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Oral Magnesium Supplementation Reduces Ambulatory Blood Pressure in Patients With Mild Hypertension

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BACKGROUND

Accumulating evidence implicates a role of Mg^{2+} in the pathophysiology of essential hypertension. Previous studies evaluating the antihypertensive efficacy of Mg^{2+} supplementation gave contradictory results. This study aimed to investigate the effect of oral Mg^{2+} supplementation on 24-h blood pressure (BP) and intracellular ion status in patients with mild hypertension.

METHODS

A total of 48 patients with mild uncomplicated hypertension participated in the study. Among them, 24 subjects were assigned to 600 mg of pidolate Mg^{2+} daily in addition to lifestyle recommendations for a 12-week period and another 24 age- and sex-matched controls were only given lifestyle recommendations. At baseline and study-end (12 weeks) ambulatory BP monitoring, determination of serum and intracellular ion levels, and 24-h urinary collections for determination of urinary Mg^{2+} were performed in all study subjects.

RESULTS

In the Mg^{2+} supplementation group, small but significant reductions in mean 24-h systolic and diastolic BP levels were observed, in contrast to control group (-5.6 ± 2.7 vs. -1.3 ± 2.4 mm Hg, $P < 0.001$ and -2.8 ± 1.8 vs. -1 ± 1.2 mm Hg, $P = 0.002$, respectively). These effects of Mg^{2+} supplementation were consistent in both daytime and night-time periods. Serum Mg^{2+} levels and urinary Mg^{2+} excretion were significantly increased in the intervention group. Intracellular Mg^{2+} and K^{+} levels were also increased, while intracellular Ca^{2+} and Na^{+} levels were decreased in the intervention group. None of the intracellular ions were significantly changed in the control group.

CONCLUSION

This study suggests that oral Mg^{2+} supplementation is associated with small but consistent ambulatory BP reduction in patients with mild hypertension.

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A role for Mg^{2+} in the pathophysiology of hypertension has been supported for many years.[1–3] Hypertensive patients were shown to have an impaired intracellular ion content, characterized by decreased intracellular Mg^{2+} and increased intracellular Ca^{2+} and Na^{+} compared to healthy controls.[4] In many cross-sectional studies, an inverse correlation between serum Mg^{2+} levels and systolic (SBP) and diastolic blood pressure (DBP) was observed,[5] while large longitudinal studies showed that low dietary Mg^{2+} intake was also associated with an increased risk for developing hypertension.[6,7]

Several human studies[8,9] investigating effects of oral Mg^{2+} supplementation on office blood pressure (BP), along with two recent meta-analyses[10,11] on the field gave contradictory results. In addition, studies using ambulatory BP monitoring (ABPM) to assess the potential BP-lowering effects of Mg^{2+} supplementation are extremely few,[12,13] although ABPM has many advantages over the conventional office BP measurement[14] and has been reported to provide more accurate information concerning the efficacy of the nonpharmacological treatment of hypertension.[15]

Furthermore, intracellular Mg^{2+} has a regulating role on the activity of major cell-membrane cation channels;[16] in this context, some data support that there may be a link between changes in intracellular ion content induced by Mg^{2+} supplementation and its BP-lowering effects.[17,18] However, none of the Mg^{2+} supplementation intervention studies using ABPM included measurement of the intracellular ion levels.

The aim of this study was to investigate the effect of oral Mg^{2+} supplementation on 24-h BP and intracellular ion status in patients with uncomplicated mild hypertension and the possible relations between potential changes in these parameters.

METHODS

Participants. A total of 48 subjects were included in the study. All subjects visited for first time the Hypertension Outpatient Clinic of our Department for hypertension of recent onset. All the examinations were conducted according to the Declaration of Helsinki (1989 amendment). The study was approved by the

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Ethics Committee of Faculty of Medicine, Aristotle University of Thessaloniki. Recruitment started in August 2004 and study was completed in March 2006.

All subjects were originally evaluated at the Hypertension Outpatient Clinic of our department. The initial evaluation included a full medical history, a physical examination and standard laboratory tests. Inclusion criteria were (i) new-onset stage I hypertension, diagnosed in three separate visits with a 1-week interval between them, according to international guidelines,[19,20] (ii) low total cardiovascular risk profile, according to guidelines,[20] and (iii) absence of any antihypertensive medication. Exclusion criteria were (i) stage II or stage III hypertension, defined as SBP >160 mm Hg and DBP >100 mm Hg, (ii) secondary hypertension, (iii) severe congestive heart failure, (iv) coronary artery disease, (v) chronic kidney disease, (vi) active liver disease, (vii) diabetes mellitus, (viii) history of malignancy, (ix) history of drug and alcohol abuse, and (x) current use of dietary supplements.

The first 26 consecutive outpatients fulfilling the inclusion and exclusion criteria that were willing to receive the Mg^{2+} intervention were assigned to receive 600 mg (25 mmol) of pidolate Mg^{2+} orally twice a day for 12 weeks, in addition to standard recommendations for lifestyle changes, according to guidelines[19,20] (intervention group). Among outpatients who fulfilled the inclusion and exclusion criteria, but were not willing to receive the study intervention, another 26 subjects (age- and sex-matched) formed the control group; this group was given only standard lifestyle recommendations and was followed for a similar period. Subjects were instructed not to use any over-the-counter dietary or other supplements (vitamins, herbs) during the study. Two patients from each study group refused to complete all the protocol procedures at study-end. Therefore, a total of 48 subjects were included in the final analysis. All subjects provided informed consent prior to enrollment.

Study protocol. Eligible patients came to the Clinical Research Laboratory of our department at 0800 hours, after a 12-h fast. In each subject, body weight and height were measured and body mass index was calculated as weight divided by height squared. Blood samples were drawn for standard laboratory tests and for determination of intraeryrthrocyte Na^+, K^+, Ca^{2+}, and Mg^{2+} levels. On the previous day, patients have performed a 24-h urinary collection to determine the urinary Mg^{2+} excretion. After blood sampling, an ambulatory BP monitor and a cuff of appropriate size were fitted and the BP recordings started.

Subjects visited the outpatient clinic every 4 weeks, for BP measurement, physical exam, and standard laboratory tests. Possible side-effects were searched with questions from a standardized questionnaire. At 12 weeks (3 months) they visited again the Clinical Research Laboratory, where all the above measurements were repeated.

Measurements

Ambulatory BP monitoring: Ambulatory BP was monitored using a Spacelabs 90207 device[21] (Spacelabs Medical, Redmond, WA) at baseline and the end of the study. The ABPM was assessed for 25 h. The data of the first hour were not included in the analysis, and this period was used to enable patients to become comfortable with the equipment. The monitor recorded ambulatory BP three times an hour between 0800 and 2400 hours, and hourly between 2400 and 0800 hours. Readings were used for the analysis only if >80% of measurements were valid with no more than two nonconsecutive day hours (0800–2400 hours) with fewer than two valid readings, and no more than one night hour (2400–0800 hours) without reading. The hypertension thresholds used were 140/90 mm Hg for daytime and 125/75 mm Hg for night time.[14] Mean SBP, DBP, mean BP, systolic and diastolic loads were calculated.

Intracellular Na^+, K^+, Ca^{2+}, and Mg^{2+} measurement: The preparation of the erythrocyte suspensions for the measurement of intracellular Na^+ and K^+ was done as follows. Fresh heparinized blood was centrifuged within 1 h of collection. The plasma, buffy coat, and the top-most layer (=10%) of the erythrocytes were discarded, and the remaining erythrocytes were resuspended in ice-cold isotonic $MgCl_2$, pH 7.4. During each of the washes that followed, the supernatant $MgCl_2$ and the top-most layer of erythrocytes were discarded. The precise hematocrit of the washed erythrocyte suspension was determined in triplicate. The Smith and Samuels method[22] was used for the measurement of intracellular Na^+ and K^+ concentrations. That is to say, an erythrocyte suspension of known volume (0.2 ml) was lysed, diluted with distilled water diluent 9.8 ml for Na^+ determination and 99.8 ml for K^+ determination, and the cation contents were determined by a flame photometer (Eppendorf type) and calculated as millimoles per liter of erythrocytes (mmol/l).

For the measurement of intracellular Ca^{2+} and Mg^{2+}, blood was collected via a vein catheter in heparinized polyethylene tubes and centrifuged at 3,000 rpm for 5 min. The plasma, buffy coat, and the top-most layer (=10%) of the erythrocytes were discarded, and the remaining erythrocytes were washed four times in an isotonic phosphate-buffered saline-glucose (20 mmol/l phosphate/150 mmol/l NaCl/2 mg/ml glucose, pH 7.4) buffer. For intracellular Ca^{2+}, the packed cells were diluted with five volumes trichloroacetic acid 10%, which contained 20,000 parts of lanthanum chloride. The solution was centrifuged again and the top-most layer was used for the assessment of intracellular Ca^{2+} with an atomic absorption spectrophotometer (503 A; PerkinElmer, Waltham, MA). For intracellular Mg^{2+}, 1 ml packed red cells was diluted in 19 ml of deionized water. The red cells were then lysed by stirring and refrigerated at 0 °C for 20 min. The cells were subsequently left at room temperature for 20 min and stirred, and refrigerated again until all cells were lysed. A total of 2 ml of $SrCl_2$ 2.5% was added to 5 ml of the hemolysate and 13 ml of deionized water. Intracellular Mg^{2+} was measured in the solution with an atomic absorption spectrophotometer (Perkin Elmer 503 A).

Statistical analysis. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 13.0 for windows XP (SPSS, Chicago, IL). Continuous variables were expressed as mean ± s.d. Baseline differences between

the two study groups were evaluated with paired *t*-tests or χ^2-tests. For comparisons between the baseline and the end of the study in each study group, paired *t*-tests or Wilcoxon's Signed Rank tests were used according to the normality of the distribution. Between-group differences were compared using unpaired *t*-tests or Mann–Whitney *U*-tests where appropriate.

Table 1 | Baseline characteristics of study participants

	Intervention group ($N = 24$)	Control group ($N = 24$)	*P* value
Age (years)	45.3 ± 10.1	46.9 ± 8.7	0.664
Weight (kg)	82.6 ± 13.4	81.6 ± 9.9	0.825
Sex (men/women)	15/9	15/9	1
BMI (kg/m^2)	28.3 ± 2.8	27.4 ± 4.1	0.468
Glucose (mg/dl)	91.8 ± 10.9	96.4 ± 7.2	0.232
Urea (mg/dl)	35.4 ± 10.1	29.5 ± 8.2	0.113
Creatinine (mg/dl)	0.91 ± 0.09	0.95 ± 0.1	0.180
Serum Na^+(meq/l)	139.8 ± 3.4	140.1 ± 2.5	0.799
Serum K^+ (meq/l)	4.4 ± 0.4	4.2 ± 0.3	0.246
Serum Ca^{2+} (mg/dl)	4.76 ± 0.15	4.7 ± 0.3	0.425
Serum Mg^{2+} (mg/dl)	2.3 ± 0.2	2.2 ± 0.1	0.263
24-h Systolic BP (mm Hg)	146.7 ± 4.1	144.7 ± 4.6	0.64
24-h Diastolic BP (mm Hg)	91.5 ± 2.6	89.6 ± 3.9	0.146

BMI, body mass index, BP, blood pressure

To identify possible relationships between the changes in the parameters under study, bivariate correlation coefficients (*r*) were calculated using the Pearson's product formula. A *P* value level <0.05 (two-tailed) was considered statistically significant.

RESULTS

Baseline demographic characteristics and baseline mean 24-h SBP and DBP levels for the Mg^{2+} supplementation and the control groups are presented in Table 1. There were no significant differences between groups in age, body weight, body mass index, serum electrolytes, and other standard biochemical parameters. In addition, the baseline mean 24-h SBP and DBP values did not differ significantly between the two study groups.

A shown in Table 2, in the group of oral Mg^{2+} supplementation small but significant reductions in mean 24-h SBP, DBP, mean BP, systolic and diastolic loads were evident between baseline and the end of the study. All these parameters were significantly decreased at the end of the study for both daytime and night-time periods. In contrast, in the control group, nonsignificant changes between baseline and the end of the study were observed. Overall 24-h changes between baseline and 12 weeks in the Mg supplementation and control groups were −5.6 ± 2.7 mm Hg vs. −1.3 ± 2.4 mm Hg ($P < 0.001$) for SBP and −2.8 ± 1.8 mm Hg vs. −1.0 ± 1.2 mm Hg ($P = 0.002$) for DBP.

At the end of the study, a significant increase in serum Mg^{2+} levels as well as in 24-h urinary Mg^{2+} excretion was observed

Table 2 | Ambulatory blood pressure (ABP) levels at baseline and study-end in Mg^{2+} supplementation and control groups and the between groups comparison

	Intervention group			Control group			Between-group comparison
	Baseline	Week 12	*P* value	Baseline	Week 12	*P* value	*P* value
24-h ABP							
SBP (mm Hg)	146.7 ± 4.1	141.1 ± 4.1	<0.001	144.7 ± 4.6	143.4 ± 5.4	0.128	<0.001
DBP (mm Hg)	91.5 ± 2.6	88.7 ± 2.9	<0.001	89.6 ± 3.9	89.5 ± 3.80	0.798	<0.001
MBP (mm Hg)	109.6 ± 2.6	105.8 ± 2.8	<0.001	107.2 ± 3.6	106.8 ± 3.7	0.443	<0.001
Systolic load (%)	65.2 ± 9.3	45.5 ± 11.0	<0.001	59.5 ± 9.8	54.5 ± 8.5	0.185	<0.001
Diastolic load (%)	60.7 ± 13.1	42.1 ± 12.1	<0.001	54.1 ± 13.6	50.6 ± 12.3	0.136	<0.001
Daytime ABP							
SBP (mm Hg)	151.0 ± 4.4	145.2 ± 4.1	<0.001	148.4 ± 5.2	146.9 ± 5.6	0.071	0.002
DBP (mm Hg)	95.1 ± 3.3	91.1 ± 3.0	<0.001	93.1 ± 3.6	92.7 ± 3.8	0.515	<0.001
MBP (mm Hg)	113.8 ± 3.0	109.2 ± 2.9	<0.001	111.5 ± 3.7	111.4 ± 4.1	0.908	<0.001
Systolic load (%)	61.9 ± 9.2	41.6 ± 9.9	<0.001	56.3 ± 3.3	51.9 ± 7.7	0.550	<0.01
Diastolic load (%)	57.0 ± 9.9	42.9 ± 10.9	<0.001	52.7 ± 10.6	52.69 ± 12.9	0.979	<0.001
Night-time ABP							
SBP (mm Hg)	138.6 ± 6.6	131.4 ± 6.6	<0.001	142.4 ± 5.3	138.8 ± 4.1	<0.05	<0.05
DBP (mm Hg)	85.6 ± 4.1	81.5 ± 3.7	<0.001	86.2 ± 2.4	85.1 ± 3.1	0.120	<0.001
MBP (mm Hg)	103.3 ± 4.4	98.1 ± 4.3	<0.001	104.9 ± 2.8	102.7 ± 2.8	<0.05	<0.01
Systolic load (%)	68.1 ± 15.3	56.7 ± 15.9	<0.001	62.7 ± 7.5	61.2 ± 8.1	0.532	<0.001
Diastolic load (%)	52.5 ± 15.4	46.8 ± 15.26	<0.001	68.6 ± 12.1	65.1 ± 13.5	0.239	<0.001

DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

Table 3 | Serum and intracellular ion concentration at baseline and study-end in the intervention and control groups and the between groups comparison

	Intervention group			Control group			Between-group comparison
	Baseline	Week 12	*P* value	Baseline	Week 12	*P* value	*P* value
Serum							
Na^+, meq/l	139.8 ± 3.4	139.1 ± 2.9	0.355	140.1 ± 2.5	141.3 ± 2.5	0.111	0.087
K^+, meq/l	4.4 ± 0.4	4.0 ± 0.3	<0.001	4.2 ± 0.3	4.3 ± 0.3	0.438	0.006
Ca^{2+}, mg/dl	4.8 ± 0.1	4.7 ± 0.1	0.043	4.67 ± 0.3	4.64 ± 0.2	0.616	0.64
Mg^{2+}, mg/dl	2.3 ± 0.2	2.44 ± 0.2	0.003	2.2 ± 0.1	2.1 ± 0.2	0.136	0.003
Intracellular							
Na^+, mmol/l	12.3 ± 1.2	10.3 ± 0.9	<0.001	11.3 ± 1.2	10.3 ± 1.1	0.092	0.017
K^+, mmol/l	96.1 ± 4.7	105.0 ± 6.8	<0.001	99.6 ± 6.8	102.6 ± 6.8	0.131	0.029
Ca^{2+}, mmol/l	0.3 ± 0.03	0.27 ± 0.02	<0.001	0.3 ± 0.05	0.3 ± 0.02	1	<0.001
Mg^{2+}, mmol/l	2.1 ± 0.08	2.4 ± 0.09	<0.001	2.2 ± 0.32	2.2 ± 0.36	0.794	<0.001
24-h urinary Mg^{2+}, mg/l	52.3 ± 50.8	178.4 ± 89.8	<0.001	65.1 ± 37.2	62.1 ± 34.9	0.257	<0.001

in the intervention group, whereas, nonsignificant changes were evident in the control group (Table 3). Among other serum electrolytes, the only significant change was a reduction in the serum K^+ levels in the intervention group. As far as intracellular ion levels were concerned, there was a significant increase compared to baseline in the intracellular Mg^{2+} and K^+ levels in the intervention group. On the contrary, intracellular Ca^{2+} and Na^+ levels were significantly decreased at the end of the study. None of the intracellular ions were significantly changed in the control group during the 12-week follow-up period (Table 3).

Correlation analysis revealed weak-to-moderate nonsignificant associations between the changes in 24-h SBP and DBP and the changes in the serum and intracellular ion levels in the intervention group (data not shown).

During the 12-week follow-up period, in the group of Mg^{2+} supplementation one patient reported an episode of mild nausea, and one patient mild diarrheic symptoms (three episodes of mild diarrhea within a day); none of these events led to discontinuation of Mg^{2+} intervention. In the control group, one patient reported two episodes of mild diarrhea.

DISCUSSION

This study aimed to evaluate the effect of oral Mg^{2+} supplementation for a 12-week period on 24-h BP and intracellular ion levels in patients with uncomplicated mild hypertension. The main finding was that oral Mg^{2+} supplementation was associated with small but statistically significant reductions in the mean 24-h SBP, DBP, mean BP, systolic and diastolic loads. All these reductions were consistent in both daytime and night-time periods. In addition, significant increases in serum Mg^{2+} levels and 24-h urinary Mg^{2+} excretion were evident at the end of the study in the intervention group. Oral Mg^{2+} supplementation was also associated with a significant increase in the intracellular Mg^{2+} levels along with a parallel significant fall in the intracellular Ca^{2+} and Na^+ concentrations, tending in this way to revert the abnormalities in the intracellular ion content that characterize patients with hypertension.

Findings deriving from previous studies on the field using casual office BP recordings are contradictory. In several studies a BP reduction after oral magnesium supplementation was reported,[8,18] but other studies failed to confirm these findings.[9,23] This inconsistence can be partially attributed to the heterogeneity across the studies concerning their clinical design, the dose and the type of Mg^{2+} supplement used, the duration of the intervention, the presence and the severity of hypertension of participants at baseline. A pooled estimate of the overall treatment effect of oral Mg^{2+} supplementation on BP was provided by two recently published meta-analyses. The first[10] included 20 studies (including 1,220 subjects), 14 of which in hypertensives and showed that oral Mg^{2+} supplementation provided only an 0.6/0.8 mm Hg average fall in SBP and DBP. The second[11] meta-analysis included 12 randomized controlled trials involving 545 hypertensive participants. The analysis showed that oral Mg^{2+} supplementation as compared to control significantly reduced DBP by 2.2 mm Hg, but the respective fall in SBP (−1.3 mm Hg) was nonsignificant.

The first study to investigate the effect of oral Mg^{2+} supplementation on 24-h BP showed a reduction of about 5 mm Hg in the averaged mean BP in 25 patients with mild hypertension.[12] However, the Mg^{2+} supplementation period in this study was only 2 weeks. In a subsequent crossover study by Kawano *et al.*[13] in 60 patients with mild-to-moderate hypertension, Mg^{2+} supplementation produced a 2.5/1.4 mm Hg decline in 24-h SBP and DBP after 8 weeks. These beneficial effects were not confirmed in another study in which 300 normotensive women from the Nurse Health Study II were randomized in K^+ supplementation (40 mmol/day), Ca^{2+} supplementation (30 mmol/day), Mg^{2+} supplementation (14 mmol/day), all three minerals together or placebo for

16 weeks (ref. 24). In this study, oral Mg^{2+} administration produced a nonsignificant reduction of 0.9/0.7 mm Hg in 24-h SBP and DBP compared to placebo. These results should be interpreted in the context of the low dose of the Mg^{2+} given and the normotensive population studied, as several previous reports indicate that the BP-lowering properties of oral Mg^{2+} supplementation are dose-dependent[25] and strongly related to the baseline BP levels.[13] Our study expands the previous findings on a beneficial effect of Mg^{2+} supplementation on ambulatory BP, showing that a medium dose of Mg^{2+} supplement in hypertensive patients has a mild hypotensive effect that is consistent throughout the 24-h period.

Despite the extensive clinical and experimental research on the field, several aspects concerning the exact mechanisms through which Mg^{2+} exerts its BP-lowering effects still remain unclear. Among the different mechanisms proposed, a pivotal role could be attributed to the effects Mg^{2+} on vascular smooth muscle cell tone, reactivity and contractility.[1,2,26] In vascular smooth muscle cells, Mg^{2+} acts extracellularly by inhibiting transmembrane Ca^{2+} transport and Ca^{2+} entry or intracellularly as a Ca^{2+} antagonist, thereby modulating the vasoconstriction action of increased intracellular Ca^{2+} (refs. 2,16,26). Further, the influence of Mg^{2+} on vascular tone and reactivity could also be mediated through its action on Na/K ATPase activity, which regulates the transmembrane Na^+ and K^+ transport.[2,16,26]

In our study, oral Mg^{2+} supplementation was associated with a statistically significant increase in the intracellular Mg^{2+} levels along with a significant fall in intracellular Ca^{2+} and Na^+. These effects on the intracellular ion content are in accordance with the findings of previous clinical[18] and experimental studies.[17,27] On the limited studies of the field that investigated ion concentrations, the BP reduction after Mg^{2+} supplementation exhibited mild correlations with the reduction in the intraeryrthrocyte Na^+[18] or with the increase in serum Mg^{2+} levels.[13] In our study, several mild correlations between the observed changes in mean 24-h SBP and DBP levels and the changes in serum and intracellular ion concentrations in the intervention group were evident, none of which was significant, possibly due to the sample size. However, the changes in the intracellular ion content we observed support the fact that reversion of the impaired intracellular ion homeostasis is perhaps the basic mechanism through which Mg^{2+} exerts its BP-lowering effects.

Despite that our findings were based on the most reliable method for measuring BP (that is ABPM) and the laborious methods for intracellular ion measurement, our study has some limitations that should be acknowledged. First, it did not follow a randomized design. However, the controls were very carefully matched to the intervention group. Second, the control group did not receive placebo and remained only on lifestyle counseling. To what extent this influenced our findings is unknown, but we have reasons to believe that this had a minimal impact, as ambulatory BP recordings are not influenced by the placebo effect.[28] Finally, although the follow-up period of our study is the longest among studies on hypertensive patients using ABPM, it is restricted only to 12 weeks; thus our findings should be confirmed in longer studies.

In conclusion, the results of this study expand the existing evidence for a mild 24-h BP-lowering effect of oral Mg^{2+} administration in patients with mild hypertension. Further, in this study Mg^{2+} supplementation was associated with several changes in the intracellular ion content that could represent a plausible mechanistic explanation of the hypotensive effect of Mg^{2+}. Future long-term clinical trials are required to fully elucidate the exact clinical significance of dietary Mg^{2+} supplementation in the management of essential hypertension.

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