Magnesium Therapy in Aged Patients with Acute Myocardial Infarction

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Zusammenfassung

Die Autoren haben eine randomisierte, gegen Placebo kontrollierte Doppelblindprüfung zur Abschätzung der Effekte von Magnesium auf die Häufigkeit von Herzrhythmusstörungen und auf die Sterberate bei 159 Patienten mit einem nachgewiesenen akuten Myokardinfarkt (AMI), bei dem keine Thrombolytikabehandlung in Frage kam, durchgeführt. 78 Patienten (Gruppe A) bekamen eine 48stündige Magnesiuminfusion und 81 Patienten (Gruppe B) isotonische Glukoselösung als Placebo. Die Sterblichkeit in der Klinik war in Gruppe A signifikant geringer als in Gruppe B (2,5 % gegen 12,3 %; $p < 0,02$). 29 % der Patienten (21 in Gruppe A und 25 in Gruppe B = 46/159) waren über 70 Jahre alt (Durchschnitt: 76 +/– 4; Extreme: 72-89). Die multifaktorielle Analyse hat gezeigt, daß die Randomisierung zufriedenstellend war. Die eine pharmakologische Behandlung erfordernden Tachyarrhythmien sanken bei den betagten Patienten in der mit Magnesium behandelten Gruppe um 38 % und bei den Placebo-Patienten um 56 %. Leitungsstörungen wurden bei 20 % der Placebo-Patienten, aber nur bei 9,5 % der mit Magnesium behandelten Patienten festgestellt. 40 % der betagten Patienten der Magnesium-Gruppe wiesen eine kongestive Herzinsuffizienz auf. Die Sterberate in der Klinik betrug 9,5 % (2 Patienten) in der Magnesium-Gruppe und 16 % (4 Patienten) in der Placebo-Gruppe.
Im Verlaufe der gesamten Prüfung trat kein signifikanter unerwünschter Effekt auf. Unsere Ergebnisse zeigen, daß die intravenöse Gabe von Magnesium bei an AMI leidenden, über 70 Jahre alten Patienten mit einer Reduzierung der Sterberate im Krankenhaus einhergeht. Möglicherweise liegt dies an einer Reduzierung der Anzahl schwererer Herzrhythmusstörungen und der Häufigkeit der Herzinsuffizienz. Dieses Präparat erweist sich somit als eine Alternative zur Behandlung betagter Patienten, bei denen keine thrombolytische Behandlung in Frage kommt.

Summary

The effects of magnesium on the incidence of arrhythmias and on mortality were evaluated in 159 patients with documented acute myocardial infarction (AMI) who could not receive thrombolytic treatment, in a randomized, double blind and placebo controlled study. Seventy eight patients (Gr A) received a magnesium infusion for 48 hours while 81 patients (Gr B) received isotonic glucose as placebo. In-hospital mortality was significantly reduced in Gr A compared to Gr B patients (2.5 % vs 12.3 %, $p < 0.02$). Twenty-nine percent of patients (46/159) were > 70 years old (range: 72–89, mean: 76 ± 4): 21 patients from Gr A and 25 patients from Gr B. The analysis of multiple factors demonstrated a statisfactory randomization. Tachyarrhythmias requiring drug therapy were observed in 38 % of the aged patients in the magnesium group and in 56 % of the placebo group. Conduction disturbances were found in 20 % of the placebo group as compared to 9,5 % in the magnesium group. Congestive heart failure was found in 40 % of aged patients who received magnesium. In-hospital mortality was 9.5 % (2 patients) in the magnesium group compared to 16 % (4 patients) in the placebo group.
No significant side effects were observed during the trial. Our findings demonstrated that intravenous magnesium administration in AMI patients > 70 years is associated with a reduction of in-hospital mortality, possibly by reduction of major arrhythmias and of the incidence of heart failure, and could be an alternative therapy for aged patients who are unsuitable candidates for thrombolytic therapy.

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Résumé

Les auteurs ont réalisé une étude randomisée, en double-insu, contrôlée contre placebo pour évaluer les effets du magnésium sur la fréquence des troubles du rythme cardiaque et sur le taux de mortalité chez 159 patients présentant un infarctus du myocarde (IM) prouvé et non justiciables d'un traitement thrombolytique. Soixante dix-huit patients (Groupe A) ont reçu une perfusion de magnésium pendant 48 heures et 81 patients (Groupe B) ont reçu, à titre de placebo, une solution isotonique de glucose. La mortalité intra-hospitalière a été significativement plus faible dans le groupe A que dans le groupe B (2,5 % contre 12,3 %, $p < 0,02$). Vingt-neuf pour cent des patients (21 dans le groupe A et 25 dans le groupe B, soit 46/159) étaient âgés de plus de 70 ans (moyenne: 76 ± 4; extrêmes: 72–89). L'analyse multi-factorielle a montré que la randomisation était satisfaisante. Les tachyarythmies nécessitant un traitement pharmacologique ont diminué de 38 % chez les patients âgés du groupe traité par le magnésium et de 56 % dans le groupe recevant le placebo. Des troubles de la conduction ont été enregistrés chez 20 % des patients sous placebo contre seulement 9,5 % des malades recevant le magnésium. Quarante pour cent des sujets âgés du groupe magnésium ont présenté une insuffisance cardiaque congestive. Le taux de mortalité intra-hospitalière a été de 9,5 % (2 patients) dans le groupe magnésium et de 16 % (4 patients) dans le groupe placebo.
Aucun effet indésirable significatif n'est apparu au cours de l'étude. Nos résultats montrent que l'administration intraveineuse de magnésium en cas d'IM chez des patients âgés de plus de 70 ans est associée à une réduction du taux de mortalité intra-hospitalière, peut-être due à une diminution du nombre des troubles majeurs du rythme cardiaque et de l'incidence des insuffisances cardiaques. Ce produit s'avère donc un traitement alternatif chez des patients âgés non justiciables d'un traitement thrombolytique.

Introduction

Over recent years evidence has accumulated that hypomagnesemia is associated with cardiac arrhythmias [1–9], sudden cardiac death from ischemic heart disease [10, 11] and, recently, with mortality in the acute stage of myocardial infarction [12–16]. While hearts from patients with acute my-

ocardial infarction (AMI) are magnesium deficient [17, 18], magnesium serum levels obtained in patients with AMI who survived are either low or normal [3, 19].

Since the era of thrombolytic therapy, in-hospital mortality of AMI patients has been significantly reduced from 10–15 % to only 3–5 % [20, 21]. Nevertheless, only one-third of the patients, at the most, are considered suitable candidates for thrombolysis. Exclusion criteria [20, 21] for thrombolytic therapy include diathesis disturbances, advanced age, time from beginning of chest pain to admission greater than four hours, recent trauma or surgery, recent stroke and no symptoms of chest pain.

The purpose of our study was to evaluate the potential effects of magnesium sulfate administration to aged patients (who were considered unsuitable candidates for thrombolytic therapy) in the acute phase of myocardial infarction on: arrhythmias, conduction disturbances, congestive heart failure and mortality.

Patients and Methods

In a prospective, randomized, double-blind, placebo controlled trial, 159 patients with the diagnosis of AMI (according to symptoms, ECG findings and serum enzymes elevation — altogether) who were unsuitable for thrombolytic treatment, received either magnesium (78 patients) or isotonic glucose as placebo (81 patients). Twenty nine percent of patients (46/159) were over 70 years old (range: 72–89, mean: 76 ± 4): 21 patients from the magnesium group and 25 from the placebo group. The baseline characteristics of the population were similar in the two groups and the analysis of multiple factors demonstrated a satisfactory randomization.

The patients received 22 gr (91.6 mmol) of $MgSO_4$ dissolved in a half liter of isotonic glucose during the first 48 hours or a half liter of isotonic glucose as placebo. The infusion rate was adjusted so that 6 gr (25 mmol) of $MgSO_4$ were given during the first 3 hours; thereafter 10 gr (41.6 mmol) during the next 21 hours and 6 gr (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 ICCU nurses. In addition, heart rhythm was continuously recorded by computerized *Holter* system 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.

Results

Seventy-eight patients with proven AMI received magnesium while 81 patients received isotonic glucose as placebo. In-hospital mortality was significantly reduced in patients who received magnesium compared to these on placebo (2.5 % vs. 12.3 %; $p < 0.02$). Twenty-nine percent of patients (46/159) were above 70 years old (range: 72–89, mean: 76 ± 4): 21 patients from the magnesium group and 25 from the placebo group. The average time from onset of chest pain to initiation of treatment was similar for the two groups. The two groups had a similar prevalence of risk factors and received the same conventional therapy in the Intensive Care Unit. No adverse reactions were observed upon administration of the intravenous magnesium. The relevant data on the outcome is illustrated in Tab. 1. Fourteen aged patients (56 %) in the placebo group had arrhythmias requiring therapy, compared to only 8 aged patients (38 %) in the magnesium group. Ten patients (40 %) from the placebo group hat congestive heart failure compared to only 6 patients (28.9 %) from the magnesium group. Five patients (20 %) who received placebo had conduction disturbances as compared to 2 patients (9.5 %) who received magnesium.

There was a reduction in hospital mortality from 16 % (4 patients) in the placebo group to 9.5 % (2 patients) in the magnesium group, possibly by the reduction of major arrhythmias and the incidence of congestive heart failure. Six patients (6 out of 10) who received placebo died from cardiogenic shock between days 1–14, of whom 4 were older than 70 years. In the magnesium group, two patients older than 70 years died, one from cardiogenic shock and the second from electromechanical dissociation.

Serum magnesium concentration rose 24 hours after the beginning of infusion, however, it did not change in the placebo group. In the placebo group there was no difference in serum magnesium levels in patients who died or those who survived.

Tab. 1: Clinical outcome of aged patients with acute myocardial infarction (double blind study) who received intravenous magnesium versus placebo.

	Magnesium		Placebo	
	No.	%	No.	%
Major arrhythmias	8	38.0	14	56
Conduction disturbances	2	9.5	5	20
Congestive heart failure	6	28.9	10	40
In-hospital mortality	2	9.5	4	16

Discussion

During the last decade, five randomized, double blind clinical controlled trials comprising a total of 588 patients with AMI have been reported [12–16, 22]. In spite of the slight differences in the study protocols, the results are very similar. The acute mortality rate was more than threefold higher in patients who received placebo than in those who received magnesium (11 % vs. 3 %). Magnesium treatment also reduced the incidence of arrhythmias in the acute phase of AMI by 50 % (34 % in the placebo group vs. 18 % in the magnesium group).

Thrombolytic agents reduced dramatically the in-hospital mortality from 10–15 % to 3–5 %. Nevertheless, only one-third of the patients, at the most, are considered suitable candidates for thrombolysis. Most protocols do not permit aged patients to receive

thrombolysis. In our cardiac care unit about 25 % of patients are over the age of 70 and in-hospital mortality with conventional therapy is 15 %. Administration of intravenous magnesium to these aged patients suffering from AMI considered unsuitable candidates for thrombolytic therapy reduces in-hospital mortality to only 9.5 %.

The beneficial effect of magnesium infusion is mainly due to a pharmacological action of magnesium rather than to repletion of a deficit. This interpretation is supported by the fact that the serum magnesium levels reached, lie well above the upper normal limit [16].

The beneficial effect of magnesium in aged patients cannot only be explained by a reduction in the incidence of arrhythmias or of congestive heart failure. A possible myocardial protection effect must be postulated to explain such a favorable effect on survival in acute myocardial infarction. Magnesium supplementation has been found to reduce the size of myocardial infarction [12, 13], platelet aggregation [24, 25], basal tone and tension of the arterioles, [26–31], and peripheral vascular resistance and blood pressure [32]: it increases coronary vasodilatation and improve the hemodynamic profile of the myocardium.

As to its potential in reducing the immediate mortality from acute myocardial infarction, we opine, as we previously reported, that this safe, inexpensive and simple therapy should be considered as yet another tool in protecting aged patients suffering from acute myocardial infarction who are considered unsuitable candidates for thrombolytic therapy.

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