J Cardiol 1999; 34: 139–147

Limited Efficacy of Magnesium for the Treatment of Variant Angina

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Abstract

Some patients with variant angina show both ST segment elevation at rest and exercise-induced ST segment elevation. Magnesium deficiency has also been observed in patients with variant angina. This study investigated the correlation between the degree of magnesium deficiency and the efficacy of intravenous administration of magnesium in patients with variant angina.

Fifteen patients with angiographically confirmed variant angina were assessed for magnesium deficiency and whether intravenous administration of magnesium (19.2 mEq/*l*) suppressed exercise-induced ST segment elevation. All 15 patients were studied with a magnesium retention test (0.2 mEq/kg over 4 hr) to analyze magnesium deficiency. In our study, magnesium retention rate in patients with variant angina was not higher than that of controls (57±24% vs 45±10%, NS). All 15 patients had anginal attacks during accelerated exercise combined with hyperventilation after placebo infusion, whereas only 8 patients had anginal attacks after magnesium administration. ST segment elevation occurred in 14 patients after placebo infusion, but in only 4 patients after magnesium administration. There were no correlations between disease activity, degree of magnesium deficiency or failure of suppression of ST elevation by the intravenous administration of magnesium. Intravenous administration of magnesium can suppress exercise-induced coronary spasms in some patients with variant angina, but the degree of magnesium deficiency did not correlate with the suppressions of exercise-induced ST elevation after magnesium administration.

Intravenous administration of magnesium had limited efficacy in patients with variant angina and exercise-induced ST segment elevation.

J Cardiol 1999; 34(3): 139–147

Key Words

■ Coronary vasospasm ■ Magnesium ■ Acetylcholine ■ Exercise

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Manuscript received January 7, 1999; revised April 21, 1999; accepted June 2, 1999

INTRODUCTION

Variant angina is characterized by electrocardiographic ST segment elevation during chest pain attack[1]. Some patients with variant angina show exercise-induced ST segment elevation probably due to coronary spasms[2-5]. Magnesium lowers systemic vascular resistance, dilates coronary arteries[6], improves myocardial metabolism[7] and stabilizes cell membranes[8]. We and other authors have reported that patients with variant angina show magnesium deficiencies[9-12], and intravenous injection of magnesium was effective in suppressing both exercise-induced ST segment elevation[13] and anginal attacks induced by hyperventilation in patients with variant angina[14]. However, the correlation has not been investigated between the degree of magnesium deficiency and the efficacy of magnesium administration for suppressing exercise-induced ST elevations in patients with variant angina.

This study examined whether patients with variant angina had magnesium deficiencies and investigated the correlation between the degree of magnesium deficiency and the usefulness of intravenous administration of magnesium to suppress exercise-induced ST segment elevation in patients with variant angina.

METHODS

Study patients

Fifteen patients with variant angina were studied by provoking anginal attack with accelerated exercise test combined with hyperventilation. This new combined method involved 5-minute mild hyperventilation followed by the treadmill exercise test staged up every minute based on Bruce's protocol[15]. As shown in **Table 1**, the patients were all men with a mean age of 63 years. Eight patients had no fixed stenosis and the other 7 patients had organic stenosis of over 50%. Spontaneous ST segment elevation was observed in only 2 patients (Cases 8, 15) before admission. Thirteen patients had ST segment elevation under the combined procedure for the first time. The duration from onset was within 6 months in 10 patients and over 6 months in the other 5 patients. Before admission, 10 patients had chest pain attacks at $<$ 2/week and 5 patients had chest pain attacks at $\geq$ 2/week. Calcium-channel blocker had been administered before admission in 6 patients. Reproducible exercise-induced chest pain associated with ST segment elevation or depression during the combined method was obtained in all 15 patients. Five patients had hypertension, 8 hyperlipidemia, 3 diabetes mellitus and 14 were habitual smokers.

Table 1 Patient characteristics

Number of patients	15
Male	15
Age (yr)	63±5
Risk factor	
Hypertension	5
Hyperlipidemia	8
Smoking	14
Diabetes mellitus	3
Spontaneous ST elevation	2
Exercise-induced ST elevation	13
Organic stenosis	
≥50%	7
<25%	8
Duration from onset	
<6 months	10
6≤ <12 months	2
≥12 months	3
Disease activity	
<2 attacks/week	10
≥2 attacks/week	5
Calcium-channel blocker	
Before admission	6
After admission	9

Spasm provocation test of acetylcholine

Coronary arteriography was performed with the Sones technique in the morning after medication was stopped for at least 24 hr. Control coronary arteriography of the left coronary artery in the right anterior oblique view with caudal projection and of the right coronary artery in the left anterior oblique view with cranial projection was obtained by injection of 8−10 ml of isopamidol (Iopamiron®). A USCI bipolar electrode catheter was inserted into

Table 2 Coronary arteriographic findings after isosorbide dinitrate and during acetylcholine test

No	Age (yr)	Sex	Coronary arteriographic findings			
			After ISDN	ACh dose (RCA)	ACh dose (LCA)	After ACh
1	63	Male	Normal	50	100	#2(f)
2	55	Male	Normal	20	50	#1(f), #7(f)
3	64	Male	Normal	20	20	#2(f), #6(f)
4	65	Male	Normal	80	50	#4(f), #8(f)
5	65	Male	Normal	20	100	#3(f)
6	67	Male	Normal	50	100	#4(f)
7	55	Male	Normal	50	100	#3(f), #6(f)
8	55	Male	Normal	20	20	#1(f), #6(f)
9	67	Male	#5(50%), #8(50%)	80	50	#8(f)
10	64	Male	#2(75%), #6(90%)	50	20	#2(f), #6(f)
11	62	Male	#6(50%)	50	50	#4(f), #6(f)
12	72	Male	#6(75%), #11(75%)	50	100	#7(f)
13	49	Male	#7(90%)	20	20	#2(f), #7(f), #12(f)
14	74	Male	#3(50%), #7(50%)	50	20	#1(d), #7(f)
15	69	Male	#7(75%)	80	20	#1(f), #7(f)

ISDN=isosorbide dinitrate; ACh=acetylcholine; RCA=right coronary artery; LCA=left coronary artery; f=focal spasm; d=diffuse spasm.

the right ventricular apex through the femoral vein and was connected to a temporary pacemaker, setting the rate at 45 beats/min.

The spasm provocation test was performed by intracoronary injection of acetylcholine. Acetylcholine chloride dissolved in 10 m*l* of warmed 0.9% saline solution was administered over 20 sec. Acetylcholine was injected in incremental doses of 20, 50 and 80 μg into the right coronary artery and 20, 50 and 100 μg into the left coronary artery with at least a 3-minute interval between each injection[16]. Coronary arteriography was performed when the ST segment changed or chest pain or both occurred or at 1 min after completion of each injection. When a coronary spasm was provoked and did not resolve spontaneously within 3 min after the completion of the acetylcholine injection, or when hemodynamic instability due to coronary spasm occurred, 2.5 to 5.0 mg of isosorbide dinitrate was injected into the responsible vessel. A spasm was defined as positive if total or subtotal occlusion occurred. After intracoronary injection of 2.5 mg isosorbide dinitrate, atherosclerosis was determined. Coronary stenosis and the site of the coronary spasm using an acetylcholine test were determined as shown in **Table 2**.

Study protocol

This study was performed with a single-blind placebo-controlled protocol. The combined procedure was performed between 9: 00 am and 11: 00 am with magnesium infusion (19.2 mEq/*l*) and with saline infusion as a control. All medications were discontinued for at least 24 hr before the study except for nitroglycerine, which was stopped 3 hr before the study. Magnesium and saline were administered intravenously for 4 min before the commencement of the combined protocol.

Blood pressure and heart rate were monitored before, during and after the combined procedure. Within a week, the combined procedures with magnesium and saline were performed randomly. Patients were asked to report and grade any chest pain from 1 to 10 points. The intensity of usual chest pain was 10 points. The combined method was terminated when leg fatigue, severe dyspnea, progressive angina, or significant ST segment shifts developed, or when a patient reached his age-adjusted target heart rate (submaximal exercise: 85%). Mild hyperventilation with a frequency of 24 times was selected because the patients were able to walk after the hyperventilation test.

The degrees of ST segment depression were measured at 80 msec after the J point. Significant

Table 3 Serum electrolyte levels in patients with variant angina before and after magnesium infusion

	Before	After magnesium administration (n=8)			
		10 min	20 min	30 min	60 min
Serum magnesium concentration (mg/dl)	2.1±0.2	3.8±0.2	3.5±0.2	3.2±0.3	2.8±0.3
Serum calcium concentration (mg/dl)	8.5±0.7	8.2±0.7	8.3±0.6	8.4±0.7	8.2±0.6
Serum potassium concentration (mg/dl)	3.3±0.5	3.0±0.6	2.9±0.5	2.9±0.4	3.1±0.6

Values are mean±SD.

Table 4 Magnesium retention rate

	Control (n=10)	Variant angina (n=15)	p value
Magnesium retention rate (%)	45±10	57±24	NS

Values are mean±SD.

ST depression was defined as horizontal or downsloping if the depression was more than 0.1 mV and defined as junctional if the depression was more than 0.2 mV. ST elevation was considered significant when there was more than a 0.2 mV shift from the baseline. Blood samples were obtained before, during and after the combined procedure in 8 of the 15 patients.

The concentration of serum magnesium, calcium and potassium were calculated before, 10, 20, 30 and 60 min after magnesium administration. The magnesium retention test was performed according to the method of Ryzen *et al.*[17] Intravenous magnesium at 0.2 mEq/kg lean body weight was given over 4 hr. After completion of the 24-hour urine collection, serum and urine magnesium concentrations were measured. Then, the 24-hour magnesium retention rate was calculated.

A control group consisted of 10 male patients with normal coronary arteries, normal left ventricular function and no spasms induced by either intracoronary injection of acetylcholine or ergonovine.

Written informed consent was obtained from all patients before the study and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

Statistical analysis

The serum electrolyte values and hemodynamic parameters were expressed as mean ± SD and statistically analyzed using Student's paired t-test. Fisher's exact test was used to compare the incidence of anginal attack and ST segment elevation during the combined procedure with magnesium and saline.

RESULTS

Serum magnesium, calcium and potassium levels after intravenous injection of magnesium sulfate

Blood samples were obtained before and after magnesium infusion (10, 20, 30, 60 min) in 8 patients. Serum magnesium levels after magnesium administration were significantly higher (about 1.5−1.8 times) during the combined procedure than before infusion (**Table 3**). Serum calcium and potassium levels after the administration of magnesium sulfate did not change significantly compared to levels before the injection.

Magnesium retention rate

There was no difference between the mean value of the 24-hour magnesium retention rate in patients with variant angina and that in controls (57±24% vs 45±10%, NS; **Table 4**).

Results of the combined procedure

Anginal attacks were induced during the treadmill exercise with placebo infusion in all 15 patients, but in only 8 patients with magnesium administration ($p < 0.01$; **Tables 5, 6**). ST elevation occurred after placebo infusion in 14 patients, but in only 4 patients after magnesium administration ($p < 0.01$). ST depression was determined in one patient (Case 6) after the placebo and in 2 patients (Cases 2, 13) after magnesium administration. The exercise time after magnesium infusion was significantly ($p < 0.01$) longer than that after placebo infusion (204±46 vs 148±36 sec). However, there were no significant differences in heart rate, systolic blood pressure or rate-pressure product between values after magnesium adminis-

Table 5 Comparisons between exercise-induced anginal attack, disease activity and 24-hour magnesium retention rate with and without magnesium administration

No	With placebo		With magnesium		Attack during hospital	Magnesium retention rate (%)
	ECG change	Chest pain	ECG change	Chest pain		
1	II, III, aVF ↑ (2.0)	10/10	No ST change	6/10	1	50
2	II, III, aVF ↑ (2.0)	3/10	V_4–V_6 (J) ↓ (2.0)	10/10	2	48
3	II, III, aVF, V_1–V_4 ↑ (2.0)	10/10	No attack	0/10	1	64
4	II, III, aVF ↑ (2.0)	5/10	No ST change	3/10	0	53
5	II, III, aVF ↑ (3.0)	3/10	No attack	0/10	0	98
6	V_4–V_6 (DS) ↓ (2.0)	2/10	No attack	0/10	0	58
7	V_1–V_3 ↑ (2.0)	10/10	No attack	0/10	3	11
8	V_1–V_4 ↑ (3.0)	3/10	V_1–V_4 ↑ (5.0)	2/10	0	24
9	I, aVL, V_5–V_6 ↑ (5.0)	10/10	I, aVL, V_5–V_6 ↑ (2.0)	5/10	0	100
10	V_1–V_3 ↑ (3.0)	5/10	V_1–V_3 ↑ (4.0)	4/10	0	96
11	V_1–V_3 ↑ (5.0)	10/10	No attack	0/10	0	62
12	V_1–V_5 ↑ (7.0)	10/10	No attack	0/10	0	32
13	V_1–V_5 ↑ (3.0)	20/10	V_3–V_6 (H) ↓ (2.0)	5/10	0	97
14	II, III, aVF, V_1–V_6 ↑ (10.0)	10/10	No attack	0/10	0	9
15	II, III, aVF, V_1–V_6 ↑ (5.0)	6/10	V_1–V_4 ↑ (10.0)	3/10	0	51

ECG=electrocardiogram; H=horizontal; DS=down sloping; J=junctional.

Table 6 Dynamic parameters during exercise test

	With placebo	With magnesium	*p* value
Heart rate			
Before (beats/min)	68±9	67±10	NS
After (beats/min)	109±19	116±13	NS
Systolic blood pressure			
Before (mmHg)	128±16	128±12	NS
After (mmHg)	160±23	171±33	NS
Diastolic blood pressure			
Before (mmHg)	81±8	76±6	NS
After (mmHg)	81±13	74±18	NS
Double product (beats/min·mmHg)	16,978±3,448	19,985±5,228	NS
Exercise time (sec)	148±36	204±46	<0.01

Values are mean±SD.

tration and after placebo infusion.

Correlations between degree of magnesium deficiency and the efficacy of magnesium administration to suppress exercise-induced ST segment elevation

Magnesium administration did not suppress exercise-induced ST elevation in 3 of 4 patients with high magnesium deficiency and 24-hour magnesium retention rate of over 70%, whereas angina attacks disappeared after the administration of magnesium in 8 of 11 patients with magnesium retention rate of under 70% (**Fig. 1**). However, there was no correlation between the degree of magnesium deficiency and the efficacy of magnesium administration for suppressing exercise-induced ST segment elevation.

Six patients without suppression of electrocardiographic changes by magnesium administration

There was no correlation between disease activity and failure to suppress electrocardiographic changes by intravenous administration of magne-

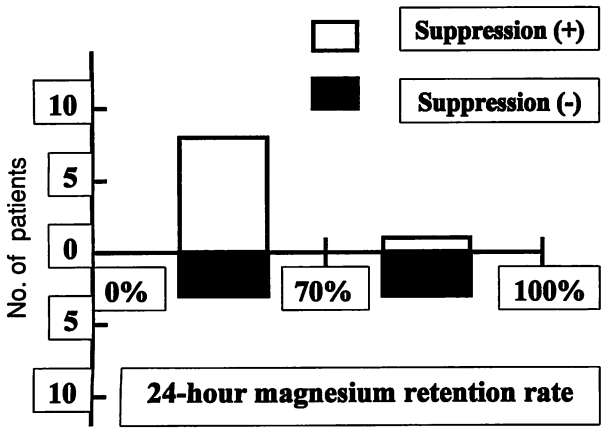

Fig. 1 Correlation between the suppression of electrocardiographic change by magnesium administration and the degree of magnesium deficiency
Three of 4 patients with high magnesium deficiency (≥70%) receiving magnesium had no suppression of attacks, whereas angina attacks disappeared after the administration of magnesium in 8 of 11 patients with magnesium retention rate of <70%.

sium. Only 4 patients (Cases 1, 2, 3, 7) complained of chest pain attacks during the hospital stay even under the treatment of calcium-channel blockers. However, only one of 4 patients disclosed positive electrocardiographic change after magnesium infusion. Three of 6 patients without suppression of exercise-induced ST elevation when receiving magnesium had severe magnesium deficiency. However, the magnesium retention rate was not different between the patients with suppression of electrocardiographic changes after magnesium infusion and the patients without suppression of electrocardiographic changes (48±22% vs 71±30%, NS).

There was no correlation between the degree of magnesium deficiency and the efficacy to suppress electrocardiographic changes with magnesium administration.

Comparison of the appearance of chest pain and positive electrocardiographic changes according to various clinical findings

There was no difference in the frequency of chest pain and positive electrocradiographic changes between patients with and without organic stenosis (**Table 7**). Moreover, there was no difference between patients with and without recurrence of chest pain attacks, between patients with and without long history of chest pain or between patients with and without calcium-channel blocker medication before admission. Magnesium retention rate was not also different between the various clinical classifications.

DISCUSSION

Deficiency of magnesium

Experimentally, low extracellular magnesium concentration was associated with high basal tone of the isolated canine coronary artery, and high magnesium concentration with low basal tension of the artery[6]. On the other hand, clinical, magnesium deficiency may lead to the occurrence of myocardial infarction, unstable angina, fatal arrhythmia and coronary vasospasm[18-20]. Intravenous administration of magnesium is effective to reduce arrhythmia and mortality in patients with myocardial infarction and to suppress hyperventilation-induced and exercise-induced angina in patients with variant angina. Magnesium deficiency was observed in patients with active variant angina, but not in control patients, although there was no difference in the concentration of serum magnesium between the 2 groups. However, this magnesium deficiency difference was not determined in this study. Because all patients in this study were treated with calcium-channel blockers just after admission, their disease activity may have been decreased. Moreover, medication with calcium antagonist was stopped only 24 hr before the study, which was shorter than in other reports.

Efficacy of magnesium administration

Miyagi *et al.*[14] reported that an attack was not induced by hyperventilation in 14 (70%) of 20 variant angina patients with reproducible hyperventilation-induced ST segment elevation after intravenous administration of magnesium. However, an attack was provoked in the other 6 patients with significantly higher disease activity. Kugiyama *et al.*[13] also reported that after the administration of magnesium, an attack was induced in only 5 of 15 variant angina patients and ST segment elevation occurred transiently after placebo infusion during the exercise-induced attack in 11 of 15 patients, but in only 2 patients after magnesium administration.

In our study, anginal attacks associated with significant electrocardiographic change appeared in all 15 patients with variant angina when receiving the placebo, whereas anginal attacks disappeared in 7 patients and significant electrocardiographic change

Table 7 Comparison of the appearance of chest pain and positive electrocardiographic changes according to the clinical findings

	Chest pain	Electrocardiogram change	Magnesium retention rate (%)
Duration from onset			
<6 months (n=10)	6(60)	4(40)	49±23
≥6 months (n=5)	2(40)	2(40)	73±39
Disease activity before admission			
<2 attacks/week (n=10)	5(50)	4(40)	50±32
≥2 attacks/week (n=5)	3(60)	2(40)	71±24
Organic stenosis			
With (n=7)	4(57)	4(57)	64±36
Without (n=8)	4(50)	2(25)	51±26
Calcium-channel blocker			
Before admission (n=6)	3(50)	2(33)	54±29
After admission (n=9)	5(56)	4(44)	59±33

( ): %. Values are mean±SD.

also disappeared in 9 patients when receiving magnesium. The efficacy of the administration of magnesium in our study was lower than that of other reports[13,14]. The method for the induction of coronary artery spasm was hyperventilation by Miyagi *et al.* and electrically graded bicycle ergometer starting at a work load of 50W with increments of 25W every 3 minute by Kugiyama *et al.* In our study, the combined procedure of 5-minute mild hyperventilation followed by the treadmill exercise test staged up every minute based on the Bruce protocol was used. The difference of this noninvasive method for the induction of spasm may have led to the decreased efficacy after magnesium administration, because our combined procedure might be a more powerful spasmogenic stimulus than a single procedure.

Correlation between magnesium deficiency and suppression of ST elevation after magnesium administration

Supposing that magnesium deficiency causes a predisposition to coronary spasms, there may be a relationship between the degree of magnesium deficiency and the efficacy of magnesium administration. However, the present study is the first investigation of the correlation between the degree of magnesium deficiency and the suppression of ST segment elevation and chest pain attacks after intravenous administration of magnesium in patients with variant angina. We found that the degree of magnesium deficiency was inversely correlated with the efficacy of intravenous administration of magnesium in patients with variant angina. Three of 4 patients with high magnesium deficiency and magnesium retention rate of ≥ 70% had no suppression of attacks when receiving magnesium, whereas angina attacks disappeared after the administration of magnesium in 8 of 11 patients with magnesium retention rate of < 70%. In patients with variant angina with high magnesium deficiency, the total amount of 19.2mEq magnesium may not have been enough to supply the deficiency of magnesium in the intracellular space.

This study failed to demonstrate that patients with variant angina had high magnesium deficiency, and there was no tendency for the intravenous administration of magnesium to suppress exercise-induced ST segment elevation or angina attacks. Considering these results, magnesium deficiency may not be the only cause of coronary spasms, so several factors may be involved in the pathogenesis of coronary spasms.

Clinical implications

Coronary spasms are thought to be important in the pathogenesis of variant angina, unstable angina and acute myocardial infarction. Intravenous administration of magnesium as well as calcium-channel blockers is effective to reduce exercise-induced coronary spasms in some patients with variant angina. In patients with refractory spasms and acute coronary syndrome due to coronary spasms, intravenous administration of magnesium

may be useful to stabilize coronary tone regardless of magnesium deficiency.

Study limitations

This study has 4 limitations. The first is that the medication was not discontinued for several days before the combined procedure. The second limitation is that the study included a small number of patients. The third limitation is that the majority of patients had moderately low disease activity because only 2 patients had spontaneous ST segment elevation before the study. We selected medication with calcium-channel blocker and isosorbide dinitrate in preference to the detection of spontaneous ST segment elevation during hospital stay. The fourth limitation is that we did not measure the intracellular magnesium concentration[21]. In this study, we could not estimate the efficacy of intravenous administration of magnesium to suppress exercise-induced ST segment elevation from the data of 24-hour magnesium retention rate or serum magnesium level. Further study including the analysis of intracellular magnesium concentration is necessary to investigate the correlation between the magnesium deficiency and efficacy of intravenous administration of magnesium to suppress exercise-induced ST segment elevation in patients with variant angina.

Acknowledgement

We acknowledge the helpful comments of Yuji Shigematsu, MD, Associate Professor Mareomi Hamada, MD, and Professor Kunio Hiwada, MD.

要　約

異型狭心症例におけるMg治療効果の限界

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異型狭心症は，安静時のみならず運動誘発性のST上昇を認める例も存在し，またMg欠乏状態も報告されている．本研究の目的は異型狭心症例におけるMg欠乏状態と経静脈投与Mgの効果との関係を検討することである．

血管造影で冠攣縮が確認された異型狭心症15例を対象として，Mg負荷試験(0.2mEq/kgのMgを4時間で点滴)を施行しMg欠乏が存在するか否か，または運動誘発性のST上昇発作がMg投与(19.2mEq/l)で抑制されるか否かを検討した．24時間Mg停滞率は対照群に比べ高値であったが，差異は認められなかった(57±24% vs 45±10%)．過換気負荷後の急速運動負荷試験で15例全例でコントロール時に胸痛発作の出現を認めたが，Mg投与後は8例に減少した．また，コントロール時には15例中14例にST上昇を認めたが，Mg投与後では4例にST上昇を認めたのみであった．異型狭心症の活動度，Mg欠乏の程度と経静脈投与後のST上昇発作抑制との間には有意の相関関係は認められなかった．

経静脈投与のMgは異型狭心症患者のある一群には有用と思われるが，そのMg欠乏の程度とST上昇発作抑制との間には有意の関係は認められなかった．

J Cardiol 1999; 34(3): 139−147

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