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Long-Term Outcome of Intravenous Magnesium Therapy in Thrombolysis-Ineligible Acute Myocardial Infarction Patients

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Key Words
Magnesium · Myocardial infarction · Coronary disease · Clinical trials · Mortality

Abstract
The aim of our study was to analyze the long-term survival and cardiac function in 194 consecutive, thrombolysis-ineligible acute myocardial infarction (AMI) patients receiving 48-hour intravenous magnesium sulfate (22 g) – 96 patients, compared with placebo – 98 patients. After a mean 4.8-year follow-up, all-cause mortality and cardiac mortality were significantly lower in the magnesium compared to the placebo group [(18 vs. 33 patients, $p < 0.01$) and (12 vs. 30 patients, $p < 0.001$), respectively]. Rest radionuclide ventriculography tests for left-ventricular ejection fraction (LVEF) were assessed in surviving patients up to completion of follow-up. Magnesium-treated patients had a significantly higher LVEF (0.51 ± 0.10 vs. 0.44 ± 0.14, $p < 0.05$) and a lower incidence of heart failure compared to placebo-treated patients (12 vs. 3 patients, $p = 0.02$). Beneficial effects of intravenous magnesium therapy in thrombolysis-ineligible AMI patients appeared to last for at least 4.8 years, concomitant with preserved LVEF, suggesting a favorable role for acute magnesium treatment in these patients.

Introduction

Since the advent of thrombolytic therapy, the in-hospital mortality rate of patients with acute myocardial infarction (AMI) has been reduced from 15% to between 6 and 8% [1]. However, it is estimated that two thirds of AMI patients do not receive reperfusion therapy [2] (i.e. thrombolytic agents or coronary angioplasty) and their in-hospital mortality rate, particularly in the elderly, is in the high range of 14–20% [3–5]. During the last decade, efforts have been made to find additional adjunctive pharmacologic treatments with the use of agents such as nitrates and angiotensin-converting enzyme inhibitors. More recently, the use of magnesium has been introduced for further reduction of mortality [5].

The benefit of routine intravenous magnesium treatment in patients with AMI is controversial [7, 8]. Data on acute magnesium treatment suggest that a combination of mechanisms may act additively or even synergistically to protect myocytes [6, 9]. Magnesium protects myocytes against calcium overload by inhibiting calcium influx, a major problem at the time of reperfusion [10]. Magnesium improves myocardial metabolism [11], reduces the incidence of arrhythmias [11, 12], cardiac workload, the need for cardiac oxygen [13, 14] and the extent of catecholamine secretion in the myocardium, thereby preventing extension of the infarct [15]. In addition, magnesium

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reduces platelet aggregation [16] and thrombus formation [17, 18], systemic and pulmonary vascular resistance [19], vulnerability to oxygen-derived free radicals [20, 21] and reperfusion injury [22].

Our group has previously reported that 48-hour intravenous magnesium sulfate significantly reduced in-hospital mortality in AMI patients [23], including 2 high-risk subsets: patients ineligible for thrombolysis and elderly patients [24]. The aim of our current study was to analyze the long-term survival and cardiac function of the same study population.

Methods

Study Design and Patients

The study protocol described previously [24] comprised a prospective, randomized, double-blind, placebo-controlled trial of 194 AMI patients, considered unsuitable for thrombolysis, admitted to the intensive coronary care unit of our Medical Center, where they received either intravenous magnesium sulfate (n = 96) or isotonic glucose as placebo (n = 98).

Study Medication

Patients received 22 g (91.6 mmol) of magnesium sulfate dissolved in 500 ml of isotonic glucose, or 500 ml of glucose as placebo, during the first 48 h [24]. The study was approved by the Institutional Review Board, and all participants gave their written informed consent.

Long-Term Follow-Up

All patients were followed at the out-patient clinic of our Heart Institute every 4–6 months by a senior cardiologist (one of the authors), who was blinded to the patients' treatment (magnesium or placebo). At each visit, the following were recorded: 12-lead ECG, blood pressure, heart rate, concomitant medications and dosage, symptoms and/or complaints, hospitalizations since last visit, new coronary events (including coronary catheterizations and/or percutaneous interventions), any other surgical intervention, functional class assessment (according to the New York Heart Association class for heart failure), complete physical examination, lipid panel and electrolytes, and noninvasive evaluations, such as echocardiography, 24-hour Holter monitoring, chest X-ray or nuclear imaging. Signs and symptoms of adverse events occurring at any stage during the study were recorded in detail on the subject's chart. Heart failure was defined at the time of physical examination by the presence of rales, S_3 gallop, pulmonary congestion on the chest radiograph, or a combination of any of these.

All trial patients were 'flagged' in the National Health Service Central Register for notification to the investigators of date and certified cause of death. Without knowledge of the trial group, underlying causes of death were coded according to the *9th revision of the International Classification of Diseases* (ICD 9). Follow-up was extended to the censoring date 2 years after the end of randomization. Cardiac mortality was defined as death due to fatal myocardial infarction, sudden death, death in the hospital after possible myocardial infarction, death due to heart failure or any other coronary cause. Eleven patients, none of whom could be identified in the Central Register, were lost to follow-up (6 from the magnesium and 5 from the placebo group). We included in the final analysis all 194 patients who were randomized in the original study [24]. Average follow-up was 4.8 years (range 1.0–8.7 years).

Left-Ventricular Function Assessment

All patients who survived up to the last year of follow-up were assessed for left-ventricular ejection fraction (LVEF) by rest radionuclide ventriculography testing, performed by a cardiologist blinded to the study medication and the clinical course of the patient. The time period to follow-up of LVEF was approximately the same in both groups. Left ventricular function was assessed by equilibrium radionuclide ventriculography (MUGA) at rest. The red blood cells were labeled in vivo with 20 mCi (74 MBq) of technetium-99m and 24 (64 × 64 matrix) images were collected in the 45° left anterior oblique view (best septal view, 8 min per view) using a single-head gamma camera (SP4, Elscint Inc., Haifa, Israel) equipped with a low-energy high-resolution parallel-hole collimator (APC 4, Elscint Inc.). Global LVEF was calculated using a semi-automatic, commercially available software protocol (Elscint Inc., Haifa, Israel).

Statistical Analysis

Group data are expressed as mean ± SD. Categorical variables including clinical endpoints in table 2 were compared by χ^2 statistic and Fisher's exact test, when appropriate. Kaplan-Meier estimates of survival probability were calculated and the difference in the distribution of survival time between treatment groups was tested by the log-rank and Wilcoxon tests. Treatment effects on the mortality rate and its 95% confidence interval were estimated in a proportional hazards model from the coefficient and standard error of treatment group as the sole covariate. A p value of 0.05 was required to reject the null hypothesis.

Results

Patients from both groups (magnesium and placebo) had a similar prevalence of risk factors for coronary artery disease [24], infarct location and clinical criteria, and received the same conventional therapy in the coronary intensive care unit (including oral aspirin and intravenous heparin). During the follow-up (table 1) there were no significant differences between the treatment groups regarding cardiac medications (aspirin, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, digoxin, diuretics, coumadin, amiodarone, lipid-lowering therapy and long-acting nitrates), and no patient received oral magnesium treatment during this period.

Survival probability of the study cohort during 8.7 years of follow-up was not significantly different between the two treatment groups, using the log-rank test (0.239); however, it was significantly higher in patients from the magnesium group compared with placebo using the Wilcoxon test (0.038) (fig. 1). After 4.8 years, survival proba-

bility was 0.638 in the placebo compared with 0.795 in the magnesium group ($p < 0.01$); whereas after 8.7 years it was 0.550 in the placebo compared with 0.547 in the magnesium group ($p = 0.26$). The absolute difference in the estimated mortality rate (between magnesium- and placebo-treated patients) at 1, 2, 3, 4, 5, 6 and 7 years was 15, 18, 16, 17, 12, 7 and 4%, respectively (fig. 1).

Overall, the mean survival time from initiation of therapy (magnesium or placebo) to the end of follow-up was significantly longer in the magnesium compared with the placebo group (5.4 ± 2.7 vs. 4.3 ± 3.2 years, $p < 0.02$). The length of time from initiation of therapy to the end of follow-up in patients who survived the last year of follow-up was similar in both groups (6.3 ± 2.0 vs. 6.2 ± 2.0 years, respectively, $p = 0.85$). However, the average time from initiation of therapy to death was significantly longer in the magnesium compared with the placebo group (3.6 ± 2.8 vs. 1.4 ± 2.3 years, respectively, $p = 0.0007$). The mean age in both groups was similar at the time of death (70 ± 12 vs. 71 ± 10 years, respectively, $p = 0.64$). The mean age of patients who survived the last year of follow-up was also similar in the two groups (64 ± 11 vs. 64 ± 13 years, respectively, $p = 0.90$).

After a mean follow-up of 4.8 years, the rate of all-cause mortality was significantly lower in the magnesium group compared with placebo (18 vs. 33 patients, respectively, $p < 0.01$), but was almost the same after 8.7 years (32 vs. 38 patients, respectively, $p = 0.26$) (fig. 1). After a mean follow-up of 4.8 years, the rate of cardiac mortality was also significantly lower in the magnesium group compared with placebo (12 vs. 30 patients, respectively, $p < 0.001$), but was only slightly lower after 8.7 years (22 vs. 33 patients, respectively, $p = 0.06$). Of the 98 patients

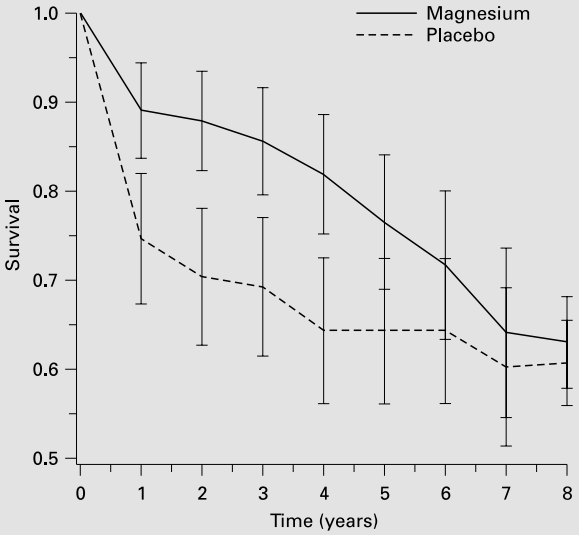

Fig. 1. Rates of survival with 95% confidence interval for each year of follow-up in 194 thrombolysis-ineligible patients with AMI. After 4.8 years of follow-up, the survival probability rate was 0.638 in the placebo group (n = 98) compared to 0.795 in the magnesium group (n = 96) ($p < 0.01$). However, after 8.7 years, it was 0.550 in the placebo, compared to 0.547 in the magnesium group ($p = 0.26$).

Table 1. Baseline characteristics and medications of study population throughout the entire follow-up period (p = n.s. for all)

	Magnesium (n = 96)	Placebo (n = 98)
Age (years ± SD)	73 ± 10	73 ± 10
Hypertension	45 (47%)	42 (43%)
Diabetes	16 (17%)	22 (22%)
Current smokers	19 (20%)	25 (25%)
Previous anterior myocardial infarction	51 (53%)	55 (56%)
β-Receptor antagonists	40 (42%)	44 (45%)
Calcium antagonists	15 (16%)	21 (21%)
Digitalis	3 (3%)	5 (5%)
Diuretics	5 (6%)	13 (13%)
Aspirin	88 (92%)	91 (93%)
Coumadin	3 (3%)	1 (1%)
Long-acting nitrates	21 (22%)	21 (21%)
Angiotensin-converting enzyme inhibitors	35 (36%)	42 (43%)
Amiodarone	3 (3%)	5 (5%)
Lipid-lowering agents	63 (65%)	68 (69%)
Oral anti diabetic agents	2 (2%)	8 (8%)

Table 2. Coronary events throughout the long-term follow-up period

	Magnesium (n = 96)	Placebo (n = 98)	p
Recurrent myocardial infarction[1]	1 (1%)	3 (3%)	0.31
Coronary bypass grafting	2 (2%)	12 (12%)	0.005
Coronary angioplasty	03 (3%)	1 (1%)	0.30
Angina pectoris	5 (5%)	12 (12%)	0.06
Chronic heart failure	3 (3%)	12 (12%)	0.02
Composite end point[1]	14 (15%)	40 (41%)	0.005

[1] Myocardial infarction, coronary bypass grafting, coronary angioplasty, angina pectoris, and chronic heart failure.

(17.3%) receiving placebo, 17 died in hospital compared with only 4 patients (4.1%) who received magnesium (p = 0.01), corresponding to an odds ratio of 0.21 (0.07–0.64) [24]. All-cause 4.8-year mortality rate was reduced by 28%: 22/98 (22.4%) patients in the placebo group (including 1 noncardiac death) compared with only 6/96 (6.2%) in the magnesium group ($p < 0.001$). After 8.7 years 70/194 (36%) patients died: 32/96 (33%) receiving magnesium compared with 38/98 (39%) on placebo (p = 0.26). Cardiac death was diagnosed in 55 patients: 22/96 (23%) on magnesium therapy and 33/98 (35%) on placebo (p = 0.06), with 15 noncardiac deaths: 10/96 (10%) from the magnesium and 5/98 (5%) from the placebo group (p = 0.07).

Significantly more patients from the placebo group had to undergo coronary artery bypass grafting than from the magnesium group (table 2). There were no significant differences in the recurrence of myocardial infarction, percutaneous transluminal coronary angioplasty and angina pectoris between the placebo and magnesium groups. However, the composite end point of myocardial infarction, coronary artery bypass surgery, angina pectoris, percutaneous transluminal coronary angioplasty and heart failure, occurred significantly more frequently in the placebo- than in the magnesium-treated patients (table 2).

LVEF performed in all surviving patients at the last year of follow-up (38 magnesium, 36 placebo patients, average follow up time 4.8 ± 3.9 years) was significantly higher in patients who received magnesium compared with placebo (0.51 ± 0.10 vs. 0.44 ± 0.14, $p < 0.05$), but was not significantly different from LVEF measured 1–2 months from randomization. Clinical congestive heart failure was significantly more frequent in the placebo than in the magnesium group (table 2).

Discussion

Our current study demonstrates that the favorable effects of acute intravenous magnesium therapy given over 48 h in thrombolysis-ineligible AMI patients, appear to last for at least 4.8 years, along with preserved left-ventricular function. These results substantiate previous observations, where we demonstrated that intravenous magnesium therapy reduced in-hospital mortality in AMI thrombolysis-ineligible patients [24]. The long-term favorable effects of magnesium therapy up to 8.7 years after a single 48-hour intravenous magnesium infusion may be justified by the limitation of the patient's infarct size and improved LVEF, compared with placebo. In our original study [24], we found that LVEF, measured at 72 h and 1–2 months following AMI, was higher in patients who received magnesium than in those taking placebo (0.49 vs. 0.43 and 0.52 vs. 0.45, respectively; p = 0.01). The LVEF data from our current long-term follow-up study support the hypothesis that magnesium cardioprotection results in the reduction of ischemia and heart damage. It should be noted, however, that the LVEF data apply only to the subset of patients who survive long-term. This is an unavoidable limitation, but it should be pointed out that in each arm of the trial the patients with the worst LVEF were selectively removed by their increased mortality rate.

Magnesium supplementation may influence infarct size in seven possible ways:

(1) Acute elevation of extracellular magnesium levels reduces the toxic calcium overload in the mitochondria of myocytes (as occurs in ischemia), while the equilibrium between calcium transport and adenosine triphosphate synthesis is shifted toward adenosine triphosphate synthesis [25]. (2) Soon after the onset of myocardial ischemia, magnesium infusion may limit the progression of ischemia to the infarcted myocardium and reduce the risk of arrhythmias being induced by raised local concentrations of catecholamines [15]. It may be assumed therefore that magnesium reduces the incidence of arrhythmias [11, 12], reduces cardiac workload and cardiac oxygen need [13, 14], and limits infarct size [13, 26, 27]. (3) Magnesium induces coronary vasodilation, thereby improving coronary blood flow [19]. (4) Extra-cellular magnesium reduces the extent of catecholamine secretion in the myocardium [15]. This prevents intramyocardial lipolysis, which binds and inactivates myocardial magnesium. Both improved coronary blood flow and inhibition of catecholamine release caused by the stress of the infarction prevent infarct expansion [15]. (5) Magnesium deficiency might adversely influence the healing and re-endothelialization of vascular injuries, the healing of a myocardial infarction, and might also result in delayed or inadequate angiogenesis [28], effects of which potentially lead to infarct expansion and inadequate collateral development. (6) Magnesium may protect viable cells against oxygen-derived free radicals [20, 21] and reperfusion injury [22]. (7) Recently, our group has demonstrated that magnesium inhibited platelet-dependent thrombosis in CAD patients, even in the presence of aspirin therapy [18].

Our results are concordant with Rasmussen et al. [29] who reported on a one-year death rate in 270 patients with suspected AMI, initially treated with intravenous magnesium or placebo. All-cause mortality was 20% in patients who received magnesium, compared with 32% in

patients who received placebo (p = 0.018), and mortality from ischemic heart disease was 15% compared with 28% (p = 0.006), respectively. This mortality reduction occurred mainly during the initial 30 days after treatment, and was partially linked to a reduced incidence of arrhythmias and infarction during the initial hospitalization period. Similar results were found by Woods and Fletcher [30] who reported a 21% reduced mortality rate from ischemic heart disease (p = 0.01) and 16% from all-cause mortality (p = 0.03) in 2,316 patients with suspected AMI who received magnesium compared with placebo in a mean follow-up of 2.7 years in the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2).

The subsequent Fourth International Study of Infarct Survival (ISIS-4) [31] included almost 58,000 patients with suspected or definite AMI, of whom almost 70% received thrombolytic therapy. The mortality rate at 35 days was 7.6% in the magnesium group compared with 7.2% in the placebo group, suggesting no benefit from magnesium administration on mortality, with even possible slight deleterious effects. The magnesium dose was almost identical to that of LIMIT-2, but with open control. However, the time from onset of symptoms to randomization was substantially longer (median of 8 h vs. 3) and the 30% of patients who did not receive thrombolytic therapy were randomized at a median of 12 h after onset of symptoms [7, 32]. A lack of a therapeutic effect after magnesium therapy as administered in ISIS-4 is in full accord with the results of experimental models. The late administration of magnesium in ISIS-4 might have contributed towards infarct extension due to hypotension, which was indeed more pronounced in patients who received magnesium compared with placebo, whereas this was not the case in LIMIT-2 [30].

Magnesium may reduce myocardial damage and mortality in subsets of high-risk AMI patients including the elderly and/or patients not suitable for reperfusion therapy (intravenous thrombolysis or percutaneous transluminal coronary angioplasty), provided it is administered before reperfusion occurs [32, 33]. The causes of death in the original study [24] were consistent with the hypothesis that magnesium helps reduce mortality by a direct myocardial protective effect. In the placebo group, 11 patients died during hospitalization from cardiogenic shock, 2 from electromechanical dissociation, 2 from myocardial rupture and 1 from cardiac arrest. By contrast, in the magnesium group, 1 patient died of cardiogenic shock, 1 from myocardial rupture, and 2 from electromechanical dissociation. LVEF, measured 72 h and 1–2 months after admission, was higher in patients receiving magnesium therapy compared with those on placebo (0.49 vs. 0.43 and 0.52 vs. 0.45 respectively; p = 0.01) [24].

The recently published Magnesium in Coronaries (MAGIC) trial [34], randomized 6,213 patients = 65 years, of whom an unexpected high percentage (45%) were females with acute ST elevation AMI <6 h who were eligible for reperfusion therapy (median age 73 years) (stratum 1); or patients of any age who were not eligible for reperfusion therapy (median age 67 years) (stratum 2), to a 2-gram intravenous bolus of magnesium sulfate, administered over 15 min, followed by a 17-gram infusion of magnesium sulfate over 24 h (n = 3,113); or matching placebo (n = 3,100). Early administration of magnesium (median time from the onset of symptoms: 3.8 h) in high-risk patients with acute ST elevation AMI <6 h had no effect on 30-day mortality. At 30 days (the longest follow-up period), 475 (15.3%) patients in the magnesium group and 472 (15.2%) in the placebo group had died. Intravenous magnesium therapy did not change the incidence of heart failure compared with placebo. Compared with the MAGIC trial our current study population comprised thrombolysis-ineligible AMI patients, of whom one third was >75 years, and therefore quite similar to the stratum 2 patients in MAGIC. However, our patients received higher doses of intravenous magnesium sulfate for longer periods of time compared with MAGIC (22 vs. 19 g and 48 h compared with 24 h, respectively). A significantly higher proportion of the MAGIC study population received aspirin, β-blockers and angiotensin-converting enzyme inhibitors than our current study population, and as a result the postulated cardioprotective actions of magnesium could have been superseded by the effects of these medical regimens [34].

Our study not only confirms the findings of Rasmussen et al. [29] who state that the beneficial effect of magnesium on mortality in a high-risk population (patients ineligible for thrombolysis and the elderly) is mainly during the first month after AMI, but continues to demonstrate an extended beneficial effect up to 4.8 years after AMI, concomitantly with a higher LVEF. However, it should be noted that the added beneficial effects of intravenous magnesium therapy observed in the current study could also be due to statistical bias or chance.

Conclusion

Magnesium is an inexpensive, natural, easy to handle, and reasonably safe element. The beneficial effects of intravenous magnesium therapy appear to last for at least

4.8 years after acute treatment, along with preserved LVEF. These results suggest a favorable role for magnesium supplementation in thrombolysis-ineligible AMI patients.

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