Beneficial Effect of Magnesium in acute Myocardial Infarction

A review of the Literature

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Zusammenfassung

Innerhalb der letzten 5 Jahre wurden 5 kontrollierte, randomisierte klinische Doppelblindprüfungen mit 588 Myokardinfarkt-(MI)-Patienten durchgeführt. 286 Patienten (49 %) erhielten Magnesium auf dem intravenösen Weg, und 302 Patienten (51 %) erhielten Placebo. Bei letzteren traten mehr Arrhythmien auf als bei den mit Magnesium behandelten Patienten (34 gegen 18 %). Die Matalität belief sich insgesamt auf 7,1 % (42/588). Es verstraben 33 Placebo-Patienten (11,2 %) gegen nur 9 (3 %) Magnesium-Patienten. Die günstigen Effekte von Magnesiuminfusionen beruhen hauptsächlich auf der pharmakologischen Wirkung und weniger auf einer Mangelkorrektur. In Anbetracht des Vermögens diese Präparats, die sekundär auf akuten Myokardinfarkt auftretende Mortalität zu reduzieren, sind wir der Meinung, daß diese preiswerte, risikolose und leicht einsetzbare Schutzbehandlung generell allen an dieser Erkrankung leidenden Patienten verordnet werden sollte.

Summary

During the last five years five randomized, double blind clinical controlled trials, consisting of a total of 588 patients with acute myocardial infarction (AMI) have been reported: 286 patients (49 %) were given magnesium intravenously and 302 patients (51 %) received placebo. Those who did not receive magnesium had more arrhythmias than those who were given magnesium (34 vs 18 %). Overall mortality was 7.1 % (42/588): 33 patients (11.2 %) who received placebo died compared to only nine patients (3 %) who were given magnesium. The beneficial effect of magnesium infusions is due mainly to its pharmacological action rather than to repletion of a deficit. In view of its potential in reducing the immediate mortality from AMI, it seems to us that this inexpensive, safe and simple therapy be considered in protecting patients suffering from acute myocardial infarction.

Résumé

Au cours des cinq dernières années, cinq édudes cliniques contrôlées, randomisées et à double-insu, incluant 588 patients atteints d'infarctus du myocarde (IM) ont été menées: 286 patients (49 %) ont reçu du magnésium par voie intraveineuse et 302 patients (51 %) ont reçu un placebo. Ces derniers ont présenté plus d'arythmics que ceux recevant du magnésium (34 contre 18 %). La mortalité totale s'est élevée à 7,1 % (42/588): 33 patients (11,2 %) recevant la placebo sont décédés, contre 9 seulement (3 %) de ceux recevant la magnésium. Les effets bénéfiques de perfusions de magnésium sont dus principalement à son action pharmacologique plutôt qu'à une correction d'une carence. Au vu de son aptitude à réduire la mortalité secondaire à un infarctus aigu du myocarde, il nous semble que ce traitement protecteur, d'un coût peu élevé, sans risque et d'instauration aisée, devrait être prescrit chez tous les patients présentant cette pathologie.

Tab. 1: Magnesium in AMI – randomized trials.

	ARRHYTHMIAS (%)		MORTALITY (%)		OVERALL MORTALITY RATE (%)	1-YEAR MORTALITY RATE (%)	
	Mg	P	Mg	P		Mg	P
MORTON			1 (2.5)	2 (5.0)	3/76 (3.9)		
RASMUSSEN	21	47	4 (7.0)	14 (19)	18/130 (13.8)	20* 15**	32* 28**
SMITH	5	9	2 (2.0)	7 (8.0)	9/185 (4.8)		
ABRAHAM	14.6	34.8	1 (2.0)	1 (2.1)	2/94 (2.1)		
SHECHTER	32	45	1 (2.0)	9 (17)	10/103 (9.7)		
TOTAL	18	34	9 (3.0)	33 (11.2)	42/588 (7.1)		

* OVERALL MORTALITY; ** MORTALITY FROM ISCHEMIC HEART DISEASE
+ MAGNEZIUM; ++ PLACEBO

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Hypomagnesemia was shown to be associated with cardiac arrythmias [1–9], sudden cardiac death from ischemic heart disease [10, 11] and recently with mortality in the acute stage of myocardial infarction [12–15]. Furthermore, low levels of magnesium (Mg) were found in myocardial tissue obtained at necropsy from patients with acute myocardial infarction (AMI) [16, 17]. The disturbance in Mg metabolism thus occurs during the acute phase of the AMI, where a high incidence of life-threatening arrythmias and a high rate of mortality co-exist [3, 12, 17]. The serum levels obtained in patients with AMI who survived were either low or normal [3, 12–15, 18]. While the metabolism of Mg in AMI

and the incidence of arrythmias was the topic of interest in many studies [1–9], only sporadic efforts were made to evaluate the potential of Mg administration to high risk patients. Until now, we could find only five randomized trials which examined the potential effects of Mg in AMI. Herein is a review of the trials (Tab. 1).

1. *Morton* et al. [19–21]

Morton et al. were the pioneers who carried out a prospective, randomized double-blind trial of intravenous magnesium therapy in acute myocardial infarction. They included 81 patients with acute transmural myocardial infarction. The exclusion criteria were age above 70 years, onset of symptoms of infarction 8 hours or longer, Killip class III or IV at time of admission and II°-III° atrioventricular block. Patients were randomly allocated to a 36 hours intravenous infusion of magnesium sulphate (0.75 meq/kg/12 hours) ore saline solution. Within 36 hours, the patients in the magnesium group received about 21 gm of $MgSO_4$ (87.5 mmol). Measurements were made of serum MB-CK and total CK activity every 2 hours and serum magnesium concentration every 6 hours. Heart rhythm was monitored for the first 48 hours by computerized holter monitoring.

Results: Five patients were excluded from analysis. Of the 76 patients available for analysis, 40 had been allocated to the magnesium treatment group and 36 to the control group. The groups did not differ in age (54 in the magnesium group vs 57 in the placebo), sex (32 male vs 32, respectively), previous infarct (11 vs 9, respectively) or duration of acute symptoms before entry (5.3 hours vs 4.7 hours, respectively).

As determined by the EKG, there were more anterior infarcts in the control group than in the magnesium group (47 % vs 30 %, respectively). At entry there were more patients in Killip class II in the magnesium group vs the placebo group (18 vs 6). However, 48 hours after admission showed a trend toward improvement in heart failure in both groups (13 patients in Killip Class II vs 3 in Killip Class II, respectively). The mean infarct size in the treated group was smaller than in the control group (37.4 ± 4.3 vs 45.6 ± 4.6 [MB-CK gm EQ SEM], respectively) although without statistical significance. Nevertheless, there was a significant reduction in infarct size only in patients in the magnesium group who were in Killip Class I at the time of entry (31.6 5.8 vs 44.7 4.8, respectively).

There was a trend toward a lesser frequency of ventricular premature beats in the treated group, although there was no difference either in the frequency of ventricular fibrillation or in ventricular tachycardia in both groups.

In hospital mortality: one patient who received magnesium died compared to two patients who received placebo. The death rate was 3.9 % (3/76).

2. *Rasmussen* et al.

Rasmussen et al. published their double-blind placebo controlled study of 130 patients (80 men and 50 women) with proven acute myocardial infarction in the Lancet at the beginning of February 1986 [12]. Exclusion criteria were renal failure, atrio ventricular blocks of second or third degree and insulin-dependent diabetes mellitus. Fifty six patients received magnesium intravenously for 48 hours and 74 received placebo (isotonic glucose), as follows: during the first 24 h, the patients received 50 mmol (12.3 gm) of $MgCl_2$ dissolved in 1000 ml of isotonic glucose or placebo (1000 ml of isotonic glucose). The infusion rate was 100 ml/h during the first 6 h and 22 ml/h the next 18 h. During the second day the patients received 12 mmol (3 gm) of $MgCl_2$ dissolved in 1000 ml of isotonic glucose or placebo in a rate of 42 ml/h. During the first 7 days the patients were monitored electrocardiographically by trained coronary care nurses. There were more men than women (43 pts vs 39 pts; p = 0.27), and a lower prevalence of previous cardiovascular diseases (17 % vs 7 %; p = 0.60) in the magnesium group than in the placebo group. The patients in the magnesium group were also slightly younger (mean age in years for men 67.8 in magnesium group vs 65.4 in the placebo group and for women 67.3 vs 62.5 respectively; p = 0.11).

The overall proportion of patients with arrhythmias that needed treatment was 21 % in the magnesium group, compared with 47 % in the placebo group (p = 0.004). There was no significant difference in serum magnesium between the two groups on admission to hospital. The mean value in the placebo group fell to 0.72 mmol/l (177 mg/dl) on day 2, whereas it rose to 1.23 mmol/l (3.03 mg/dl) in the patients treated with magnesium.

Mortality: During the first 4 weeks after treatment mortality was 7 % (4/56) in the magnesium group and 19 % (14/74) in the placebo group. Fifty percent (7/14) of the deaths in the placebo group, but non of the deaths in the treated group, were due to cardiogenic shock. The overall death rate in the study is 13.8 % (18/130). *Rasmussen* et al. were criticized by *Lievre* and *Leizorowicz* [22] for having analyzed only the 130 patients with proven AMI and not the remaining 143 patients, who were initially included in the study but did not have AMI and therefore were dropped from the study. As a consequence, in June 1988, *Rasmussen* et al. [23] described the results of a one-year survey in 270 of the patients who were available for follow-up. Patients were equally divided : 135 received Mg and 135 received placebo. Mg treatment was associated with a marked reduction in one year death rate from 32 % in the placebo group to 20 % in the Mg group (p = 0.018). However, if only death from ischemic heart disease was considered, the figures were 28 % in the placebo group as opposed to 15 % in the Mg group (p = 0.006). This reduction was mainly due to a reduction in

mortality during the initial 30 days after iclusion in the study (17 % vs 7 %), after which the difference in mortality between the two groups did not reach statistical significance (18 % vs 15 %, p = 0.56). The beneficial effect of Mg on mortality was partly linked to a reduced incidence of arrhythmias during the first week after inclusion in the study (27 % vs 16 %) and partly to a reduced incidence of infarction (63 % vs 48 %) during the initial hospitalization. Magnesium treatment significantly influenced the development of AMI : 85 of 135 (63 %) of the placebo-treated patients but only 65 of 135 (48 %) of the Mg-treated patients developed an AMI during the first year (p = 0.019). Magnesium treatment reduced the frequency of patients who developed an infarction only within the initial 14 days after inclusion in the study. Thereafter, no difference in AMI developing between the two groups, was observed.

3. *Smith* et al. [24]

In 1986 *Smith* et al. published a double blind placebo controlled study of 185 patients (148 male) with acute myocardial infarction in the International Journal of Cardiology. The aim of the study was to increase serum magnesium levels twofold, and this was considered accomplished by giving 15.6 gr (65 mmol) of $MgSO_4$ at fixed rate over 24 hours. 93 patients received saline as placebo and 92 received intravenous magnesium sulphate for 24 hours. Patients were observed using standard cardiac monitoring techniques for the first 24 hours. There was no significant differences between the two groups with regard to therapy prior to or after admission, site of infarction (45 patients in the placebo group had anterior myocardial infarction vs 37 patients in the magnesium group), admission serum magnesium concentrations, and peak serum CPK levels. Ventricular dysrhythmias requiring treatment were reduced on magnesium therapy and more than halved between 1 and 24 hours, however this difference were not significant in either group (5 % in the magnesium group vs 9 % in the placebo group). There were 7 deaths in the placebo group during the infusion period (0–24 hours) compared with 2 deaths in the magnesium group and the overall 24 h mortality rate was 9/185 (4.8 %).

4. *Abraham S. Abraham* et al. [25–26]

In 1987 *Abraham* et al. described a trial of 94 patients with AMI who received either magnesium intravenously (49 pts) or placebo (46 pts) as the following : on admission venous blood was withdrawn for estimation of serum K and Mg and lymphocyte K and Mg concentration. Thereafter, the patients received either 2.4 gm of $MgSO_4$ (10 mmol) in 50 ml of isotonic glucose or placebo (50 ml of isotonic glucose alone) intravenously over a 20 minute period. (This was a prospective, randomized, double-blind, placebo controlled study). Two hours after the end of the infusion, a second blood sample was taken for serum and lymphocyte K and Mg concentrations. This procedure was repeated for three days, each patient receiving the same magnesium or placebo solution on each day. All patients were continously monitored over the 72 hours period of study. The appearance of ventricular triplets, R-on-T phenomenon, or ventricular tachycardia or fibrillation classified the patient into the arrhythmia-positive group.
Results: The two groups were comparable for age, sex size of infarct and maximum enzyme elevations, and time from onset of symptoms to treatment. Initial serum K and Mg levels were also similar in both groups.
Arrythmias: 34.8 % (16/46) of patients in the placebo group and 14.6 % (7/48) of the patients in the magnesium group had serious arrhythmias on the first day of admission ($p < 0.02$). Most patients (14/16) in the placebo group had their first arrhythmia within two hours of the start of the protocol, whereas the first arrhythmia in most of the magnesium treated patients did not appear until four to six hours after the start of therapy ($p < .001$). No serious arrhythmias were observed on the second or third days. Seventy-four patients had serum Mg levels less than 2.65 mg/dl (1.09 mmol/l) and of these, 19 (26 %) had arrhythmias. On the other hand, of the 20 patients with serum Mg levels greater than 2.65 mg/dl (1.09 mmol/l) (all in the Mg-treated group), only two (10 %) had arrhythmias.
Serum and lymphocyte K levels were not different in the two groups either before or after the infusion. However, when lymphocyte K concentration was less than 1.37 ng/100 cells, the incidence of arrhythmias was reduced from 26.9 % to 15.4 % (p = 0.25) nevertheless, from 53.8 % to 15.4 % in patients with higher concentrations ($p < 0.05$). Lymphocyte Mg concentrations were 0.15 ± 0.03 ng/100 cells in the placebo group vs 0.26 ± 0.05 ng/100 cells in the Mg-treated group.
Side effects: About one third of the patients experienced flushing on receiving the Mg infusion and three developed severe hypotension.
Mortality: In hospital, mortality was 2.1 % (2/94): One patient who received placebo of cardiogenic shock and one patient who received magnesium, probably of cardiac rupture.
As a result of these findings, *Abraham* et al. [26] treated 100 AMI patients with a continuous infusion of 11.5 gm $MgSO_4$ (47.9 mmol) for 24 hours after admission. One patient had ventricular fibrillation and 9 had nonsustained ventricular tachycardia 3 to 11 complexes. In 4 patients the infusion had to be discontinued because of a drop in blood pressure.
Mortality: 4 % (4/100) died within the 12 days of hospitalization.

5. *Shechter, M.* et al. [14, 15, 27, 28]

In a randomized, double-blind, placebo controlled trial, 115 patients

with the diagnosis of AMI received either magnesium (59 pts) or placebo (56 pts) in an i.v. drip for 48 h starting immediately after admission to the ICCU. Patients were excluded if circulatory shock or complete bundle branch block or advanced atrioventricular block were present on admission. The patients received 22 gm (91.6 mmol) of $MgSO_4$ dissolved in 500 ml of isotonic glucose during the first 48 hours or placebo (500 ml of isotonic glucose). The infusion rate was adjusted so that 6 gm (25 mmol) of $MgSO_4$ were given during the first 3 hours, thereafter 10 gm (41.6 mmol) during the next 21 hours and 6 gm (25 mmol) during the last 24 hours. The placebo group received the equivalent volumes of isotonic glucose. During the first 7 days all patients were monitored electrocardiographically by trained coronary nurses. In addition, the patients' rhythm was continuously recorded by a computerized Holter system for the first 48 hours. Blood samples for Mg, cardiac enzymes and electrolytes were obtained on admission and every day for the first 5 days.

Results: 50 patients with proven AMI received $MgSO_4$ and 53 received placebo. The baseline characteristics of the population were similar in the 2 groups, however, there were more hypertensive patients (46 %, vs. 28 %; p = 0.06) and more anterior Q wave AMI (50 % vs. 28 %) in the magnesium group than in the placebo group respectively. 24 patients (45 %) from the placebo group had arrhythmias requiring therapy, compared to only 16 patients (32 %) in the magnesium group (p = 0.19). 12 patients (23 %) who received placebo had conduction disturbances compared to 7 patients (14 %) who received magnesium (p = 0.24). There was no difference in the number of patients with congestive heart failure during the study in both groups.

Mortality: There was a highly significant difference in mortality between 2 groups: 17 % (9 patients) mortality in the placebo group compared to only 2 % (1 patient) in the magnesium group. 6 patients (6/9) who received placebo died from cardiogenic shock between days 1–14. In the magnesium group, one patient, aged 76, died from cardiogenic shock on day 7.

No adverse effects of the intravenous magnesium administration were observed.

Discussion

When we combine the results of these five randomized trials, we can see that 286/588 (49 %) patients received magnesium and 302/588 (51 %) received placebo. Those who did not receive magnesium had more arrhythmias than those who received magnesium (34 % vs 18). Overall mortality was 7.1 % (42/588) — nine patients (3.0 %) who received magnesium died compared to 33 patients (11.2 %) who received placebo.

Rasmussen et al [23] found a significant reduction in 1-year death rate in patients who received magnesium. However, this was mainly due to a reduction in the in-hospital mortality during the first month.

The beneficial effect of magnesium infusions is due mainly to a pharmalogical action of magnesium rather than repletion of a deficit. This interpretation is supported by the fact that serum magnesium levels achieved lie well above the upper normal limit [12, 14 ,21].

The fact that the magnesium treatment reduced the incidence of patients who developed AMI, further contributes to the observed reduction in mortality. A possible myocardial protective effect must be postulated to explain such a favourable effect on survival in AMI. Several studies have demonstrated possible mechanism for the cardioprotective effects of magnesium. Thus, magnesium supplementation has been found to reduce the size of myocardial infarction [21], reduce the platelet aggregation [30, 31] reduce basal tone and tension of the arterioles [32, 33], reduce peripheral vascular restistance, increase coronary vasodilatation [33] and improve the hemodynamic profile of the myocardium. Magnesium is also a calcium antagonist, possibly due to its structural similarity as a divalent cation [34, 35]. (Several animal experiments have shown that perfusates containing high Mg concentrations have a protective effect against ischemia and reperfusion [36, 37].)

Mg is a competitive inhibitor of cardiac mitochondrial calcium transport [38] and inhibits mitochondrial calcium accumulation [39]. After severe myocardial ischemia, there is a reduction in the myocardial Mg content which favours mitochondrial calcium accumulation and reduction in the adenosine triphosphate (ATP) synthesis [39, 40]. An increase in extracellular Mg concentration, however, reduces mitrochondrial calcium accumulation and improves mitrochondrial ATP synthesis [39].

Extracellular Mg can also reduce the size of catecholamine-induced myocardial necrosis which occurs in AMI and prevents extension of the infarct [41].

It is not clear whether the cardioprotective effect of Mg supplementation in patients with AMI is due to a correction of hypomagnesemic state or to the raising of Mg above normal levels. A rapid and adequate correction of the relative Mg deficiency, such as that most probably achieved by rapid intravenous administration, could therefore have a cardioprotective role in reducing the myocardial injury and therefore improving immediate survival.

In respect of its potential in reducing the immediate mortality from AMI it appears to us that this inexpensive, safe and simple therapy should be considered as yet another tool in protecting patients suffering from AMI.

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