levels were kept normal. The overall incidence of postoperative arrhythmias with Mg supplementation did not reach statistical significance.

The limitations of this study were a small number of patients, and previous history of atrial fibrillation was not considered in this study.

Timing of prophylactic Mg might be important. In the present study, Mg was given after induction and before bypass surgery. In the previous studies prophylactic Mg infusion was given in the postop period despite of normal Mg levels and was associated with lower incidence of atrial fibrillation (whether levels were normal or low).<sup>17</sup>

England et al noticed decreased incidence of ventricular arrhythmias when 2 gm prophylactic Mg was given intraoperatively while it had no effect on supraventricular arrhythmias.<sup>1</sup> In the present study, Mg group had higher incidence of ventricular arrhythmias and bradycardia, while supraventricular arrhythmias were low. Most of the ventricular arrhythmias occurred after release of cross clamp, which was not considered in England study and they included only ICU patients.

Some studies were done strictly after stopping  $\beta$ -blockers and Calcium channel blockers<sup>17</sup> or investigators chose those patients who were not on these drugs, while in other studies these drugs were continued. It has been seen that combination of  $\beta$ -blockers with Mg has no additive effect than their use alone. It is also revealed that incidence of postop A. Fib is increased in patients in whom  $\beta$ -blockers were withheld preoperatively, presumably due to enhanced action of catecholamine. The  $\beta$ -blockers presumably prevent the loss of intracellular Mg.<sup>18</sup>

### Conclusion

The overall incidence of arrhythmia after CABG surgery with single dose magnesium supplement did not reach statistical significance as in some of the other studies. Low magnesium sulphate levels were found in the placebo

group in this study as well, but a significant benefit for prevention of arrhythmia could not be attained with administration of magnesium sulphate.

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