The Systemic Review of Magnesium Sulfate Infusion in Patients with Acute Myocardial Infarction

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ABSTRACT

Despite improvements in the outcome of patients with acute myocardial infarction during the last three decades, room for improvement exists in the elderly patients and in patients who are not candidates for thrombolysis. Statistical analysis of randomized trials of magnesium in myocardial infarction reveals a gradient of response. When higher risk patients were enrolled, a greater benefit of magnesium was observed; progressively smaller benefits of magnesium occur as control group mortality approached 7%, at which point no benefit was detected. Although the ISIS-4 study enrolled more than 58,000 patients, no reduction in mortality was seen, probably as a result of low control group mortality and relatively late administration of magnesium. Because the potential benefits of magnesium in myocardial infarction remains an open question, additional trials are needed before this inexpensive and early-administered therapy is prematurely cast aside.

INTRODUCTION

Heart disease is the most prevalent disease in society today. Its economic effects are staggering, thus the need to find alternative, cost-effective alternatives to therapy.

Magnesium is the fourth most abundant cation in the body and the second most prevalent intracellular cation.

The beneficial effects of magnesium sulfate in patients with acute myocardial infarction, based on animal studies, are said to be due to the reduction of infarct size and prevention of reperfusion injury. Magnesium infusion leads to a reduction of toxic calcium overload in myocardial mitochondria, resulting in coronary vasodilatation, reduction of occurrence of arrhythmia and reduction of catecholamine secretion from the adrenal gland.[3,8]

The objectives of this paper are to review the different studies available on the possible effects of magnesium sulfate infusion on the mortality of patients with acute myocardial infarction and the reason why these studies yielded conflicting results, thus preventing us to give final judgment on this drug.

METHOD

Medline search was used to gather all literature regarding the usage of magnesium in myocardial infarction. All trials that were randomized and placebo controlled were included in this study. We found eleven trials that fit into the inclusion criteria. Reduction of fatal mortality will be used as the end point for this review.

RESULTS

Eight studies were done in the pre-thrombolytic era whereas the last 2 studies, LIMIT 2 (Leicester Intravenous Magnesium Intervention)[10] and ISIS IV (International Study of Infarct Survival)[4] were done in the thrombolytic era (table 1). Their clinical characteristics were not significantly different from the placebo-controlled group.

Meta-analysis of all the studies done until the publication of LIMIT-2 showed a beneficial effect of magnesium infusion in AMI. In LIMIT-2, the mortality rate among the patients who were given magnesium was 7.8%, whereas mortality in the control group was 10.3% (p=0.04), a 24% relative reduction of mortality. In 1995, a mega-trial of more than 50,000 patients was published. This trial, named ISIS-IV, contradicted all previous trials on magnesium in AMI because it did not show any ben-

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Table 1. Eight Studies in The Pre-Thrombolytic Era

Study	No. Patients	Treatment	Results
Morton et al	40	Mg sulfate 9 mg/kg over 36 hrs	Decrease in infarction size in Mg-treated patients p<0.05
	36	placebo	
Ramussen et al	56	Mg chloride 15.5 g over 48 hrs	1 month mortality: Mg7%, placebo19% p=0.045
	74	placebo	
Smith et al	93	Mg sulfate 0.67/hr for 24h	Mortality Odds ratio Mg:Placebo 28 days:0.64 1 year:0.77
	92	Placebo	
Braham et al	48	Mg SO4 2.4g OD for 3d IV	No difference in mortality
	46	placebo	
Schechter et al	50	MgSO4 22g over 48 hours	Mortality Mg: 2% Placebo17% p=0.01
	53	placebo	
Hod et al	78	MgSO4 22g over 48h	Mortality Mg: 2.5% Placebo:17% p=0.01
	81	placebo	
LIMIT-2	1159	MgSO4 2g over 5 min then 16g over 24hr	Mortality Mg:7.8% Placebo:10.3% p=0.04
	1157	placebo	
ISIS-4	29011	8mmol MgSO4 over 15 min then	Mortality Mg 7.64% Placebo7.24% 2p=0.04 (NS)
	29039	72 mmol over 24h placebo	

eficial effect of magnesium infusion in AMI. The mortality rate among patients who were given magnesium was higher than the control group (7.64% vs 7.24%). There was a 6% proportional increase in the odds of death if the patients were given magnesium infusion. This slight increase in mortality among patients who were given magnesium was not statistically significant (2p=0.07). However, it was done in a very large study population so ISIS-IV was thought to be more reflective of the true effect of magnesium infusion in AMI patients. These controversies on the effect of magnesium infusion in AMI patients have persisted until the present time. In the subsequent discussion, we shall discuss the different protocols involved in LIMIT-2 and ISIS-IV, which might be responsible for their conflicting results.

DISCUSSION

Meta-analysis of the studies up to LIMIT 2 showed beneficial effects of magnesium infusion in patients with AMI (figure 1). Its beneficial effect was due to the reduction of the incidence of heart failure.[8]

However, ISIS-4, a mega trial with a population of more than 50,000 patients, negated the beneficial effects of magnesium sulfate. It was even associated with an increase in mortality rate, although not statistically significant (figure 2). Because of this megatrial, the American college of Cardiology classified magnesium as class 2b in the AMI guideline, which meant that magnesium is potentially harmful to patients with AMI. However, a closer look on all of these studies reveal four clinically important dissimilarities among the protocols used in the nine small studies, LIMIT-2, and ISIS-4. The following dissimilarities affected the comparative mortality rates:

1. Time of initiation of magnesium treatment after AMI and thrombolytic therapy
2. Dosage of magnesium in the first 24 hours after AMI
3. Time elapsed between onset of AMI and onset of magnesium infusion

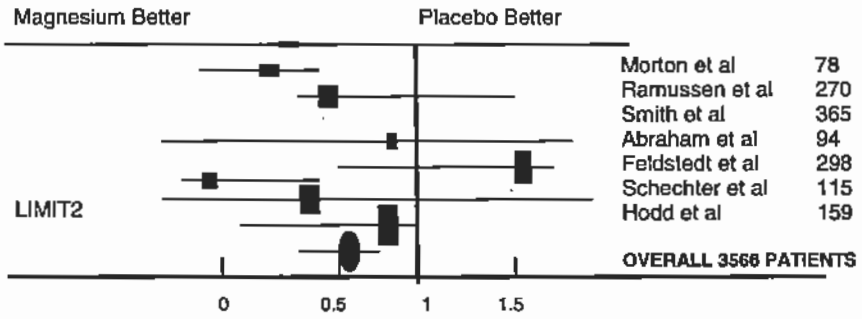

Figure 1. Overview of Mortality of Magnesium Sulfate Infusion in MI

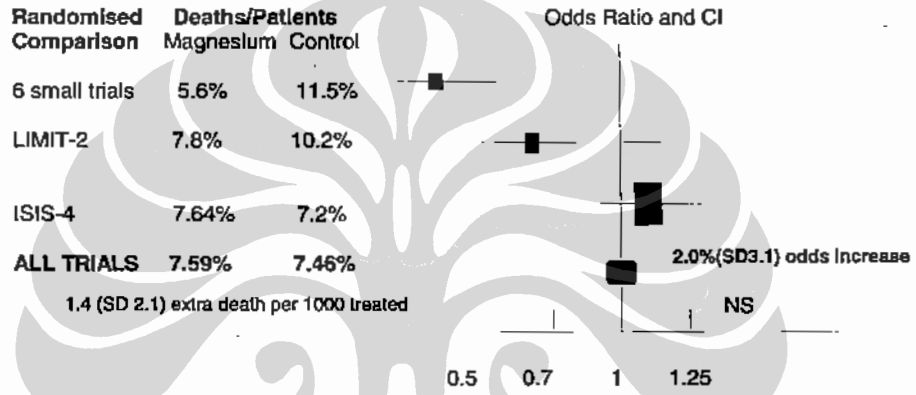

Figure 2. Overview of Effects on Short-term Mortality of Magnesium Infusion in Acute Myocardial Infarction

4. Differences in patients' risks in the control and treatment groups.[1,2,3]

Although restoration of blood flow in the infarct-related artery is critical for minimizing necrosis and salvaging the myocardium, it comes at the cost of possible reperfusion injury.[7] Experimental and clinical investigations have shown that administration of magnesium improves myocardial energy production, inhibits calcium cellular overload, stabilizes injured cell membranes, diminishes free-radical induced damage, and thus preventing reperfusion injury. Inhibition of calcium influx, which is responsible for reperfusion injury, by administration of magnesium at the time of reperfusion minimizes myocardial dysfunction.

Nevertheless, in order for magnesium to be beneficial, the magnesium blood level ought to be in optimal level no later than 45 minutes after the occurrence of reperfusion. Several studies on animal models show that infarct size is reduced when magnesium is administered before coronary occlusion, and no later than 45 minutes after reperfusion.[2] These suggest that the time window for administration of magnesium is relatively short (probably less than 1 hour) in patients undergoing pharmacologic or catheter-induced reperfusion. We can conclude that magnesium must be provided as soon as possible after acute myocardial infarction and before reperfusion.

In LIMIT-2 and the other smaller studies, magnesium was administered as soon as possible after the onset of symptoms, before or without subsequent thrombolysis, therefore magnesium blood levels must have been optimal to prevent reperfusion injury. Woods et al attributed the 24% reduction in the 28-day mortality in LIMIT-2 to its prompt administration before thrombolysis. However, in ISIS-4, half of the patient population was given magnesium infusion 2 hours after undergoing thrombolysis, and about one forth of the patients were even given magnesium infusion 2 to 6 hours after the thrombolysis. By delaying the administration of magnesium infusion and by giving it sometime after thrombolysis, the protective effect of prompt magnesium adminstration could

have been reduced or eliminated. On the other hand, the results of ISIS-4 also suggest that magnesium infusion does not seem to be beneficial if the patient has been given thrombolysis. This groups experienced an increased mortality from heart failure and cardiogenic shock. In the ISIS-4, wherein 70% of the population received thrombolysis, intravenous magnesium was associated with small but significant increases in heart failure, cardiogenic shock, and death.

The amounts of magnesium infused over a 24-hour period may account for differences in mortality after infusion of magnesium in AMI patients. Galloe and Graudal[13]suggest that the optimal total amount of magnesium in the first 24 hours should be 55 mM to 65 mM, and that doses >75 mM may increase mortality. In LIMIT-2, the 24-hour dosage was 73 mM; 24-hour post infusion serum level average was 1.55 mM/l. In ISIS-4, 80 mM was given over 24 hours. The excessive doses used in ISIS-4 were later on followed by higher incidence of heart block, heart failure and mortality due to hypermagnesemia among patients who were given magnesium infusion. Hypermagnesemia, by inducing generalized vasodilatation, can cause profound hypotension, which could increase the risk of cardiogenic shock and extension of myocardial necrosis.[5]

Meta-regression analysis of all the available trials through LIMIT-2 is performed, as shown in figure 3. The results of the meta-regression analysis indicate a progressive decrease in the estimated beneficial treatment effect of magnesium as the control group mortality rate declines.[1]

The curvilinear relationship crosses the line of an O.R.=1.0 at a control group mortality rate about 7%. Thus a clinical trial with a control group mortality of 7% or less would be anticipated to show a null effect or no beneficial effect of magnesium on the mortality rate in patients with acute myocardial infarction or in other word the higher the mortality rate in the control group, the beneficial effect of magnesium will be more prominent. The higher control mortality rate in LIMIT-2 than in ISIS-4 may reflect the fact that the fewer LIMIT-2 controls underwent thrombolysis or received anti-platelet therapy (Table 2). The greater than 50% reduction in mortality in magnesium-treated patients versus controls in the small studies reflects high mortality rates in controls, possibly because anti-platelet and fibrinolytic therapy was not customary in the 1980's, when the small studies were performed. Thus, the late administration of magnesium (probably several hours after reperfusion in majority of patients) and the high rate of use of other mortality-reducing therapies such as thrombolytics and aspirin might explain the absence of therapeutic benefits of magnesium infusion in ISIS-4 study. On the other hand above findings also suggests that patients who have a higher risk of mortality from AMI will be the ones who will gain benefit from magnesium infusion compared to patients who have received thrombolytic and antiplatelet therapy, and thus have a lower risk of mortality from AMI.

Table 2. Comparison of Trials: LIMIT-2 and ISIS-4

	LIMIT-2	ISIS-4
Total number of randomized patients	2,316	58,050
Entry window (hour)	24	24
Chest pain randomization (hour-median)	3	8
Proportion treated with thrombolytic	36%	70%
Proportion treated with ASA	66%	94%
Mortality (28-35 days):		
Control	10.3%	7.24%
Magnesium	7.8%	7.64%

CONCLUSION

Prompt initiation of magnesium infusion with the optimal dosage of magnesium, with or without thrombolysis, is necessary to achieve maximal benefits from magnesium therapy. The above requirements were not met in the protocol of ISIS-4 study. Hence, the beneficial effects of magnesium infusion were not shown in ISIS-4. Based on animal studies, future trials to evaluate the effects of magnesium in coronaries should meet the following criteria:

1. Study population consisting of patients with higher risk of mortality from AMI such as elderly, and whom thrombolytics are not administered
2. Time of administration within 6 hours from the onset of chest pain
3. Total dose of magnesium should not exceed 77.8 mmol/24hours.

Doses between 63 to 67 mmol/24hours had the best improvement in mortality rates. At present time, Magnesium In Coronaries[12](MAGIC) trial is being conducted. It will involve more than 10,000 high-risk AMI patients. The patients will be randomized either to receive magnesium infusion or placebo. Hopefully, this trial will be able to shed light into these controversies. Magnesium infusion if proven beneficial in AMI, will have a great impact in our country. Magnesium is a more cost-effective alternative to thrombolytics, which some of our patients cannot avail of.

REFERENCES

1. Antman EM. Is there a place for magnesium in the treatment of acute myocardial infarction? Am Heart J 1996;471-7.
2. Christensen C. Magnesium sulfate reduces myocardial infarct size when administered before and after coronary reperfusion. A canine model. Circulation 1995;92:2617-21.
3. Herzog W. Timing of magnesium therapy affects experimental infarct size. Circulation 1995;92:2622-6.
4. ISIS-4. A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulfate in 58,050 patients with suspected acute myocardial infarction. Lancet 1995;345:669-85.
5. Ising H. Correlation between ventricular arrhythmias and electrolyte disturbances after myocardial infarction. Magnesium trace element 1990;9:205-11.
6. Feldstedt M. Magnesium substitution in acute ischemic heart syndromes. Eur Heart J 1991;12:1215-8.
7. Shaheen B. Magnesium in the treatment of acute myocardial infarction. Clinical pharmacy 1993;12:588-96.
8. Shechter M. The rationale of magnesium supplementation in acute myocardial infarction. A review of literature. Archive of Int Med 1992;152:2189-96.
9. Steures G. Acute myocardial infarction, reperfusion injury, and intravenous magnesium therapy: Basic concepts and clinical implications. Am Heart J 1996;132:478-82.
10. Woods K. Intravenous magnesium sulfate in suspected acute myocardial infarction: Result of second leicester intravenous magnesium intervention (LIMIT-2). Lancet 1992;339:1553-8.
11. Yusuf S. Intravenous magnesium in acute myocardial infarction. An effective and inexpensive intervention. Circulation 1995;87:2043-6.
12. Magic Steering Committee. Rationale and design of the magnesium in coronaries (MAGIC) study: A clinical trial to reevaluate the efficacy of early administration of magnesium in acute myocardial infarction. Am Heart J 2000;139(1 pt.1):10-4.
13. Galloe A, Graudal N. Magnesium and myocardial infarction [letter]. Lancet 1994;343:807-9.