Magnesium in Acute Myocardial Infarction: Clinical Benefits of Intravenous Magnesium Therapy

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Zusammenfassung

Die intravenöse Magnesiumtherapie bei akutem Myokardinfarkt war ein Forschungsschwerpunkt der vergangenen Jahre. Meta-Analysen von Daten randomisierter Studien ergaben einen Vorteil der Magnesiumtherapie in bezug auf Reduktion der Mortalität bei Patienten mit akutem Myokardinfarkt. Der Second Leicester Intravenous Intervention Trial (LIMIT-2) erbrachte eine eindrucksvolle Bestätigung der Magnesiumbehandlung mit dem Ergebnis einer 24% Mortalitätsreduktion. Die Daten von der Forth International Study of Infact Survival (ISIS-4) lösten jedoch große Kontroversen über den klinischen Nutzen der intravenösen Magnesiumtherapie aus. Diese Megastudie mit über 58 000 Patienten mit akutem Myokardinfarkt zeigte keinen Effekt der Magnesiumverabreichung auf die Mortalität. Die unterschiedlichen Resultate von ISIS-4 und früheren Studien könnten jedoch auf Unterschiede im Studiendesign und Patientenformatierung zurückgeführt werden. Der späte Einsatz der intravenösen Magnesiumtherapie in ISIS-4 könnte für das Therapieversagen verantwortlich sein, da aus experimentellen Daten hervorgeht, daß die günstigen Effekte von Magnesium bei akutem Myokardinfarkt auf der Abschwächung von Reperfusionsschäden basieren. Darüber hinaus war das durchschnittliche Mortalitätsrisiko in ISIS-4 verhältnismäßig niedrig im Vergleich zu früheren Studien. Ein Regressionsmodel unter Verwendung zusammengefaßter Daten aus randomisierten Studien vor ISIS-4 legt eine Beziehung zwischen Mortalitätsrisiko der Patienten und erwartetem Nutzen der Magnesiumtherapie nahe. Zusammenfassend bedarf die Darstellung des klinischen Effektes der Magnesiumtherapie bei akutem Myokardinfarkt weiterer Aufklärungen über Studien mit differenziertem Protokoll unter besonderer Berücksichtigung des Einsatzzeitpunktes der Magnesiumverabreichung.

Summary

Intravenous magnesium therapy for acute myocardial infarction has been a focus of research over the past decade. Meta-analyses of data from randomized trials revealed a benefit of magnesium therapy in reducing mortality of patients with acute myocardial infarction. The most compelling confirmation was provided by the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) which reported a 24% mortality reduction with magnesium treatment. Recent data from the Forth International Study of Infarct Survival (ISIS-4), however, caused major controversies about clinical benefits of intravenous magnesium therapy. This large-scale trial of over 58 000 patients with suspected acute myocardial infarction showed no mortality benefit of magnesium administration. Differences in results between ISIS-4 and previous trials, however, may be attributed to differences in trial design and patient characteristics. Late initiation of intravenous magnesium therapy as was performed in ISIS-4 may be accounted for therapy failure, since experimental data suggest that the beneficial effects of magnesium in acute myocardial ischemia are mediated by attenuation of reperfusion injury. Furthermore, the average mortality risk in ISIS-4 was relatively low in comparison to previous trials. A regression model using pooled data from randomized trials prior to ISIS-4, however, suggest a relationship between the baseline mortality risk of patients and the expected benefit of magnesium therapy. In summary, the clinical benefit of magnesium therapy in acute myocardial infarction still awaits complete elucidation and needs further well-designed trials with special attention to timing of magnesium administration.

Résumé

La magnesium thérapie intraveineuse après l'infarctus du myocarde aigu était le point de l'investigation de la décade passée. Les méta-analyses des résultats d' études randomisées ont révélé un avantage du traitement de magnésium en ce qui concerne la réduction de la mortalité chez des patients avec un infarctus du myocarde aigu. Le "Second Leicester Intravenous Intervention Trial" (LIMIT-2) éprouvait une confirmation impressionante du traitement de magnésium qui résultait dans une réduction de 24% de la mortalité. Les résultats de "Forth International Study of Infarct Survival" (ISIS-4) pourtant déclenchait des grandes controverses sur l'avantage clinique de la thérapie intraveineuse de magnésium. Cette méga-étude sur 58 000 patients à la suite d'un infarctus du myocarde aigu ne montrait pas un effet de l'administration de magnésium sur la mortalité. Les résultats différents de ISIS-4 et des études antérieures pourraient cependant être attribués au dessin des études et à la formation des patients. L'application tarde de la magnesium thérapie intraveineuse pendant ISIS-4 pourrait être responsable pour la défaillance du traitement, les données expérimentelles éprouvant que les effets favorables du magnésium chez l'infarctus du myocarde aigu se fondent sur un affaiblissement des dommages de réperfusion. En outre, le risque moyen de la mortalité dans ISIS-4 était comparativement bas, comparés aux études antérieures. Un modèle de regression utilisant les résultats concentrés résultant des études randomisées avant ISIS-4 nous suggère qu'il y a une corrélation entre le risque de la mortalité des patients et l'avantage présumé du traitement de magnésium. En résumé, la démonstration de l'effet clinique du traitement de magnésium chez les patients d'infarctus du myocarde aigu a besoin de renseignements ultérieurs par le moyen d' études comportant un protocole différentié, en particulièrement tenant compte du moment de la prise du magnésium.

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The management of patients with acute myocardial infarction (AMI) has improved dramatically over the last three decades. Recently, attention has turned to additional adjunctive pharmacologic measures such as magnesium, nitrates, and angiotensin converting enzyme inhibitors to determine their potential for reducing mortality further.

Supplemental administration of magnesium is a reasonable avenue to pursue. Are patients with AMI "deficient" in magnesium? The answer to this question is almost certainly, yes, but is multifactorial and may vary amongst patients. Patients with AMI may be deficient in magnesium because of advanced age, prior diuretic treatment for congestive heart failure, low dietary intake of magnesium, or trapping of free magnesium in adipose sites as free fatty acids released by catecholamine-induced lipolysis produce soaps that complex magnesium. Even patients with normal magnesium stores can experience a decline in plasma magnesium concentrations with the onset of AMI.

Since 1984, at least 10 randomized control trials (RCTs) of intravenous magnesium for AMI have been reported. Several statistical models exist for pooling the data from multiple RCTs in a meta-analysis and estimating the treatment effect of magnesium. The *fixed effects* model assumes that the RCTs are sampled from a homogeneous group of trials. Under the homogeneity assumption, each RCT provides an estimate of the true treatment effect and differences between the estimates from the various RCTs are due only to experimental error (within-trial variability). The *random effects* model assumes the RCTs are heterogeneous and that differences between their estimates of the treatment effect are due both to experimental error (within-trial variability) and real differences among the trials such as trial design and characteristics of the patients enrolled (between-trial variability).

Meta-analyses of the 7 RCTs published between 1984–1991 provided an estimated odds ratio (OR) for mortality of magnesium treated patients of 0.44 (0.27, 0.71) using the fixed effects model and 0.45 (0.23, 0.86) using the random effects model [1]. LIMIT-2 reported a 24% reduction in mortality with magnesium treatment ($P<0.04$), confirming the benefit of magnesium in reducing mortality in MI [2].

The situation became unexpectedly complicatd with the presentation of the ISIS-4 results, initially reported in November 1993. The ISIS-4 investigators enrolled over 58 000 patients. The mortality by 35 days was 7.6% in the magnesium group and 7.2% in the control group (OR 1.06 [.99, 1.31]) suggesting no mortality benefit of magnesium administration and even the slight possibility of harm. When ISIS-4 is added to the preceding 8 RCTs the fixed effects model (driven heavily by the large sample size of ISIS-4) indicates no beneficial effect of magnesium while the random effects model suggests that magnesium may reduce mortality.

Two important differences between ISIS-4 and the preceding trials are:

1. **Magnesium was administered late in ISIS-4** (several hours after pharmacologic or spontaneous reperfusion). Several animal models [3–9] of AMI indicate that magnesium reduces infarct size. This appears to be mediated by attenuation of reperfusion injury, possibly by decreasing the incidence of lethal reperfusion injury to myocytes that were viable at the time of restoration of coronary blood flow. The timing of administration of magnesium is critical – elevation of magnesium levels (and presumably tissue concentrations of magnesium) must occur either before coronary occlusion, at the time of coronary occlusion, or at the time of reperfusion of the infarct vessel. Administration of magnesium as little as 15 minutes after reperfusion has elapsed minimizes its ability to reduce infarct size; administration 45–60 minutes following reperfusion has no effect on infarct size in animal models.

2. **The control group mortality in ISIS-4 was only 7.2%.** Analysis of all the clinical trial results prior to publication of ISIS-4 using a regression model relating control mortality and the treatment effect of magnesium showed a curvilinear relationship between the patient's baseline risk of mortality and the expected benefit of magnesium. Thus patients with mortality rates between 10% and 20% had marked reductions in mortality when treated with magnesium. The regression model predicted that patients with a baseline mortality risk of 7% would have no benefit of magnesium – this is exactly the result that was observed in ISIS-4.

The ISIS-4 investigators recorded the time from onset of chest pain to randomization but did not report the time from chest pain to thrombolysis and most importantly did not report the time from thrombolysis (received by 70% of the patients in the trial) to actual administration of magnesium. In the absence of precise information on the timing of administration of magnesium, it is difficult to be assured that the magnesium levels were elevated at the time of reperfusion in any subgroup in ISIS-4. This is further confounded by the relatively low average mortality risk in the trial.

Shechter and colleagues [10] recently randomized 194 patients with AMI considered unsuitable from thrombolysis to control (N = 98) or intravenous magnesium (N = 96). They reported 17 deaths (17.3%) in the placebo group and 4 deaths (4.2%) in the magnesium group corresponding to an OR of 0.21 [.07, 0.64]). Consistent with the hypothesis that magnesium helped reduce mortality by a direct myocardial protective effect was a striking reduction in the incidence of cardiogenic shock in the magnesium group.

How might one synthesize the available data to date on magnesium in AMI? [1]

Although ISIS-4 randomized an extremely large number of patients, its results should not be viewed as the definitive answer to whether magnesium is beneficial for patients with AMI. Rather, ISIS-4 provides biologically useful and clinically important information in the continuum of RCT experience with magnesium. Magnesium seems to reduce mortality in higher risk patients such as those studied by *Shechter* et al. (e.g., elderly and/or those not suitable for thrombolysis).

It is critically important to administer magnesium as soon as possible after the onset of infarction. Using the short-term and long-term results of LIMIT-2 (24% reduction in all cause mortality at one month that appears to be maintained during a follow-up of nearly 5 years), a cost effectiveness model of magnesium in AMI was constructed. Under a variety of assumptions about magnesium's ability to reduce infarct size and minimize the risk of congestive heart failure, magnesium appears to be an extremely cost effective therapy with incremental cost effectiveness ratios ranging between $ 2 000.00 and $ 6 000.00 per additional year of life saved.

Given the abundant, extremely encouraging experimental data and the positive results of the small and intermediate sized trials to date, it would be premature to cast aside such an inexpensive, readily available therapy that is associated with little toxicity and can be administered in the pre-hospital phase, early hospital phase, and CCU phase of treatment for AMI. Despite the large number of patients enrolled in ISIS-4, the question of magnesium's benefit in AMI remains an open one and needs to be addressed in a future trial with careful attention to timing of administration of the agent.

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