

Intravenous Magnesium in Acute Myocardial Infarction

An Effective, Safe, Simple, and Inexpensive Intervention

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In recent decades, the management of patients with suspected acute myocardial infarction (MI) has progressed substantially through the testing (and acceptance or rejection) of a number of different hypotheses. In the 1960s, recognition of the risks of early ventricular fibrillation led to the establishment of coronary care units, emphasis on early hospitalization of patients, and often, the use of prophylactic antiarrhythmic agents (e.g., lidocaine).^{1,2} Various estimates suggest that these approaches were associated with a substantial reduction in early mortality, but the possibility that at least some part of this apparent benefit was due to the hospitalization of lower-risk individuals cannot be ruled out. In the 1970s and early 1980s, the concept of myocardial salvage was extensively evaluated by testing drugs with a variety of different mechanisms of action.³ This included early intravenous β -blockers, hyaluronidase, nitrates, glucose-insulin potassium, calcium blockers, etc.⁴ Of these agents, the value of intravenous β -blockers has been confirmed by large randomized trials⁵ and that of intravenous nitrates by meta-analyses of several smaller trials.⁶ However, the use of early intravenous β -blockers in clinical practice is generally low, and this may relate chiefly to concerns about precipitating heart failure in patients with large MI.⁷ The late 1980s and early 1990s have seen a shift in focus to various antithrombotic strategies; of these, the value and efficacy of a thrombolytic agent and aspirin have been demonstrated and are widely accepted.⁸ The benefit of thrombolytic therapy is greater among patients treated early, with only modest benefits among patients treated within 6–12 hours after the onset of symptoms.⁹ Although the benefits of thrombolytic therapy are considered to be mediated by a reduction in infarct size and improvement in ventricular function, improvements in ejection fraction have not been dramatic.⁹ Moreover, some of the adverse effects result in permanent morbidity (e.g., reinfarction and strokes), and costs of some of these agents are substantial. Although the least expensive thrombolytic agent, streptokinase, is affordable in most Western societies, it still represents a large and

often unaffordable cost to many patients with acute MI in Eastern Europe, Africa, Asia, and some Central and South American countries. Some scientists in the Western world have been focusing on more aggressive “antithrombotic” therapies (i.e., newer thrombolytic agents) and acute interventional strategies (e.g., rescue percutaneous transluminal coronary angioplasty); however, none of these have been shown to be superior to a regimen of streptokinase, aspirin, and perhaps heparin followed by a strategy of investigation of selected patients with specific complications such as ischemia or unexplained pump failure. Moreover, the newer antithrombotics and aggressive interventional strategies are likely to be considerably more expensive and therefore affordable to only a small proportion of patients with MI, even in the wealthiest countries.

There are at least three good reasons to explore fundamentally new strategies to further improve upon the combination of interventions known to be effective (an inexpensive thrombolytic agent plus aspirin; and heparin, β -blockers, and nitrates in selected patients). First, based on data from community-based studies, it appears that our current treatments have little or no impact on deaths caused by cardiogenic shock.¹⁰ Second, major gains are more likely to be realized when an effective treatment that works by a fundamentally different mechanism is used, whereas only modest further gains may be obtained by further refinements of already-proven interventions or agents working by the same mechanism (e.g., a more effective thrombolytic agent or newer antiplatelet agent) (advances by “revolution” versus increments by “evolution”). Third, in order to have a significant public health impact worldwide, the intervention should be simple to use, have few side effects, be easily available, and be inexpensive. These requirements seem to be challenging, but clearly, aspirin fits the bill. Are there other interventions that may act by a mechanism that has been largely unexplored and yet are as effective, inexpensive, and easily available as aspirin?

Magnesium in Acute Myocardial Infarction

Reports of the use of intravenous magnesium in acute MI date back to the 1960s, with the rationale that the agent has an antiarrhythmic effect.¹¹ Although there have been several small randomized trials, the results were generally inconclusive, and the mainstream of investigative cardiologists were preoccupied with other more fashionable hypotheses. Therefore, the role of

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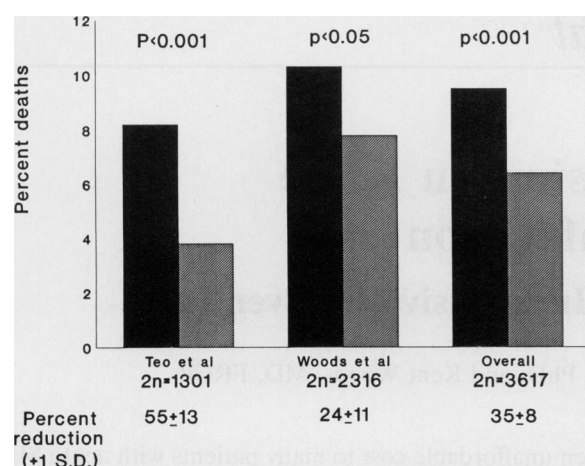


FIGURE 1. Bar graph shows effect of intravenous magnesium on mortality in acute myocardial infarction: Reductions in mortality are shown in the overview by Teo et al¹² (similar results were obtained by Horner et al¹³), in the LIMIT-2 study, and in the overall combined data from all trials.

magnesium was never properly evaluated, and it was largely considered to be an interesting curiosity. Renewed interest in magnesium has been sparked by two recently published and independently conducted meta-analyses of the randomized trials.^{12,13} These two meta-analyses, one conducted by our group¹² and another by Horner,¹³ both indicate that mortality was significantly reduced (see Figure 1). In our overview, there were 25 deaths in 657 patients in the magnesium group versus 53 of 644 in the placebo group ($p<0.001$). Similar results were obtained by Horner.¹³ Although these data suggest a large effect (OR, 0.45), the confidence limits are wide and include the possibility of a more modest but worthwhile effect, such as a 25% reduction in mortality. Furthermore, the results of these two concordant meta-analyses should be taken with considerable caution. First, there is no guarantee that all randomized trials were included, and it may well be that some small unpromising trials that were not published were overlooked. Second, these trials were conducted before the widespread use of thrombolytic agents, aspirin, and nitrates, and it is possible that the benefits of magnesium when used with the above interventions may be more modest. Third, in both meta-analyses, the apparently large treatment effects that were obvious on an informal perusal of the data must have influenced the decision of the authors to perform a more systematic overview and publish the results. This is similar to the data-dependent premature termination of trials that occurs because of an unexpectedly large treatment benefit. In such cases, the observed benefits are likely to be exaggerated compared with the real treatment effects. Nevertheless, these two meta-analyses suggest that there may be some benefit from treatment with intravenous magnesium in acute MI, although there is considerable uncertainty about the actual size of effect. The most appropriate conclusion of these two overviews is that intravenous magnesium is a promising intervention that deserves to be evaluated in large, well-designed randomized trials.

The Second Leicester Intravenous Magnesium Intervention Trial

In response to earlier studies, investigators at the Leicester Royal Infirmary, England,¹⁴ randomized 2,316 (52%) patients with suspected MI out of 4,508 consecutive admissions to the coronary care unit into a placebo-controlled trial of intravenous magnesium sulfate. The main reasons for exclusion were low probability of MI (30%), administrative reasons (22%), randomization on an earlier admission (21%), or absence of informed consent (12%). The trial treatment was an intravenous bolus of 8 mmol magnesium sulfate injected over 5 minutes and followed by 65 mmol by constant infusion over 24 hours. Serum magnesium was thereby approximately doubled for 24 hours after admission, returning to the normal range about 48 hours after randomization. The placebo group received equal volumes of saline. At 28 days, mortality was 90 of 1,150 (7.8%) in the magnesium group and 118 of 1,150 (10.3%) in the placebo group ($p=0.04$), a 24% relative reduction in mortality (95% CI, 1–43%). The observed mortality reduction appeared constant across all subgroups examined, including those with and without thrombolytic or aspirin treatment in the acute phase. Analysis of complications recorded in the coronary care unit showed that the magnesium group had a 25% lower incidence of left ventricular failure (11.2% versus 14.9%; $p=0.009$) corroborated by lower use of loop diuretics and vasodilators for heart failure. No significant differences were seen in the incidence of hypotension (4.8% in each group), heart block (7.8% versus 6.0%, active versus control), tachyarrhythmias, or the use of antiarrhythmic treatments. Side effects of magnesium were confined to transient flushing during the bolus injection and an increased incidence of sinus bradycardia (10.8% versus 8.0%).

Although the reduction in mortality observed in the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) is smaller than that seen in the overview of trials, the confidence intervals overlap and the best current estimate of treatment effect is a weighted average of the results of the previous meta-analyses and LIMIT-2 (115 deaths among 1,807 patients given magnesium and 171 among 1,794 patients in the control group, $p<0.001$). LIMIT-2 does not confirm earlier reports of an antiarrhythmic action of magnesium in acute myocardial infarction. In the earlier trials, the definitions of arrhythmias varied and may have been data dependent. It is in any case, unlikely that magnesium could reduce early mortality by 25% through an antiarrhythmic action alone, since few in-hospital deaths are primarily arrhythmic. The reduction in pump failure events in LIMIT-2 was of the same magnitude (about 25%) as the overall mortality reduction. The earlier trials did not systematically record the effect on heart failure, and the available data on heart failure from the older trials are not reliable.

Mechanism of Action

The effect of doubling serum magnesium is to reduce peripheral vascular resistance by about 20% with a compensatory rise in cardiac output; blood pressure and heart rate are little changed (Table 1).^{15,16} In experimental studies, coronary vasodilation also occurs, accompanied

TABLE 1. Cardiovascular Effects of Supraphysiological Mg^{2+} of Potential Relevance to the Clinical Evidence of a Protective Action of Intravenous Magnesium Salts in Suspected Acute Myocardial Infarction

Site of action	Effect	References
Vascular smooth muscle	Coronary vasodilatation	Kimura et al, 1989 ²⁷
		Vigorito et al, 1991 ¹⁶
		Kugiyama et al, 1988 ²⁸
Platelet	Reduced peripheral vascular resistance	Mroczek et al, 1977 ¹⁵
		Nadler et al, 1987 ²⁹
		Adams and Mitchell, 1979 ^{22*}
Myocardium	Inhibition of aggregation; disaggregation of platelet thrombi	Watson et al, 1986 ²³
		Hearse, 1977 ^{30*}
	Preservation of high-energy phosphates	Borchgrevink et al, 1989 ^{21*}
		Favaron and Bernardi, 1985 ¹⁹
		Ferrari et al, 1986 ^{20*}
	Protection of mitochondrial function against Ca^{2+} overload	Barros et al, 1988 ^{31*}
		Crampton and Clark, 1983 ^{32*}
		Haverkamp et al, 1988 ^{33*}

*Animal studies. All others conducted in humans or on human tissue in vitro.

See Reference 34 for detailed review of the mechanisms of action of magnesium.

by a significant increase in coronary perfusion.¹⁶ The relaxation of resistance vessels by magnesium results from direct competitive antagonism of calcium at the cell membrane of vascular smooth muscle.¹⁷ The hemodynamic effects of the intravenous magnesium regimens used in acute MI are, however, transient despite raised levels of serum magnesium being maintained for several hours. It is unlikely, therefore, that the reduction in mortality and in the incidence of left ventricular failure seen in LIMIT-2 can be attributed to afterload reduction. A more plausible basis for the therapeutic effect is a direct protective action on the myocardium during ischemia and reperfusion, which has been observed experimentally.¹⁸ Possible mechanisms include reduction in cytoplasmic calcium overload or mitigation of its adverse effects on mitochondrial function, phosphate depletion, and oxidative phosphorylation.^{19–21} Although there are no studies in which left ventricular function was directly measured, it is likely that ventricular function improves.

At the serum concentrations attained in the trials, magnesium has antiplatelet effects both in vivo and in vitro^{22,23} that may in part be mediated by the release of prostacyclin from endothelium. The possible contribution of this action to the therapeutic effect of magnesium in acute MI is unclear. The increased incidence of sinus bradycardia in patients infused with magnesium probably reflects Mg^{2+} regulation of acetylcholine-activated K^+ channels in pacemaker tissue or an effect on Ca^{2+} current.²⁴ The direct inhibition of the therapeutic effect is a direct protective action on the myocardium during ischemia and reperfusion, which has been observed experimentally.¹⁸ Possible mechanisms include reduction in cytoplasmic calcium overload or mitigation of its adverse effects on mitochondrial function, phosphate depletion, and oxidative phosphorylation.^{19–21}

The direct inhibition of the sinus node by Mg^{2+} may be offset by reflex tachycardia secondary to reductions in blood pressure. It is probably for this reason that acute studies in humans have generally failed to show any significant effect on heart rate.^{24–26}

Limitations and Implications of Currently Available Data

Although data from the currently available trials are promising (Table 1^{15,16,19–21,27–34}), a few questions remain. First, a more precise estimate of the mortality reduction with magnesium can only be obtained by much larger trials. Second, does magnesium confer benefit, and is it safe when used with other vasodilators such as angiotensin converting enzyme inhibitors and nitrates? Third, do most subsets of patients benefit? The LIMIT-2 trial is not big enough to provide reliable answers on subgroup effects. Fourth, are the benefits observed at 1 month sustained or increased during long-term follow-up? Fifth, to what extent does the improvement in pump function lead to a reduction in cardiogenic shock? At present, the fourth International Study of Infarct Survival (ISIS-4) is investigating the role of intravenous magnesium given for 24 hours, captopril, and oral nitrates given for 4 weeks in a $2 \times 2 \times 2$ factorial design. This study, which has already randomized 40,000 patients and expects to randomize about 50,000, should provide clear answers to the questions posed above.

The available data on magnesium raise two important issues. First, can data from meta-analyses be sufficient grounds for the conduct of large definitive trials? We believe that, ideally, both mechanistic information and data from small trials indicating that an intervention is likely to be safe and effective are desirable before large trials are conducted. However, when the clinical data are promising for a particular intervention (as in the case of magnesium), lack of extensive knowledge of its mechanism of action should not deter mounting large randomized trials. Further information on mechanism of effect, etc., can be obtained by conducting small detailed studies either within the context of large trials or separately. Second, are the data from cumulative meta-analyses in the absence of clear evidence from separate trials sufficiently persuasive so that a new treatment is considered to be clearly indicated and

further larger trials are not necessary? It is possible that sometimes the evidence from meta-analyses is highly statistically significant ($Z > 4$) and that benefit and safety are demonstrated over and above currently available therapies and supported by persuasive mechanistic data. In such cases, we believe the totality of the evidence probably would persuade the majority of physicians to use the intervention. In the case of magnesium, although the available data are quite promising, there are several questions that remain unaddressed (see above). Although some physicians might be persuaded by the current data, others may believe that it would be prudent to await the results of the large ISIS-4 trial before routinely using magnesium.

In conclusion, it appears that intravenous magnesium is a safe, effective, widely practicable, and inexpensive intervention that has the potential of making an important impact on the management of patients with MI in most countries throughout the world.

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