Magnesium as Alternative Therapy in Patients with Acute Myocardial Infarction who are not Candidates for Thrombolytic Therapy

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Zusammenfassung

Die Krankenhaussterblichkeit von Patienten mit akutem Herzinfarkt (AMI) ist dank der Thrombolyse-Therapie während des letzten Jahrzehnts dramatisch gesunken. Ungeachtet dessen erhalten nur 15-35% der AMI-Patienten eine solche Therapie, wobei die Krankenhaussterblichkeitsrate hoch ist. Ziel dieser Studie war das Studium der Wirksamkeit von Magnesiumsulfat bei der Reduzierung der Sterblichkeitsrate von AMI-Patienten, die als ungeeignet für die Thrombolyse-Therapie angesehen werden. Intravenöses Magnesiumsulfat wurde bei 194 AMI-Patienten, die als ungeeignet für die Thrombolyse-Therapie galten, in einer randomisierten, doppelblinden, plazebokontrollierten Studie gegeben. Die Gruppe A – bestehend aus 96 Patienten – erhielt eine 48stündige intravenöse Magnesiumgabe, Gruppe B – bestehend aus 98 Patienten – erhielt isotonische Glukose als Plazebo. Die linksventrikuläre Ausstoßfraktion war bei den Patienten der Gruppe A höher als bei der Gruppe B, nach 72 Stunden und 1-2 Monate nach der Aufnahme ins Krankenhaus (49% vs 43% und 52% vs 45%; jeweils p = 0,01). Magnesium reduzierte das Aufkommen von Arrhythmien, dekompensierte Herzinsuffizienz und von Leitungsstörungen im Vergleich zu den Plazebopatienten. Die Krankenhaussterblichkeit war deutlich reduziert bei der Gruppe A verglichen mit der Gruppe B (4% vs 17%; $p < 0,01$) und auch in der Subgruppe der älteren Patienten (> 70 Jahre) (9% vs 23%; $p = 0,09$). Daraus folgt, daß Magnesium als Alternativ-Therapie zur Thrombolyse-Therapie bei AMI-Patienten in Betracht gezogen werden sollte.

Summary

In-hospital mortality of patients with acute myocardial infarction (AMI) has been reduced dramatically during the last decade mostly due to the treatment by thrombolytic therapy. Nevertheless, only 70-80% of AMI patients do not receive thrombolysis, and their in-hospital mortality is high. The aim of this study was to determine the potential of magnesium sulfate for reducing mortality in AMI patients who were considered unsuitable for thrombolytic therapy. Intravenous magnesium sulfate was evaluated in 194 AMI patients ineligible for thrombolysis in a randomized, double-blind, placebocontrolled study. Group A – 96 patients who received 48-hour intravenous magnesium; Group B – 98 patients received isotonic glucose as a placebo. Left ventricular ejection fraction was higher in patients from Group A than from Group B 72 hours and 1-2 months after admission (49% vs 43% and 52% vs 45%; $p = 0.01$, resp.). Magnesium reduced the incidence of arrhythmias, congestive heart failure and conduction disturbances compared to placebo. In-hospital mortality was significantly reduced in Group A compared to Group B (4% vs 17%; $p < 0.01$) and also in the subgroup of elderly patients (> 70 years) (9% vs 23%; $p = 0.09$). In conclusion, it appears that magnesium should be considered as an alternative therapy to thrombolysis in AMI patients.

Résumé

La mortalité en hôpital des patients à la suite d'un infarcus aigu du myocarde (AMI) a été réduite dramatiquement au cours de la décade passée, surtout dû aux traitements thrombolytiques. Néanmoins, ce ne sont que 15 à 35% des patients AMI qui recevaient cette thérapie, et la mortalité en hôpital a été énorme. Le but de cette étude est d'évaluer l'efficacité du sulfate de magnésium pour la réduction de la mortalité des patients AMI qui étaient considérés impropres pour un traitement thrombolytique. Du sulfate de magnésium intra-véineux était mesuré chez 194 patients AMI considérés impropres pour un traitement thrombolytique, au cours d'une étude randomisée, croisée en double insu et contrôlée par du placébo. Le groupe A – se composait de 96 personnes qui recevaient du magnésium intraveineux pendant 48 heures; le groupe B qui était consistué par 98 personnes recevait comme placébo du glycose isotonique. La fraction de l'éjection ventriculaire gauche était plus augmentée dans les patients du groupe A que dans le groupe B 72 heures et après 1 à 2 mois après leur admission à l'hôpital (49% vs 43% et 52% vs 45%; $p = 0.01$, resp.). Le magnésium réduisait la déclaration des arhythmies, des insuffiances cardiaques congestives et des disturbances de conduction, comparé au groupe de placébo. La mortalité en hôpital était diminuée considérablement dans le groupe A, comparée à celle du groupe B (4% vs 17%; $p < 0.01$), et aussi dans le subgroupe des patients plus âgés (> 70 ans) (9% vs 23%; $p = 0.09$). En conclusion, il apparait que le magnésium devrait être considéré comme thérapie alternative au traitement de thrombolyse dans des patients AMI.

Introduction

The rationale for the routine treatment with magnesium [8] in patients suffering from acute myocardial infarction (AMI) derives from its ability to lower systemic vascular resistance, dilate coronary arteries [9], improve myocardial metabolism [10], decrease platelet aggregation [11], stabilize cell membranes [12] and protect against catecholamine-induced myocardial necrosis [13].

Although the in-hospital mortality in AMI patients has been reduced significantly to approximately 6-8% [1-5] since the advent of thrombolysis, many patients are not treated with thrombolytic agents. It is estimated that only 15% [6] to 22% [7] of patients with AMI in the USA and

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Magnesium as Alternative Therapy in Patients with Acute Myocardial Infarction who are not Candidates for Thrombolytic Therapy

35% [5] in Israel receive thrombolytic therapy.

The purpose of our study was to evaluate the potential beneficial effects of magnesium sulfate in AMI patients who were considered, at the time of randomization, unsuitable candidates for thrombolytic therapy, and therefore, to find out if intravenous magnesium may constitute an alternative therapy in a particular subgroup of AMI patients. We studied the effect of this therapy on arrhythmias, conduction disturbances, congestive heart failure and in-hospital mortality.

Methods

Patients

In a prospective, randomized, double-blind, placebo-controlled trial, 215 patients admitted to our Intensive Coronary Care Unit (ICCU) in the years 1990–1993 with the diagnosis of AMI and who were considered unsuitable for thrombolysis, received, after having signed an informed consent, either magnesium (107 patients) or isotonic glucose as placebo (108 patients). The diagnosis of definite AMI was based on the triad of symptoms, typical ECG findings and elevation of serum enzymes. 10 patients from the placebo group and 11 from the magnesium group were excluded from the analysis for not fulfilling all 3 diagnostic criteria. Thus, 194 patients were included in the study: 96 received magnesium and 98 placebo. None of the randomized patients received prophylactic antiarrhythmic therapy. The exclusion criteria for thrombolysis at the time of admission to the ICCU: late arrival to hospital (over 6 hours from the onset of symptoms), contraindication to fibrinolytic treatment or heparin (a surgical procedure or invasive procedure or trauma within the previous two weeks; recent or current bleeding, cerebrovascular accident within the previous 6 months; uncontrolled hypertension, systolic > 200 mmHg; previous treatment with streptokinase within the past 6 months); age above 70 years.

Study Medication

The patients received 22 gm (91.6 mmol) magnesium sulfate dissolved in 500 ml of isotonic glucose during the first 48 hours of 500 ml of glucose as placebo [14]. The infusion rate was adjusted so that 6 gm (25 mmol) of magnesium sulfate were given during the first 3 hours, 10 gm (42 mmol) during the next 21 hours, and 6 gm (25 mmol) during the last 24 hours [13]. The placebo group received the equivalent volumes of isotonic glucose. During the first 7 days all patients were monitored electrocardiographically by trained coronary care nurses. In addition, heart rhythm was continuously recorded by Holter monitoring for the first 48 hours. Blood samples for magnesium, cardiac enzymes and electrolytes were obtained on admission and every day for the first 5 days. Serum magnesium concentration was determined by atomic absorption spectrophotometry [15].

Left Ventricular Function

91 consecutive study patients underwent 2 radionuclide ventriculography (MUGA) tests starting in 1991. The first was performed 72 hours after admission and the second 1–2 months later. Radionuclide studies were performed with an Elscint Apex 45 digital gamma camera. A multigated equilibrium blood pool scan was performed in the anterior and 45° left anterior oblique projection with red blood cells labeled in-vivo with technetium-99m (20 to 25 mCi). A left ventricular time-activity curve correlated to background was used to calculate the global ejection fraction semiautomatically. All radionuclide examinations and left ventricular ejection fraction (LVEF) determinations were assessed by cardiologists who were unaware of the study medication (magnesium or placebo) or of the clinical course of the patients.

Statistical Analysis

Group data are expressed as mean ± SD for continuous variables or as rates (percent) for categoric variables. These variables were compared by chi-square statistic and Fisher exact test when appropriate.

Results

The study comprised 194 patients: 96 received magnesium and 98 placebo. The 2 groups had a similar prevalence of risk factors (tab. 1), the average time from onset of chest pain to initiation of treatment was similar, and patients received the same conventional therapy in the ICCU.

The initial levels of magnesium before the beginning of the study were normal and there was no significant difference between the 2 groups. Maximal mean serum magnesium concentration in patients who received magnesium was 3.38 ± 0.52 mg/dl 24 hours after initiation of treatment and gradually decreased after cessation of the magnesium infusion. The magnesium levels in the placebo group remained constant. No adverse effects were observed to the intravenous magnesium.

Clinical Course and Mortality

Magnesium reduced the incidence of arrhythmias and conduction disturbances compared to placebo (tab. 2). LVEF was higher in patients who received magnesium compared to placebo 72 hours and 1–2 months after admission to the ICCU (49% vs 43% and 52% vs 45%; p = 0.01, resp.). In

Tab. 1: Demographic data of study population.

	Placebo (n = 98)	Magnesium (n = 96)
Male (%)	69	62
Age (yrs ± SD)	66 ± 13	66 ± 12
Time from pain to treatment (hrs ± SD)	7.1 ± 2.2	7.0 ± 4.3
Hypertension (%)	33	40
Diabetes mellitus (%)	17	15
Hyperlipidemia (%)	13	10
Cigarette smokers (> 20/day) (%)	31	26
Angina pectoris (%)	24	23
Previous myocardial infarction (%)	16	13
Anterior myocardial infarction (%)	43	46

SD = Standard Deviation

Tab. 2: Clinical outcome of 194 patients.

	Placebo (n = 98)	Magnesium (n = 96)
Arrhythmias*) (%)	39[1]	26[1]
Conduction disturbances (%)	15	10
Heart failure (%)	22	18
Hospital mortality (%)	17[2]	4[2]

*) Arrhythmias were ventricular tachycardia, ventricular fibrillation and premature beats Lown grade 2 to 5; [1] $p = 0.04$, [2] $p = 0.01$.

Tab. 3: Clinical outcome in 77 patients over the age of 70 with acute myocardial infarction.

	Placebo (n = 44)	Magnesium (n = 33)
Arrhythmias*) (%)	22	14
Conduction disturbances (%)	9	6
Heart failure (%)	11	6
Hospital mortality (%)	10[1]	3[1]

*) Arrhythmias were ventricular tachycardia, ventricular fibrillation and ventricular premature beats Lown grade 2 to 5; [1] $p = 0.09$.

addition, there was a trend toward a reduction in the incidence of congestive heart failure in patients who received magnesium compared to placebo. The remarkable finding was the reduction of in-hospital mortality in patients who received magnesium compared to placebo: only 4 patients who received magnesium died compared to 17 on placebo ($p < 0.01$). In the placebo group 11 patients died from cardiogenic shock, 2 from electromechanical dissociation, 2 from myocardial rupture and 1 from cardiac arrest, while in the magnesium group 1 patient died from cardiogenic shock, 1 from myocardial rupture and 2 in electromechanical dissociation.

77 patients, about 1/3 of the study population, constitute a subgroup of elderly patients (over 70 years old): 33 received magnesium and 44 placebo. As in the whole population, this high-risk older age subgroup shows also a reduction in the in-hospital mortality in patients who received magnesium compared to placebo (tab 3). Of those on placebo 10 patients died compared to only 3 who received magnesium.

Discussion

During the last decade 8 prospective, randomized, double-blind controlled trials comprising a total of 2306 patients with AMI not on thrombolytic therapy who received intravenous magnesium versus placebo have been reported [8, 16]. In spite of the difference in study protocols and in patient selection criteria, the results were quite similar. Although the definition of heart failure in the 8 randomized trials varied, the data also suggest that the incidence of left ventricular failure was significantly lower in patients who received magnesium compared to placebo [16, 17]. The cumulative acute mortality rate was significantly higher in patients who received placebo than in those on magnesium (13% vs 9%; $p = 0.004$), and a significant reduction of serious arrhythmias by 1/4 in the magnesium treated patients compared to placebo (23% vs 38%; $p < 0.001$) [16]. We used magnesium in our patients as a first-line therapy and not as additive therapy to thrombolysis and other agents. The population that was given placebo in our study had a high in-hospital mortality (17%). The patients (N:96) who received magnesium had a mortality of only 4% and the elderly subgroup of patients (N:33) had a mortality rate of 9%. *Maggioni* et al. [18] recently demonstrated that in-hospital mortality in patients older than 70, who presented with first AMI and were eligible for thrombolytic therapy was 19% as compared to 2.8% in the younger group. Our population had also other characteristics which raised the expected higher mortality rate. Thus, in-hospital mortality of only 9% in the elderly patients who required intravenous magnesium appears to be a marked achievement.

The ISIS-4 (4th International Study of Infarct Survival) study [19] deals with magnesium as additional therapy in AMI. Magnesium was administered late in ISIS (median of 8 hours after the onset of symptoms and 12 hours in the 30% of patients not given thrombolysis). In animal models magnesium [20] and other calcium antagonists administered late after reperfusion appear to be ineffective. The mortality rate in the control group in ISIS-4 was only 7.2%, probably the result of extensive use of thrombolysis and antiplatelet agents. Although one cannot argue with the results of a mega study, the fact that magnesium was expected to act on top of the beneficial effects of other drugs may be the reason for the negative results.

The beneficial effect of magnesium in our study cannot apparently be explained by the reduction in the incidence of arrhythmias and/or congestive heart failure. A possible myocardial protective effect should be postulated to explain such a favorable effect on survival in AMI. If we consider the cause of death in our patients, it is obvious that the high mortality in the placebo group was due to pump failure. The LVEF data support the hypothesis that the magnesium cardioprotection is in the reduction of ischemia and damage to the heart.

The mortality in our population in the patients who received magnesium was 4%, similar to that reported in patients who receive thrombolysis.

The number of elderly patients experiencing AMI is growing and their in-hospital mortality rate remains high although age per se is no longer a contraindication to thrombolysis [22, 23]. In the SPRINT study, performed before the thrombolytic era, 11% (653 of 5839 patients) were above 75 years of age and the in-hospital mortality rate was 36% [24]. The use of thrombolysis in elderly patients (aged over 75 years) reduced the in-hospital mortality to 12–13% [1, 25]. In the early 1990's *Behar* et al. [5] found that in Israel only 18% of AMI patients older than 75 years

received thrombolysis, and their in-hospital mortality was 9% compared to 33% in elderly patients who did not receive thrombolysis. *Montague* et al. [26] found that 4% of AMI patients 70 years and older received thrombolysis, and the in-hospital mortality among all the patients was 27%.

Age today is no longer considered an absolute contraindication to thrombolysis, yet it is available only to about 15–22% of the total AMI population in the USA [6, 7] and 35% in Israel [15]. In addition, the benefit of thrombolysis in patients who arrive late or are diagnosed late (after 6 hours) remains controversial. It appears to us that these late arriving patients, and those who have the accepted contraindications to thrombolysis might constitute a subgroup of patients in whom magnesium administration might be used and found to be beneficial.

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