The Preventive Effect of Magnesium on Coronary Spasm in Patients With Vasospastic Angina*

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Study objectives: Previous studies have reported that magnesium (Mg) deficiency is associated with coronary spasm. However, little is known about the preventive effect of Mg on coronary spasm. The present study investigated whether Mg prevents coronary spasm in patients with vasospastic angina (VSA).

Design: Effectiveness trial.

Setting: University medical center.

Patients: Twenty-two patients with VSA.

Intervention: Coronary spasm was induced with an intracoronary infusion of acetylcholine (Ach). After spontaneous relief of the coronary spasm, Mg sulfate (0.27 mmol/kg body weight) was infused IV over 20 min in 14 patients and isotonic glucose was infused in 8 patients as control subjects. Intracoronary infusion of Ach was then repeated, and the diameter of the coronary arteries was measured quantitatively.

Measurements and results: Mg infusion caused coronary artery dilatation at baseline in both the spastic (5.9 ± 2.3%) and nonspastic segments (5.5 ± 1.5%). Mg infusion reduced the severity of chest pain and ST-segment deviations during coronary spasm. After the Mg infusion, the percent change in the diameter of the spastic segments improved from −62.8 ± 2.6% to −43.7 ± 4.7% during coronary spasm. Overall, 10 of 14 patients (71%) responded favorably to Mg infusion. Isotonic glucose infusion did not elicit changes in chest pain severity, ST-segment deviations, or the diameter of the coronary arteries during spasm.

Conclusions: Mg infusion produces nonsite-specific basal coronary dilatation and suppresses Ach-induced coronary spasm in patients with VSA. (CHEST 2000; 118:1690–1695)

Key words: acetylcholine; magnesium sulfate; quantitative coronary angiography

Abbreviations: Ach = acetylcholine; LCA = left coronary artery; Mg = magnesium; NO = nitric oxide; NS = not significant; QCA = quantitative coronary angiography; sSTd = sum of the ST-segment deviations in 12 leads of the ECG; VSA = vasospastic angina

Coronary spasm, which results from an increased vasomotor tone of epicardial coronary arteries, can produce myocardial ischemia. Coronary spasm plays an important role in the pathogenesis of not only vasospastic angina (VSA) but ischemic heart disease as well, including other forms of angina, acute myocardial infarction, and ischemic sudden death. The precise mechanisms underlying coronary spasm remain to be elucidated, but several factors such as a change in autonomic tone, enhanced α-adrenergic receptor activity, hyperreactivity of coronary smooth muscle, and endothelial dysfunction have been implicated in the genesis of coronary spasm.

Magnesium (Mg) deficiency has also been considered as a possible factor contributing to the genesis of coronary spasm. Furthermore, it has been reported that infusion of Mg reduced coronary spasm attacks in patients with VSA. However, no report has verified the preventive effect of Mg on coronary spasm using quantitative coronary angiography (QCA). Therefore, we investigated the changes in the diameter of coronary arteries at baseline and during acetylcholine (Ach)-induced coronary spasm in patients with VSA using QCA before and after infusion of Mg.

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1690
Study Subjects

We studied 22 Japanese patients with VSA (mean age, 57 years; range, 43 to 69 years; 19 men, 3 women) who fulfilled the following inclusion criteria: (1) spontaneous chest pain associated with ST-segment elevation or depression on 12-lead ECG or ambulatory ECG at rest; (2) coronary spasm (≥ 50% reduction of the diameter of the artery during coronary angiography) in the left coronary artery (LCA) associated with ST-segment changes and/or typical chest pain after intracoronary injection of Ach; and (3) absence of organic coronary artery stenosis on angiography. Patients with prior myocardial infarction, heart failure, or other serious diseases were excluded. Written informed consent was obtained from all patients prior to the study. The protocol was approved by the ethics committee of our institution.

Study Design

The study design has been previously reported in detail. In brief, anti-anginal therapy was discontinued 48 h prior to catheterization, except for the unrestricted use of sublingual nitroglycerin, which was withheld 1 h prior to catheterization. Diagnostic right and left heart catheterization and coronary angiography were performed using the standard percutaneous femoral approach. A 6F guide catheter was introduced into the left main coronary artery. A 5F temporary pacing electrode catheter (Bard; Tewksbury, MA) was placed in the right ventricular apex via the right femoral vein and connected to a temporary pacemaker. This was set at a rate of 50 beats/min.

Study Protocol

After baseline conditions had been established, incremental doses of Ach were infused into the LCA (3, 30, and 100 µg/min) for 2 min, with 5-min intervals between consecutive doses until the induction of coronary spasm. Once coronary spasm was induced, the next infusion of Ach was withheld. Coronary spasm resolved spontaneously within 2 to 3 min without use of nitroglycerin and allowed further studies in almost all patients with VSA. Patients with prolonged coronary spasm and/or unstable hemodynamics induced by Ach infusion received an intracoronary injection of Mg sulfate. 

After a 15-min interval, when baseline conditions had been reestablished, Mg sulfate, 10% solution diluted in 50 mL isotonic glucose solution (0.27 mmol/kg body weight), was infused IV over 20 min in 14 patients (Mg group mean age, 57 years; range, 43 to 67 years; 12 men, 2 women). This dose of Mg sulfate has been shown to prevent spastic angina attacks induced by exercise or hyperventilation. An isotonic glucose solution (50 mL) was infused IV over 20 min in the eight control subjects (control group mean age, 57 years; range, 44 to 69 years; seven men, one woman). The infusion of incremental doses of Ach (3, 30, and 100 µg/min) was then repeated in the same manner, up to the same dose that produced coronary spasm. Nitroglycerin, 200 µg, was given as an intracoronary injection. Intracoronary infusion of Ach was performed using an infusion pump (TE-311; Terumo; Tokyo, Japan) set at a rate of 1 mL/min.

Coronary angiography was performed immediately after each drug administration, and 2 min after nitroglycerin injection. Arterial pressure, heart rate, and ECG were monitored continuously and recorded on a multichannel recorder (Nihonkoden Polygraph System; Nihonkoden; Tokyo, Japan).

QCA

The arterial diameters were measured without knowledge of the clinical characteristics of the patients. An end-diastolic frame was selected and images were analyzed using a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens AG; Berlin, Germany). The average value of three measurements of luminal diameter was used for analysis. Changes in the coronary diameter in response to various drugs were expressed as the percent change from the baseline measurement on the angiogram taken prior to infusion.

The diameter of the spastic and nonspastic segments were measured in each patient. Spastic segments were defined as sites with ≥ 50% reduction in diameter of the artery from the baseline by Ach infusion. The diameter of the spastic segments was defined as 0 mm during total occlusion. When coronary spasm occurred diffusely from the proximal to the distal segments of a coronary artery, the diameters were measured at both the proximal and distal segments of the spasm artery. Nonspastic segments were defined as the proximal and the distal segments of the left anterior descending artery and left circumflex coronary artery demonstrating < 40% reduction in diameter after Ach infusion. An excellent correlation for intraobserver variability was noted in each segment (r = 0.997 at the nonspastic segments, and r = 0.992 at the spastic segments during coronary spasm).

Analysis of interobserver variability in the measurement of each segment also showed high reproducibility (r = 0.985 at the nonspastic segments, and r = 0.972 at the spastic segments during coronary spasm).

Biochemical Parameters

Venous blood was obtained via the femoral sheath before and after Mg or isotonic glucose, and serum ionized electrolytes (Mg and calcium) were measured using a selective ion electrode (NOVA 8; NOVA Biomedical; Waltham, MA). All measurements were performed in duplicate.

Drug Preparations

Ach (Daichi Pharmaceutical; Tokyo, Japan) was dissolved in physiologic saline solution, and Mg sulfate (Toa Pharmaceutical; Tokyo, Japan) was diluted in isotonic glucose immediately prior to use. Nitroglycerin (Nihonkayaku; Tokyo, Japan) was used at the original concentration.

Statistical Analysis

All data are expressed as the mean ± SEM. Differences in categorical variables between two groups were analyzed by χ² analysis and goodness-of-fit tests. Changes in chest pain severity...
before and after Mg or placebo infusion were compared using the Mann-Whitney U test. Changes in electrolytes in each group and the rST8 before and after Mg or placebo infusion were compared using the Wilcoxon signed-rank test. Serial changes in hemodynamic variables and changes in epicardial coronary diameter in response to each drug were compared using a one-way analysis of variance. Serial percent changes in the epicardial coronary diameter with Mg or placebo infusion and with Ach infusion before and after the administration of Mg or placebo were compared using a two-way analysis of variance. A p < 0.05 was considered statistically significant.

Results

Clinical Characteristics

The clinical characteristics of the studied patients are listed in Table 1. No significant differences in the clinical characteristics existed between the Mg and control groups.

In the Mg group, coronary spasm was induced in seven patients by intracoronary Ach infusion at a dose of 30 μg/min, and in the remaining seven patients at a dose of 100 μg/min. In the control group, coronary spasm was induced in five patients at a dose of 30 μg/min, and in the remaining three patients at a dose of 100 μg/min. In both groups, intracoronary infusion of Ach at a dose of 3 μg/min produced no significant coronary spasm.

All patients in the Mg group experienced a body flushing sensation during the IV infusion of Mg sulfate, which was self-limited and disappeared within 5 min after termination of the infusion. Infusion of isotonic glucose as a control caused no adverse effects.

Electrolyte Variables

In the Mg group, serum ionized Mg concentration increased from 0.48 ± 0.02 to 1.24 ± 0.08 mmol/L (p < 0.0001), and serum ionized calcium concentration increased from 1.12 ± 0.01 to 1.16 ± 0.01 mmol/L (p = 0.0094) after the Mg infusion. In the control group, isotonic glucose infusion did not produce any significant change in electrolyte variables (ionized Mg, 0.49 ± 0.02 to 0.50 ± 0.03 mmol/L; ionized calcium, 1.13 ± 0.02 to 1.14 ± 0.02 mmol/L; both p = not significant [NS]).

Hemodynamic Variables

No significant changes in heart rate or mean arterial pressure occurred in response to infusion of any drug except nitroglycerin. Intracoronary infusion of nitroglycerin reduced the mean arterial pressure and increased the heart rate in both groups (p < 0.001).

Response of Basal Coronary Arteries to Mg Infusion

The spastic segments (n = 31) measured 2.01 ± 0.11 mm at baseline and 2.11 ± 0.12 mm after Mg infusion. The nonspastic segments (n = 45) measured 2.17 ± 0.10 mm at baseline and 2.28 ± 0.10 mm after Mg infusion. The spastic segments (n = 21) measured 2.00 ± 0.11 mm at baseline and 1.98 ± 0.13 mm after placebo infusion. Similarly the nonspastic segments (n = 22) measured 2.23 ± 0.16 mm prior to infusion and 2.21 ± 0.16 mm after placebo infusion in the control group. In both the spastic and nonspastic segments, responses to Mg or placebo infusion differed significantly between the two groups (spastic segments: 5.9 ± 2.3% after Mg, −1.2 ± 2.4% after placebo, p = 0.0410; nonspastic segments: 5.5 ± 1.5% after Mg, −1.3 ± 1.0% after placebo, p < 0.0001).

Chest Pain and ST-Segment Change During Coronary Spasm

Typical chest pain during coronary spasm occurred in 10 patients of the Mg group before Mg infusion and in 3 patients after Mg infusion. The chest pain score decreased from 5 ± 1 to 2 ± 1 with Mg infusion (p = 0.0244). Chest pain occurred in six patients in the control group before placebo infusion and in the same patients after infusion. The chest pain score did not change with placebo infusion (before, 4 ± 1; after, 5 ± 1; p = NS).

ST-segment shift during coronary spasm was noted in all patients. rST8 decreased from 8 ± 1 to 3 ± 1 mm (p = 0.0002) with Mg infusion, but did not change with placebo infusion (before, 8 ± 2 mm; after, 9 ± 2 mm; p = NS; Fig 1).

Examination of the degree of improvement in chest pain severity and rST8 revealed 10 responders to Mg infusion. In the remaining four nonresponders, the chest pain score did not decrease by ≥ 3 and rST8 did not decrease > 50%.

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<th>Table 1—Clinical Characteristics of the Patients*</th>
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<td>Characteristics</td>
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<td>Age, yr</td>
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<td>Men/women, No.</td>
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<td>Dose of Ach at spasm, No.</td>
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<td>Spastic segment, No.</td>
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*LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; Pro = proximal segment; mid = mid segment; dis = distal segment.
Change in Coronary Diameter During Coronary Spasm

The mean diameter of the spastic segments (n = 31) measured in the Mg group during coronary spasm prior to Mg infusion was 0.69 ± 0.06 mm, and the percent change in diameter of the spastic segments from baseline were −62.8 ± 2.6%. After Mg infusion, the mean diameter of the spastic segments increased to 1.16 ± 0.10 mm (p = 0.0002), and the percent change decreased to −43.7 ± 4.7% (p = 0.0144). Improvement of these values was greater in responders (mean diameter, 0.69 ± 0.06 mm before and 1.29 ± 0.12 mm after Mg infusion, p < 0.0001; percent change, −62.2 ± 2.1% before and −36.1 ± 5.4% after Mg infusion, p = 0.0015), whereas these values did not change in the nonresponders (mean diameter, 0.68 ± 0.14 mm before and 0.90 ± 0.19 mm after Mg infusion, p = NS; percent change, −64.0 ± 7.1% before and −59.6 ± 6.9% after Mg infusion, p = NS). In the control group, placebo infusion caused no significant change in these values during coronary spasm (n = 21; mean diameter, 0.92 ± 0.04 mm before and 0.84 ± 0.08 mm after, p = NS; percent change, −51.4 ± 2.7% before and −57.2 ± 3.6%, p = NS; Fig 2).

Response to Mg Infusion and Serum Ionized Mg Concentration

In the 10 responders to Mg infusion, the mean serum ionized Mg concentration was 0.48 ± 0.02 mmol/L at baseline and 1.29 ± 0.12 mmol/L after Mg infusion (p < 0.0001 vs before). These values in the four nonresponders were not different from the responders (baseline, 0.49 ± 0.02 mmol/L, p = NS vs

\[ \text{Figure 1. } \sigma\text{STδ during coronary spasm in the Mg (left) and control (right) groups. Vertical bars represent the SEM.} \]

\[ \text{Figure 2. Percent change in coronary diameter from baseline in the spastic segments in response to Ach before (open circles) and after (solid circles) Mg or placebo infusion in the Mg (left) and control (right) groups. Vertical bars represent the SEM.} \]
responders; after Mg infusion, 1.11 ± 0.04 mmol/L, p = NS vs responders, p < 0.0001 vs before).

**Discussion**

The present study demonstrates that Mg infusion reduces Ach-induced coronary spasm, improving not only chest symptoms and ST-segment shift but also QCA findings in the majority of patients with VSA. Coronary angiography confirms that Mg infusion dilates the coronary arteries at baseline and attenuates the vasoconstriction in the spastic segments of the coronary arteries in response to Ach.

**Previous Reports**

Prior studies

Clinical studies have demonstrated Mg deficiency in patients with VSA, suggesting that depletion of Mg is one factor in the genesis of coronary spasm. In those reports, Mg deficiency was quantified using a Mg retention test and by measuring the intracellular concentration of Mg in erythrocytes and/or mononuclear cells.

In the present study, serum Mg concentration was measured for the convenience of clinical use, but we did not find a difference in the serum ionized Mg concentration between the responders and nonresponders to Mg infusion. The serum ionized Mg concentration may not reflect the total body Mg status, and variations in the disease activity of VSA may contribute to differences in response to Mg infusion. These reasons might, in part, explain why no difference was observed in the serum ionized Mg concentration between the responders and nonresponders to Mg infusion.

**Mg Status and Coronary Spasm**

Clinical studies have demonstrated that Mg infusion reduces Ach-induced coronary spasm, improving not only chest symptoms and ST-segment shift but also QCA findings in the majority of patients with VSA. Coronary angiography confirms that Mg infusion dilates the coronary arteries at baseline and attenuates the vasoconstriction in the spastic segments of the coronary arteries in response to Ach.

**Mechanism Responsible for Prevention of Coronary Spasm**

The exact mechanism of the nonsite-specific coronary dilatation induced by Mg infusion remains to be elucidated, but the most plausible mechanism might be the calcium channel blocking effect of Mg ions at the level of vascular smooth muscle cells. Our previous study showed that extracellular Mg inhibits capacitative calcium ion entry in vascular smooth muscle cells, which has been supported by some reports indicating that extracellular Mg can act physiologically to regulate calcium ion entry into smooth muscles. Additionally, experimental evidence suggests that calcium channel blockers suppress Ach-induced coronary vasoconstriction. Therefore, the mechanism by which Mg causes dilatation of the coronary arteries at baseline and the manner in which it prevents Ach-induced coronary spasm may be explained by the calcium channel blocking effects of Mg.

Mg-induced coronary dilatation may also be mediated via intracellular cyclic adenosine 3',5'-monophosphate. Mg ions activate adenylate cyclase, an enzyme involved in the synthesis of adenosine 3',5'-monophosphate. Previous studies have shown that adenosine 3',5'-monophosphate elevations contribute to coronary dilatation. Mg infusion may cause an increase in adenosine 3',5'-monophosphate within coronary smooth muscle cells, leading to the dilatation of coronary arteries.

Some studies have reported that Mg has an endothelium-derived nitric oxide (NO)-induced vasodilatory effect. However, our previous study has demonstrated that N^G^-monomethyl-L-arginine, an NO synthesis inhibitor, had no effect on the coronary dilatation induced by an intracoronary infusion of Mg. Therefore, endothelium-derived NO may not be involved in the Mg-induced coronary dilatation we observed.

**Study Limitations**

The present study has certain limitations. The dose of Mg that we infused increased the serum Mg concentration far beyond the physiologic range. The minimum dose of Mg required to suppress Ach-induced coronary spasm remains to be elucidated.

In the present study, we excluded patients with spasm in the right coronary artery. The dose of Ach infused into the right coronary artery that is required to cause spasm in this vessel typically is smaller than the dose producing this response in the LCA. Differences in the doses of Ach used would have hindered comparison of the Ach-induced response in the right coronary artery with that in the LCA.

In addition, we excluded patients showing prolonged chest pain and/or unstable hemodynamics dur-
ing the first Ach-induced coronary spasm. If these patients with more active coronary spasm had been included, the preventive effect of Mg on coronary spasm might have shown different characteristics.

Measuring the diameter of involved arterial segment during coronary spasm was difficult, especially when some spasm occurred distally. We excluded these segments from the data analysis because of poor reproducibility.

ST-segment deviations were assessed using $\sigma_{STd}$. Since $\sigma_{STd}$ included some leads with ST-segment depression and others with ST-segment elevation, this method possibly could lead to overestimation of ST-segment deviation in patients with reciprocal ST-segment depressions induced by ST-segment elevations. However, the ST-segment deviation could not have been assessed in patients with only ST-segment depression without employing $\sigma_{STd}$.

CONCLUSION

Mg infusion causes nonsite-specific dilation of the coronary arteries and suppresses Ach-induced coronary spasm in patients with VSA. These findings suggest that IV Mg infusion may have therapeutic application in modulating the increased coronary tonus in patients with ischemic heart disease associated with coronary spasm. Furthermore, these results suggest that long-term oral Mg supplementation might prevent or reduce coronary spasm in patients with VSA.

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