Magnesium and Myocardial Infarction

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急性心筋梗塞（AMI）患者へのマグネシウム（Mg）投与の効果は一定していない。比較的ハイリスクの AMI 患者に投与した多くの比較的小規模の無作為化臨床試験では死亡が著しく減少したが，最近発表された２つの大規模な無作為化臨床試験（the Fourth International Study of Infarct Survival，Magnesium in Coronaries）では，偽薬に対する静脈内 Mg 投与の有意性を示すことができなかった。しかしながら，前述のように，動物やヒトを用いて行われた小規模臨床試験で得られた Mg 投与に関する有望な結果の数々により，Mg が理論上でも冠動脈疾患（CAD）患者で心保護薬となり得るという利点や，比較的低コストですむこと，投与の際に特別な専門知識の必要がなく，そして比較的副作用も少ないことから，Mg の投与は，CAD 患者で特に心不全を持った患者，血中 Mg 減少症を伴う高齢者や入院中のハイリスクグループへの治療薬としての位置付けが考えられるだろう。

The data on magnesium supplementation in patients with acute myocardial infarction（AMI）is conflicting. Although a number of relatively small randomized clinical trials have demonstrated a remarkable reduction in mortality when administered to relatively high risk AMI patients, two recently published large-scale randomized clinical trials（the Fourth International Study of Infarct Survival and Magnesium in Coronaries）failed to show any superiority of intravenous magnesium over placebo. Nevertheless, the theoretical potential benefits of magnesium supplementation as a cardioprotective agent in coronary artery disease（CAD）patients, in conjunction with previous promising results from work in animal and humans, its relatively low cost, easy administration, with no need for special expertise, and relatively free of adverse effects, gives magnesium a place in treating CAD patients, especially high-risk groups such as CAD patients with heart failure, the elderly and hospitalized patients with hypomagnesemia.

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Introduction

Epidemiologic evidence linking magnesium deficiency to coronary artery disease（CAD）has been investigated for more than three decades and demonstrated that serum magnesium levels were inversely associated with mortality from ischemic heart disease and all-cause mortality[1)2)].

The available data suggest that a combination of mechanisms may act additively or even synergistically to protect myocytes[3)4)]. Exogenic administration of magnesium prevents intracellular depletion of magnesium, potassium and high-energy phosphates, improves myocardial metabolism and prevents intramitochondrial calcium accumulation and reduces vulnerability to oxygen-derived free radicals[5)]. Magnesium can influence vascular tone[6)7)], cardiac arrhythmias[8)9)], lipid metabolism[10)], platelet aggregation and thrombosis[11)～15)], endothelial function[16)] and infarct size[17)18)].

Clinical trials of magnesium in AMI

1．Prior small randomized clinical trials and the LIMIT-2 trial

In the last decade, 8 prospective, randomized, double-blind controlled trials have been reported, comparing intravenous magnesium to placebo in acute myocardial infarction（AMI）patients, mainly without thrombolytic therapy[19)]. All the first seven trials comprised small numbers of patients and were performed in the prethrombolytic era. In the eighth trial, Second Leicester Intravenous Magnesium Intervention Trial（LIMIT-2）, 70% of the 2,316 patients did not receive thrombolytic therapy[20)]. Despite the difference in study protocols and in patient selection criteria, the results were similar. The mortality odds ratio of the trials without thrombolysis, demonstrated that magnesium reduced in-hospital mortality by almost 19%, mainly by reducing the incidence of serious arrhythmias and left ventricular heart failure by one-quarter[3)19)20)]. The LIMIT-2 trial[20)] randomized 2,316 patients in a median of 3 hours from the onset of chest pain（74% were actually randomized in less than 6 hours）. It was a protocol requirement that magnesium be infused coincident with thrombolysis, a treatment that was administered to 36% of patients. Thus, LIMIT-2 was likely to have achieved elevated magnesium levels at the time of reperfusion in those patients undergoing thrombolysis；the relatively early enrollment of those patients not receiving thrombolysis, combined with prompt administration of magnesium after enrollment, also suggests that magnesium levels were probably elevated when spontaneous reperfusion occurred in patients not undergoing pharmacologic reperfusion. All cause mortality was reduced by 24% at 28 days. Indirect evidence consistent with infarct size limitation as a marker of magnesium-reduced mortality in LIMIT-2, is the 25% lower rate of congestive heart failure（CHF）observed during the hospital phase of treatment, and the ＞20% reduction in ischemic heart disease-related mortality over long term follow-up, that now extends to a mean of 4.5 years[21)].

2．The Shechter's trial

In a prospective, randomized, double-blind, placebo-controlled trial, 215 AMI patients who were considered unsuitable for thrombolysis,

received either 22 g (92 mmol) of $MgSO_4$ for 48 hours (107 patients) or placebo (108 patients)[22]. The striking finding was the reduction of in-hospital mortality in patients who received magnesium compared to placebo (4% vs 17% ; $p < 0.01$).

3. The ISIS-4 trial

In the Fource International Study of Infarct Survival (ISIS-4)[23] approximately 58,000 AMI patients, almost 70% received thrombolytic therapy, the mortality rate at 35 days was 7.6% in the magnesium group and 7.2% in the placebo group, suggesting no survival-benefit from magnesium administration, and even the possibility of slightly deleterious effects. Survival curves were identical even after one year of follow-up. Of the 17,000 patients who did not receive thrombolytic therapy, the mortality rate was 9.3% in both the magnesium and in the control group. The magnesium dose was almost identical to that of the LIMIT-2 study, but with open control. However, the time from onset of symptoms to randomization was substantially longer (median of 8 hours rather than 3). The 30% patients not given a thrombolytic were randomized at a median of 12 hours after symptoms onset. The likelihood of reperfusion occurring (either induced or spontaneous) during magnesium treatment was therefore low. The low mortality rate in the ISIS-4 control group, the late enrollment of patients, particularly those who did not receive thrombolytic treatment, plus the fact that magnesium infusions were delayed by 1～2 hours after thrombolytic therapy, suggest that the possibility that the majority of patients in ISIS-4 were at low mortality risk and that an elevated magnesium blood level was not reached until well beyond the narrow time window for salvage of myocardium or prevention of reperfusion injury suggested by experimental data[17,18,24].

4. Long-term follow-up of the Shechter's trial

In a prospective, double-blind, placebo-controlled trial, our group recently randomly assigned 194 patients with AMI, considered unsuitable candidates for reperfusion therapy at the time of enrollment, to receive intravenous magnesium (96 patients) or isotonic glucose as placebo (98 patients)[25]. All-cause mortality was significantly lower after a mean follow-up of 4.5 years in the magnesium compared to the placebo group (18.7% vs 33.6%, $p < 0.01$; respectively). Rest left ventricular ejection fraction, measured in all patients who survived the last year of follow-up, was significantly higher in patients who received magnesium versus placebo (0.51 ± 0.10 vs 0.44 ± 0.14, $p < 0.05$; respectively). Thus, the favorable effects of intravenous magnesium therapy can last several years after acute treatment, probably due to preserved left ventricular ejection fraction.

5. The MAGIC trial

The recently published Magnesium in Coronaries (MAGIC) trial[26] randomized 6,213 patients ≧ 65 years, of whom an unexpected high percentage (45%) were female with acute ST elevation AMI < 6 hours 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 g intravenous bolus of magnesium sulphate, administered over 15 minutes, followed by a 17 g infusion of magnesium sulphate over 24 hours (n = 3,113) or matching placebo(n = 3,100). Early administration of magnesium (median time from the onset of symptoms was 3.8 hours) in high-risk patients with acute ST elevation AMI < 6 hours had no effect on 30-day mortality. At 30 days(the longest follow-up period), 475(15.3%) patients in the magnesium therapy and 472 (15.2%)in the placebo group died(n = 0.96). In addition, the magnesium supplementation did not change the incidence of heart failure compared to placebo. Compared to the MAGIC trial, our study[22] with thrombolysis-ineligible AMI patients, of whom one third were > 75 years and therefore quite similar to the stratum 2 patients in MAGIC received high doses of intravenous magnesium sulphate for longer periods of time compared to MAGIC(22 g vs 19 g, and 48 hours compared with 24 hours, respectively). A significant higher proportion of the MAGIC study population received aspirin, β-blockers and ACE inhibitors than in our study population[22], and as a result the postulated cardioprotective actions of magnesium could have been superseded by the effects of these medical regimens[26].

Conclusion

In conclusion, magnesium supplementation has been demonstrated both theoretically and experimentally to decrease myocardial damage and reduce mortality in subsets of high-risk patients, including the elderly and/or patients not suitable for thrombolysis if administered prior to reperfusion. It is a low cost therapy, easy to handle and relatively free of side effects. For maximum effectiveness, it appears to be important to administer magnesium as soon as possible in AMI patients (anywhere along the route between the patient's home and the coronary care unit), so that levels are elevated when spontaneous reperfusion occurs in patients who do not receive reperfusion therapy[27].

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