Original Article

Significance of serum magnesium levels in reference to acute myocardial infarction and role of intravenous magnesium therapy in prevention of cardiac arrhythmias following myocardial infarction

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Access this article online

Website: www.ijmedph.org

DOI: 10.4103/2230-8598.118969

Quick response code:

Abstract

Introduction: The role of magnesium in treating arrhythmias due to acute myocardial infarction (AMI) has been controversial. Most of the studies have reported a significant reduction in the mortality and frequency of arrhythmias in patients with AMI, who received magnesium therapy, in comparison with control with AMI, who did not receive magnesium treatment. We, therefore, decided that we would evaluate the effect of intravenous magnesium supplement therapy in patients admitted for acute myocardial infarction and if this would be helpful in reducing the morbidity and mortality in patients. **Materials and Methods:** The study was carried out as a prospective randomized controlled trial of magnesium therapy in acute myocardial infarction. Hundred patients with acute myocardial infarction were randomly divided into two groups of 50 patients each, one for trial and other for placebo therapy. Control group consisted of 20 healthy volunteers of the same age group. All of the 100 patients included in the study had reported within 12 hours of the onset of chest pain. Blood samples for estimation of serum magnesium were taken on admission and on days 2 and 5. **Results:** The mean age in the Group I and II were 59.52 years ± 15.03 and 59.14 years ± 13.41, respectively. Serum magnesium level on admission was higher in the healthy controls than in the patients of acute myocardial infarction ($P < 0.0001$). Fourteen percent patients of Group I had conduction disturbance, whereas 4% patients of Group II had conduction disturbances. Fifty percent patients of Group I developed heart failure, whereas only 30% patients of Group II developed this complication ($P < 0.005$). Incidence of cardiac arrhythmias, heart failure, and hospital mortality were significantly lower in magnesium treated group. Mortality as well as morbidity was very less in the magnesium treated group of patients as compared to placebo treated patients. **Conclusions:** Intravenous magnesium is a safe and effective method of reducing the frequency of arrhythmias and mortality following the acute myocardial infarction. Magnesium therapy reduces the incidence of arrhythmias and mortality even in the absence of demonstrable magnesium deficiency.

Key words: Cardiac arrhythmias, intravenous magnesium, myocardial infarction, serum magnesium

INTRODUCTION

In recent years, the use of intravenous (I.V.) magnesium can be considered as a major breakthrough in the treatment of myocardial infarction. It is found that in patients of myocardial infarction, who became critical and who died suddenly, had low serum magnesium levels.[1] Similarly, life-threatening arrhythmias were found to be more frequent in patients with acute myocardial infarction with low serum magnesium levels.[2,3] It was also shown that the magnesium content of the infracted/ischemic myocardium was much lower (about 40-50%) as compared to that of normal heart muscle. It has been shown that magnesium depletion modifies coronary blood flow, blood clotting, and atherogenesis.[4] Magnesium lowers systemic vascular resistance, dilate coronary arteries, decrease platelet aggregation, improve

myocardial metabolism, protect against catecholamine-induced myocardial necrosis, and stabilize cell membranes. It is also cheap and easy to handle. Thus, it would appear to be an excellent contender for a place in the routine treatment of myocardial infarction, but it has not achieved this status yet. Therefore, the use of magnesium in myocardial infarction is a worthy topic of serious consideration. We, therefore, decided that we would evaluate the effect of I.V. magnesium supplement therapy in patients admitted for acute myocardial infarction and if this would be helpful in reducing the morbidity and mortality in patients.

MATERIALS AND METHODS

The study was carried out as a prospective randomized controlled trial of magnesium therapy in acute myocardial infarction, admitted in the medical intensive care unit of Krishna Hospital and Medical Research Centre. This study was approved by the ethical committee and an informed consent was taken from all the patients included in our study.

100 patients with acute myocardial infarction (AMI) were, at random, divided into two groups of 50 patients each, one for trial and other for placebo therapy. Control group consisted of 20 healthy volunteers of the same age group. All of the 100 patients included in the study had reported within 12 hours of the onset of chest pain.

Group-I: 50 patients included in the placebo group received 1,000 ml of normal saline in the first 24 hours and 1,000 ml in the second 24 hours period.

Group-II: The 50 patients in this group received magnesium infusion. During the 1st 24 hours, all 50 patients received a bolus of 2 g over 15 minutes followed by an infusion of 18 g over 24 hours.

Group-III: The control group included 20 healthy subjects in the age group of 40-65 years. Serum magnesium levels of these controls were determined on one occasion only.

Reagents consisted of Calmagite 100 μmol/L, ethyleneglycotetraacetic acid (EGTA) 1.09 mmol/L. The Calmagite reacts with the Mg present in the sample in the alkaline medium resulting in the formation of a coloured complex that can be measured by spectrophotometry. The concentration of Mg in the sample is directly proportional to the color of the complex. EGTA is included in the reagent to remove calcium interference. Normal value of Mg is 0.66-1.07 mmol/L or 1.6-2.6 mg/dl. Apart from $MgSO_4$, patients were treated with routine treatment of AMI and its complication as and when the need arose. Patients received analgesics, routine sedatives, vasodilators, thrombolytics, and were on anti-platelet and anticoagulant therapy during their hospital stay. During the first 7 days, all the patients of Group I and Group II were constantly monitored electrocardiographically. All arrhythmias and/or conduction abnormalities were recorded. Mortality and the causes of death were noted. Patients were followed for 4 weeks.

The data was tabulated and statistically evaluated by the student's '*t*' test and Chi-square test.

RESULTS

The mean age in the Group I and II were 59.52 years ± 15.03 and 59.14 years ± 13.41, respectively. There was no significant difference in sex distribution of patients in Group I and Group II [Figure 1].

Serum magnesium level on admission was higher in the healthy controls than in the patients of acute myocardial infarction [Table 1]. The difference was statistically significant ($P < 0.0001$).

Our study reveals a statistically significant decrease in the incidence of arrhythmias in Group II [4/50 (8%)]. The pattern of arrhythmias seen was as follows:

Group-I: Supraventricular arrhythmias seen in four patients and ventricular arrhythmias seen in 13 patients

Group-II: Supraventricular arrhythmias seen in one patient and ventricular arrhythmias seen in three patients.

Seven out of 50 (14%) patients of Group I had conduction disturbance, whereas two out of 50 (4%) patients of Group II had conduction disturbances. However, 25 out of 50 (50%) patients of Group I developed heart failure, whereas only 15 out of 50 (30%) patients of Group II developed this complication. The difference was statistically significant ($P < 0.005$) [Figure 2].

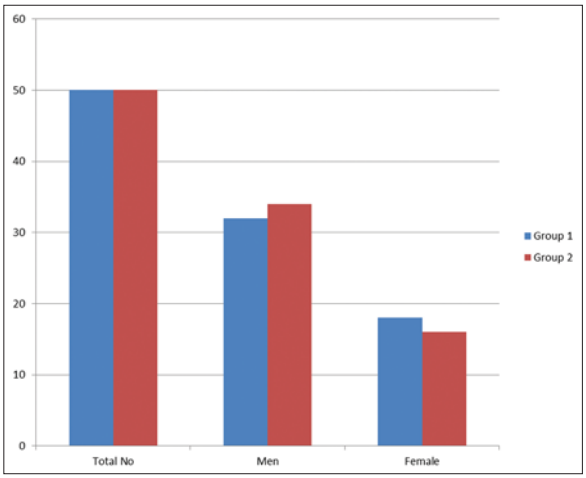

Figure 1: Chart showing no difference in the age and sex distribution of the patients in Group I and Group II

Table 1: The higher serum magnesium level on admission (mean±S.D.) (in mg/dl) in the healthy controls as compared to that in the patients of acute myocardial infarction (*P*<0.0001)

Group	No. of patients	Serum magnesium levels on admission
Healthy controls	*n*=20	2.2±0.20
Patients of AMI	*n*=100	1.4±0.27

AMI=Acute myocardial infarction, S.D=Standard deviation

Hospital mortality in the 4-week-period after myocardial infarction was 10 out of 50 (20%) in Group I and three out of 50 (6%) in Group II which was statistically significant ($P < 0.05$) [Figure 3]. The causes of death comprised of cardiogenic shock, arrhythmias, pulmonary edema, pulmonary embolism, reinfarction, and myocardial rupture etc., [Table 2].

Table 2 also shows the clinical data of the 10 patients who expired in Group I of which the cause of death in six patients was cardiogenic shock, two patients died of pulmonary edema, one patient died of ventricular tachycardia, and one patient died of ventricular fibrillation. In Group II, in all three patients, the cause of death was cardiogenic shock.

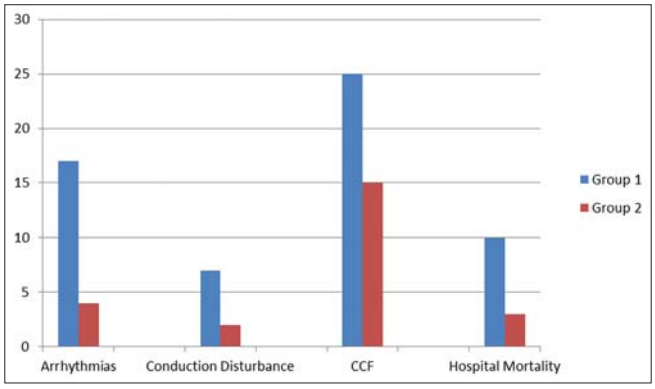

Figure 2: Incidence of arrhythmias, heart failure, and in-hospital mortality is significantly lower in Group II as compared to Group I

As expected we found an increase in the serial magnesium concentration in the sample taken from patients of group II on day 2 and 5, which gradually decreased after cessation of magnesium sulfate infusion. Above levels of serum magnesium between the two groups were statistically significant ($P < 0.0001$). There was no statistical difference in serum magnesium levels between survivors and non survivors in both the groups [Table 3].

DISCUSSION

Rasmussen *et al.*,[5] came to similar conclusions where the complications in patients who received magnesium therapy was

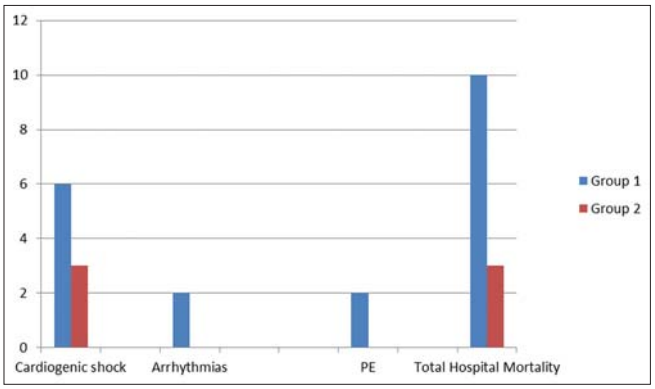

Figure 3: Chart showing the reduced incidence of morbidity and mortality in the magnesium-treated group of patients as compared to placebo-treated patients

Table 2: Clinical data of patients who expired following the acute myocardial infarction

No.	Age in years	Sex	Day on which patient expired	Ck-mb on admission	Sr. Mg levels			Cause of death
					Day 1	Day 2	Day 3	
Group 1								
1	58	F	8th day	32	10.2	10.2	10.2	Cardiogenic shock
2	60	F	15th day	100	10.2	10.2	10.3	Pulmonary oedema
3	62	M	12 hrs	215	00.9	-	-	Pulmonary oedema
4	70	F	24 hrs	90	1	-	-	Ventricular fibrillation
5	80	F	5th day	78	10.6	10.6	10.6	Cardiogenic shock
6	55	M	24hrs	106	10.2	-	-	Cardiogenic shock
7	75	M	3th day	90	00.8	1	-	Cardiogenic shock
8	71	M	6hrs	58	00.9	-	-	Ventricular tachycardia
9	59	M	12hrs	92	10.204	-	-	Cardiogenic shock
10	80	M	24hrs	40	1	-	-	Cardiogenic shock
Group 2								
1	60	M	6th day	156	1	10.5	10.5	Cardiogenic shock
2	70	M	6th day	30	1	10.2	10.1	Cardiogenic shock
3	60	M	12 hrs	122	00.7	-	-	Cardiogenic shock

Table 3: Mean serum magnesium levels in all patients of acute myocardial infarction was significantly higher in Group II patients on day 2 and 5 (*P<0.0001) (****P<0.0003)**

Day	Group 1			Group 2		
	All patients	Survivors	Non survivors	All patients	Survivors	Nonsurvivors
1	1.22±0.26	1.26±0.29	1.10±0.22	1.232±0.269	1.248±0.239	0.989±0.261
2	1.30±0.28	1.30±0.28	1.27±0.24	1.748***±0.284	1.750±0.287	1.701±0.284
5	1.43±0.26	1.40±0.29	1.39±0.24	1.623****±0.259	1.622±0.263	1.662±0.201

linked with a fall in the number of arrhythmias which needed treatment during the first week in hospital. Magnesium therapy inhibits the post-infarctional hypomagnesemia.

Iseri *et al.*,[6] in their study treated multifocal atrial tachycardias successfully with parenteral magnesium and potassium. Magnesium administered together with potassium, stabilizes the ionic balance of the cells and thus prevents spontaneous ectopics.

Lezek Ceremuzynski *et al.*,[7] proved that life threatening arrhythmias in AMI are prevented by I.V. magnesium sulfate. This was in agreement with the findings of Rasmussen *et al.,* and Smith *et al.*,[8] Schechter *et al.*,[9] and this encourages implementation of magnesium treatment into clinical practice.

Ising *et al.*,[10] performed the following study. Seven 24 hours electrocardiograph (ECG) recordings and blood samples were taken within 3 weeks in 42 patients. Ca^{++}, K^{+}, and Mg^{++} concentrations in serum, and K^{+} and Mg^{++} in the erythrocytes, were determined by atomic absorption spectroscopy. One half of the patients were infused with 81 mmol/day as $MgSO_4$ for 3 days. In patients who exhibited intense electrolytic alterations 10-20 days after AMI, there was a significantly higher rate in the frequency of couplets and/or tachycardia in the 2-20 days period after AMI. In patients infused with $MgSO_4$, the fluctuation in serum electrolytes and the rate of arrhythmias were significantly reduced.

Kent L. Woods *et al.* proved in "Leicester Intravenous magnesium intervention trials", the efficacy of I.V. magnesium in reducing the mortality in patients of acute myocardial infarction. They conducted a double blind placebo controlled study in 2,316 patients who received either I.V. magnesium sulfate or physiological saline. The primary outcome measure was the 28 days mortality which was ascertained in 99.3% of patients. The groups were well balanced for prognostic factors. By intention to treat, mortality from all causes was 7.8% in the magnesium group and 10.3% in the placebo group, a relative reduction of 2-4%. Koon K. Teo[11] conducted a study of the seven randomized trials conducted by Morton *et al.*, Rasmussen *et al.*, Smith *et al.*, Abraham *et al.*, Feldstedt *et al.*, Schechter *et al.*, Ceremuzynski *et al.* Considering the seven trials collectively, it was proved that there were 25 (3.8%) deaths among 657 patients allocated to receive magnesium and 53 (8.2%) deaths among 644 patients allocated control during the 4-week-period. This represents a 55% reduction in the odds of death ($P < 0.001$). A number of reports particularly from European countries have shown subjective and objective improvements in patients with ischemic heart disease treated with magnesium salts.

The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) included 2,316 patients, who were randomized to receive I.V. magnesium sulfate or matching placebo. Patients received placebo or magnesium for 5 min before initiation of thrombolytic therapy, followed by an infusion for the next 24 h. It concluded that there was 24% reduction in 28-day mortality, a 25% reduced incidence of left ventricular failure, and an improvement in long-term survival in terms of reduction of long-term mortality from ischemic heart disease (average follow-up period of 2.7 years).[12,13]

Magnesium treatment may reduce the incidence of ventricular fibrillation, ventricular tachycardia, severe arrhythmia needing treatment or Lown 2-5, but it may increase the incidence of profound hypotension, bradycardia, and flushing.[14]

Magnesium probably functions as an inorganic calcium channel blocker and there are several plausible mechanisms for a beneficial effect in acute myocardial infarction (Woods 1991). Research on animals and humans has shown that magnesium is a peripheral (Mroczek 1977) and coronary vasodilator (Vigorito 1991). It can increase the threshold for depolarization of cardiac myocytes, thereby reducing the likelihood of cardiac arrhythmia caused by injury currents near ischemic or infarcted tissue (Haverkamp 1988; Tzivoni 1990). Magnesium decreases reperfusion injury by preventing or lessening mitochondrial calcium overload in ischemic myocardial cells during the first few minutes of reperfusion (Ferrari 1986) (namely, the restoration of blood flow to an organ or tissue) and preserving intracellular Adenosine Triphosphate (ATP) and creatine phosphate reserves (Borchgrevink 1989), and inhibits platelet function, perhaps indirectly by release of prostacyclin (Watson 1986). Thus, magnesium-infusion started early after the onset of myocardial ischemia might limit infarct size, prevent serious arrhythmias, and reduce mortality.

Time is critical in management of AMI. If thrombolytic treatment is not given, spontaneous reperfusion occurs in at least a third of patients during the first 12-24 hours after AMI (Woods 1995). The benefits from supplemental magnesium administration may be lost when there is a delay of more than 15-45 minutes after the onset of reperfusion (Antman 1995b). Careful laboratory studies, conducted since the Fourth International Study of Infarct Survival (ISIS-4) findings, have continued to explore the role of magnesium in reducing myocardial damage around the time of reperfusion, and have demonstrated its critical nature, with any benefit lost if treatment is delayed (Christensen 1995; Herzog 1995; Ravn 1999).

CONCLUSIONS

Serum magnesium levels on admission were significantly low in patients of acute myocardial infarction as compared with healthy controls. Hypomagnesemia is often associated with acute myocardial infarction. Our study proves that exogenously administered magnesium to patients of acute myocardial infarction in the immediate post infarctional period (<12 hours) has a cardio protective action, thus reducing the incidence of arrhythmias and the mortality during the first 4 weeks after myocardial infarction.

Magnesium therapy reduces the incidence of arrhythmias and mortality even in the absence of demonstrable magnesium deficiency. The present study is a good enough reason to include I.V. magnesium sulfate as an add-on prophylactic treatment in the acute coronary syndrome's management protocol.

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How to cite this article: Mhaskar DM, Mahajan SK, Pawar KC. Significance of serum magnesium levels in reference to acute myocardial infarction and role of intravenous magnesium therapy in prevention of cardiac arrhythmias following myocardial infarction. Int J Med Public Health 2013;3:187-91.

Source of Support: Nil, **Conflict of Interest:** None declared.