Effects of Oral Magnesium Therapy on Exercise Tolerance, Exercise-Induced Chest Pain, and Quality of Life in PatientsWithCoronaryArteryDisease

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Previous studies have demonstrated that magnesium supplementation improves endothelial function in patients with coronary artery disease (CAD). However, the impact on clinical outcomes, such as exercise-induced chest pain, exercise tolerance, and quality of life, has not been established. In a multicenter, multinational, prospective, randomized, double-blind and placebo-controlled trial, 187 patients with CAD (151 men, 36 women; mean ± SD age 63 ± 10 years, range 42 to 83) were randomized to receive either oral magnesium 15 mmol twice daily (Magnosolv-Granulat, total magnesium 365 mg provided as magnesium citrate) (n = 94) or placebo (n = 93) for 6 months. Symptom-limited exercise testing (Bruce protocol) and responses given on quality-of-life questionnaires were the outcomes measured. Magnesium therapy significantly increased intracellular magnesium levels ([Mg]i) in a substudy of 106 patients at 6 months compared with placebo (35.5 ± 3.7 vs 32.6 ± 2.9 mEq/L, p = 0.0151). Magnesium treatment significantly increased exercise duration time compared with placebo (8.7 ± 2.1 vs 7.8 ± 2.9 minutes, p = 0.0075), and lessened exercise-induced chest pain (8% vs 21%, p = 0.0237). Quality-of-life parameters significantly improved in the magnesium group. These findings suggest that oral magnesium supplementation in patients with CAD for 6 months results in a significant improvement in exercise tolerance, exercise-induced chest pain, and quality of life, suggesting a potential mechanism whereby magnesium could beneficially alter outcomes in patients with CAD. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;91:517–521)

We have recently reported, in a short-term ancillary trial,[1] that oral magnesium supplementation improves endothelial function, measured by brachial artery flow-mediated dilation. The effect of oral magnesium on endothelial function was shown to be similar to the beneficial extent observed in lipid-lowering studies.[2] We hypothesized that magnesium supplementation would improve outcomes related to myocardial ischemia in patients with coronary artery disease (CAD) because of its beneficial impact on endothelial function. The present study compares the effect of oral magnesium intervention with placebo on exercise tolerance, exercise-induced ischemia, and quality of life in patients with CAD.

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METHODS

Study design and population: Patients from Israel, the United States, and Austria were recruited consecutively into a randomized, prospective, multicenter, double-blind, and placebo-controlled trial. An ancillary trial, performed only at the United States site, assessed brachial artery flow-mediated dilation, has been previously published.[1] Inclusion criteria included those patients who were >20 years of age with CAD documented by a previous myocardial infarction, and patients who had undergone coronary artery bypass surgery, or coronary angiography or angioplasty. Patients were excluded if they had unstable angina, congestive heart failure more than New York Heart Association functional class III, chronic diarrhea, renal failure (serum creatinine >3 mg/dl), acute myocardial infarction within the preceding 3 months, hyper/hypothyroidism, insulin-dependent diabetes mellitus, peripheral vascular disease, history of drug or alcohol abuse, or chronic liver disease. The study was approved by the institutional review boards in Israel, United States, and Austria, and all participants gave written informed consent.

Study protocol: Patients were randomized by a computerized randomization program (Rancode-Plus, version 3.1, IDV Data Analysis, Munich, Germany) to either oral Magnosolv-Granulate (15 mmol magnesium ions, total magnesium 365 mg provided as a citrate and 5.4 mmol potassium as a hydrogen-carbon-

0002-9149/03/$–see front matter
doi:10.1016/S0002-9149(02)03297-6

TABLE 1 Baseline Characteristics of Study Population

Variable	Magnesium (n = 94)	Placebo (n = 93)
Age (yrs)	64 ± 10	62 ± 10
Systemic hypertension	46 (49%)	47 (51%)
Diabetes mellitus	21 (22%)	25 (27%)
Current smoker	18 (19%)	19 (21%)
Previous myocardial infarction	61 (65%)	66 (72%)
Previous coronary angiography	83 (88%)	82 (88%)
Previous coronary angioplasty	50 (53%)	50 (54%)
Previous coronary bypass	25 (27%)	23 (25%)
β-receptor antagonist	46 (49%)	44 (47%)
Calcium antagonists	14 (15%)	19 (20%)
Digitalis	4 (4%)	6 (7%)
Diuretics, K-sparing	2 (2%)	0
Diuretics, non–K-sparing	7 (8%)	7 (8%)
Aspirin	89 (95%)	89 (96%)
Long-acting nitrates	17 (18%)	29 (31%)
Angiotensin-converting enzyme inhibitors	52 (55%)	57 (61%)
Lipid-lowering agents	62 (66%)	62 (67%)

Values are expressed as mean ± SD.
p = NS.
K = potassium.

ate [Asta Medica Arzneimittel Ges.m.b.H., Vienna, Austria]) or placebo twice daily for 6 months. Patients were instructed to continue with their regular medications and diet during the study. At entry and after 6 months, patients underwent a physical examination, exercise testing (treadmill or bicycle), blood tests for measurements of lipids, blood cell count, electrolytes, and also filled out quality-of-life questionnaires. Sublingual intracellular magnesium levels ([Mg]i) were measured in 106 consecutive patients at the United States and Israeli sites.

Exercise and quality-of-life testing: After an overnight fast and a 24-hour withdrawal of β-receptor antagonists, calcium channel blockers, and angiotensin-converting enzyme inhibitors, all patients underwent a maximum symptom-limited exercise test (treadmill or bicycle, using the Bruce protocol).[3] Blood pressure and heart rate at each exercise stage and at peak exercise; time to onset of angina and 1-mm ST-segment depression; ST-segment depression at peak exercise; maximal ST-segment depression; presence of cardiac arrhythmias; double-product (heart rate [beats per minute] × systolic blood pressure [mm Hg]) achieved; and total exercise duration were recorded. Myocardial ischemia was defined as the presence of ≥1.0 mm horizontal or downsloping ST-segment depression 80 ms after the J-point during exercise or recovery. Cardiac arrhythmias were defined as ventricular premature beats of Lown grade ≥II.[4] Quality of life was documented at entry and after 1, 3, and 6 months (study exit) using 2 different self-assessment questionnaires: (1) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Care 30 (EORTC QLQ-C30; version 2.0) as a general questionnaire and (2) the disease-specific Seattle Angina Questionnaire, designed for patients with CAD.

Intracellular magnesium and lipid measurements: Tissue [Mg]i **was measured in sublingual epithelial cells,** using a scanning electron microscope (Philips, Einthoven, The Netherlands) and radiographic analysis of individual epithelial cells **(EXA test, Intracellular Diagnostics, Inc. Foster City, California)**(normal mean ± SD values 37.9 ± 4.0 mEq/L). Reported values were the mean of 5 to 10 cells per patient; a specimen was rejected if variance was >2%. Sublingual epithelial cell [Mg]i correlates well with human atrial [Mg]i.[5] Fasting blood samples were analyzed for total cholesterol, high-density lipoprotein (HDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglyceride concentrations. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald formula.[6]

Statistical analysis: All statistical evaluations and analyses were performed using TESTIMATE software package (Test & Estimation, IDV, Gauting, Germany). The Wilcoxon-Mann-Whitney U test was used to calculate differences over time and to compare the treatment groups. Significance calculations for maximal exercise time were performed using the documented data; the last value carried forward method was also used. For all other objectives, the documented data were analyzed and missing data were treated as missing values. All patients randomized into the trial were included in the final analysis by intention to treat. Per protocol, efficacy analysis and intention to treat analyses for safety were performed. The significance level was 0.05 and the type 2 error was chosen to be 0.1.

RESULTS

Patient demographics: The study population consisted of 187 patients with CAD (151 men, 36 women; mean age of 63 ± 10 years, range 42 to 83) recruited in Austria (81 patients [43%]), Israel (56 patients [30%]), and the United States (50 patients [27%]). All patients had CAD documented by a previous coronary angiography (n = 165), myocardial infarction (n = 127), coronary artery bypass surgery (n = 48), or coronary angioplasty (n = 100) (Table 1). No significant group differences in baseline characteristics were seen (Table 1). Overall mean LDL cholesterol at study entry was 102 ± 14 mg/dl (range 43 to 186). There were no significant changes in the use of concomitant medications throughout the course of the study. At 6 months, 75 patients (80%) who had received magnesium and 86 patients (93%) who had received placebo completed the study and were included in the safety analysis. Two patients in each group did not perform an exercise test and therefore failed to complete the study protocol. Additional reasons for discontinuing of the study included: (1) patient decision but not due to adverse events (12 of 19 patients in the magnesium group vs 3 of 7 in the

Sublingual Epithelial Cell Data (Exatest) Dr. B. Silver

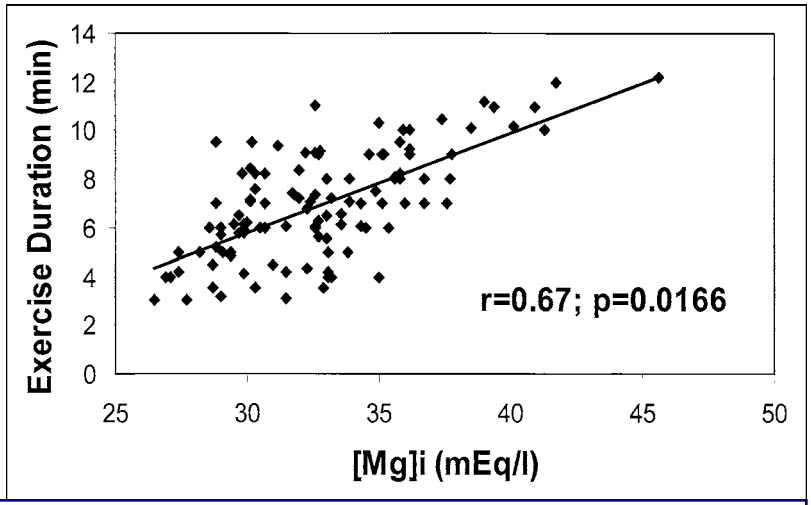

FIGURE 1. Correlation of [Mg]i and exercise duration in a substudy performed at the United States (n = 50) and Israeli (n = 56) sites, demonstrating a linear correlation.

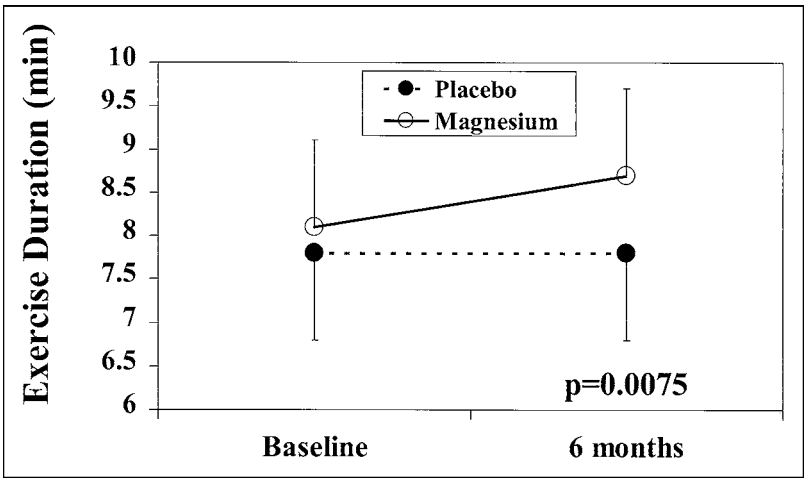

FIGURE 2. Exercise duration in the placebo group *(black circles)* (n = 93) compared with the magnesium group *(white circles)* (n = 94) at baseline and after 6 months.

placebo group, p = 0.3526); (2) poor study drug compliance (3 of 19 magnesium group vs 4 of 7 placebo group, p = 0.2734); (3) adverse events: diarrhea (2 of 19 magnesium group vs 0 placebo group, p = 0.5168), abdominal pain and constipation (1 of 19 magnesium group vs 0 placebo group, p = 0.6782); and (4) elective surgery (1 of 19 magnesium group only). Therefore, 73 patients (78%) who had received magnesium and 84 (90%) who had received placebo were included in the efficacy analysis.

Effect of treatment on intracellular magnesium levels: In the [Mg]i substudy in the United States[1] and Israeli sites, 36 of 50 (72%) and 44 of 56 (79%) of the patients with CAD, respectively, had baseline [Mg]i below normal levels (37.9 ± 4.0 mEq/L). Baseline [Mg]i was similar between the groups (33.2 ± 3.2 vs 33.7 ± 2.7 mEq/L, p = 0.6151). Magnesium therapy significantly increased [Mg]i versus placebo (35.5 ± 3.7 vs 32.6 ± 2.9 mEq/L, p = 0.0151). There was a significant correlation in the total population between exit [Mg]i and exercise duration (r = 0.63, p = 0.0166) (Figure 1). Patients with [Mg]i ≥37.9 mEq/L (n = 26)**had a significantly greater exit exercise duration**(9.1 ± 2.1 vs 6.9 ± 1.8 minutes, p <0.0001) than those with [Mg]i <37.9 mEq/L (n = 80).

Treatment effect on exercise performance: Exercise duration differed significantly at 6 months (study exit) (8.7 ± 2.1 vs 7.8 ± 2.9 minutes, p = 0.0075) (Figure 2). Patients receiving magnesium had a significant 14% improvement in exercise duration compared with no change among those receiving placebo.

Patients assigned to magnesium supplementation or to placebo were comparable at baseline, as assessed by chest pain caused by exercise-induced ischemia (20% vs 21%, p = 1.0000), and ST-segment depression at peak exercise (33% vs 37%, p = 0.3400). After 6 months, there were substantially fewer patients in the magnesium group with exercise-induced chest pain than in the placebo group (8% vs 21%, p = 0.0237), and fewer patients whose exercise test had to be discontinued because of angina (7% vs 17%, p = 0.0522) (Table 2). There were no significant differences in the hemodynamic parameters of resting and exercise heart rate, blood pressure and double-product, and the percent target heart rate achieved between the groups at baseline and at 6 months (Table 2).

The impact of oral magnesium on quality of life and functional class: Most quality-of-life parameters were significantly improved in the magnesium group after 6 months of treatment, whereas fewer parameters demonstrated significant improvement in the placebo group (Table 3). General pain assessment was significantly improved within the magnesium group during the study (p = 0.0026). At 6 months, the percentage of patients who answered affirmatively to the question "Did the present medication improve your condition?" was significantly higher in the magnesium group compared with the placebo group (66% vs 47%, p = 0.0165). There were no differences between the groups in New York Heart Association functional class.

The impact of oral magnesium on lipids: Overall, the mean ± SD population baseline total cholesterol (190 ± 38 mg/dl), triglycerides (149 ± 88 mg/dl), HDL cholesterol (42 ± 13 mg/dl), and LDL cholesterol (102 ± 14 mg/dl) were near optimal, due to the high prevalence of lipid-lowering medication use (Table 1); there were no significant differences between the mag-

TABLE 2 Exercise Parameters at Six Months

Variable	Placebo (n = 84)	Magnesium (n = 73)	p Value
Supine heart rate (beats/min)	72 ± 14	70 ± 14	0.4407
Standing heart rate (beats/min)	74 ± 14	72 ± 13	0.5955
Systolic blood pressure supine (mm Hg)	140 ± 19	139 ± 17	0.5190
Diastolic blood pressure supine (mm Hg)	80 ± 13	81 ± 14	0.6969
Heart rate at maximum exercise (beats/min)	135 ± 19	131 ± 18	0.6019
Double-product (beats/min × mm Hg)	24,695 ± 5,744	25,555 ± 5,326	0.3103
Exercise-induced chest pain	18 (21%)	6 (8%)	0.0237
Time to chest pain (min)	6.2 ± 1.5	6.9 ± 1.8	0.7196
Test termination due to angina	14 (17%)	5 (7%)	0.0522
ST-segment depression	42 (50%)	31 (42%)	0.5244
Time to 1 mm ST-segment depression (min)	3.6 ± 2.2	4.4 ± 2.6	0.1787
Cardiac arrhythmias*	3 (4%)	3 (4%)	1.0000

Values are expressed as mean ± SD.
*Cardiac arrhythmias indicate ventricular premature beats of Lown grade ≥II.

TABLE 3 Quality-of-Life Assessment

	Placebo			Magnesium			p Value for Δ (baseline–6 mo)
Test	Baseline	6 mo	p Value	Baseline	6 mo	p Value	Magnesium vs Placebo
EORTC QLQ C-30							
Functional Scale*							
Physical functioning	83	85	0.6695	84	91	0.0053	0.1340
Role functioning	78	80	0.2823	76	86	<0.0001	0.1843
Emotional functioning	70	75	0.0545	74	78	0.0168	0.3718
Cognitive functioning	75	78	0.0969	77	80	0.1106	0.6452
Social functioning	79	81	0.6439	78	87	0.0012	0.3417
Symptom Scale†							
Fatigue	28	27	0.6190	27	19	<0.0001	0.0515
Nausea & vomiting	8	10	0.1691	8	4	0.0120	0.1009
Pain	21	20	0.5149	22	14	0.0026	0.2318
Dyspnea	23	24	0.6095	22	19	0.1857	0.3082
Insomnia	32	25	0.0634	27	21	0.0708	0.3284
Appetite loss	12	14	0.2859	13	12	1.0000	0.9574
Constipation	16	14	0.3833	18	7	0.0016	0.0420
Diarrhea	10	11	0.3513	8	25	<0.0001	0.0040
Financial impact	22	18	0.1594	15	14	0.6975	0.5115
Global Health Status‡	63	67	0.0349	67	73	0.0021	0.0847
Seattle Angina Questionnaire§							
Physical limitation	67	68	0.5653	68	71	0.0156	0.5760
Anginal stability	57	60	0.2012	53	65	<0.0001	0.2093
Anginal frequency	65	70	0.0117	68	76	<0.0001	0.0972
Treatment satisfaction	65	70	0.0146	68	76	<0.0001	0.1072
Disease perception	67	71	0.0336	64	75	<0.0001	0.2609

All scales are 0 to 100 points.
*A higher score for a functional scale represents a higher level of functioning.
†A higher score represents a higher level of symptomatology.
‡A higher score represents a higher quality of life.
§Lower scores indicate more frequent angina, and higher scores less frequent angina.

nesium and placebo groups at baseline and after 6 months for these parameters.

Adverse events: At month 1, there were no significant differences in adverse events between the magnesium and placebo groups (53% vs 50%, p = 0.6541). At 6 months, however, adverse events were significantly more frequent in the placebo group compared with magnesium group (61% vs 32%, p = 0.0054). Serious adverse events were reported in 3 patients on placebo (1 hospitalization for nonspecific chest pain, 1 appendectomy, and 1 hospitalization for chest pain, coronary angioplasty, and stenting) and in 2 patients on magnesium (1 hospitalization for chest pain and one 48-hour hospitalization for fever).

DISCUSSION

This is the first clinical trial to demonstrate that oral magnesium supplementation improves cardiac exercise tolerance, exercise-induced chest pain, and quality of life in patients with CAD. Magnesium therapy signi cantly improved these clinically related parameters in patients who were receiving near optimal medical treatment for CAD (96% received aspirin, 66% were on lipid-lowering medications, 48% re-

ceived β-receptor antagonists, and 55% were on angiotensin-converting enzyme inhibitors). The [Mg]i subgroup data, **demonstrating a significant increase** [Mg]i in response to oral magnesium therapy, support the beneficial effects attributed to magnesium supplementation. Furthermore, these prospective results substantiate our previous work, which demonstrated a significant cross-sectional association between [Mg]i and exercise tolerance in patients with CAD.[7] Previous work from our laboratory has demonstrated a beneficial reduction in platelet-dependent thrombosis measured ex vivo in patients with CAD who were randomized to an oral magnesium supplement.[8]

There may be multiple mechanisms underlying these beneficial effects of magnesium. Higher [Mg]i levels may improve intracellular adenosine triphosphate production and glucose use because magnesium is a cofactor of adenosine triphosphate.[9] Magnesium is considered nature's physiologic calcium blocker,[9–11] reducing the release of calcium from and into the sarcoplasmic reticulum, while protecting the cells against calcium overload under conditions of ischemia. Magnesium reduces systemic and pulmonary vascular resistance, with a concomitant decrease in blood pressure and a slight increase in the cardiac index.[9,12–14] Elevation of extracellular magnesium levels reduces arteriolar tone and tension in a wide variety of arteries,[9] and potentiates the dilating effects of some endogenous (adenosine, potassium, and some prostaglandins) and exogenous (isoproternol and nitroprusside) vasodilators.[9] As a result, magnesium can mildly reduce systolic blood pressure,[15] thereby unloading the ischemic ventricle.[7,9,10] Our prior work in the substudy of the present study among the United States patients demonstrated that oral magnesium supplementation for 6 months improved brachial artery endothelial function in patients with CAD.[1]

Our substudy in the United States and Israeli patients also demonstrated that 75% of the patients with CAD had less than normal baseline [Mg]i levels (37.9 ±4.0 mEq/L), reflecting a magnesium-defcient state. The mechanisms responsible for this are probably multifactorial.[9,16] Evidence suggests that the occidental "American diet" is relatively deficient in magnesium, whereas the "oriental diet," characterized by a greater intake of fruits and vegetables, is richer in magnesium.[17] It has also been observed that patients with CAD absorb more magnesium during magnesium loading testing than those without CAD, suggesting that CAD itself may be associated with excessive magnesium loss and a relative magnesium deficient state.[18]

Our demonstration of improved ability to exercise longer without pain and improvement in quality of life with oral magnesium supplementation supports the addition of this inexpensive and essentially safe nutritional supplement as adjuvant therapy for patients with CAD.

APPENDIX

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