Neurol Med Chir (Tokyo) 49, 139～145, 2009

Initial Clinical Experience of Vasodilatory Effect of Intra-cisternal Infusion of Magnesium Sulfate for the Treatment of Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

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Abstract

The vasodilatory effect of intra-cisternal infusion of magnesium sulfate solution was evaluated in 10 patients with symptomatic vasospasm after aneurysmal subarachnoid hemorrhage (SAH) who underwent early clipping surgery. Cisternal drainage was installed in the prepontine and/or sylvian fissures. Carotid angiography was performed immediately after the onset of symptomatic vasospasm, then intracisternal infusion of 15 mmol/l magnesium sulfate in Ringer solution was started at 20 ml/hr and continued until day 14. Irrigation was performed from the cisternal tube (inlet) to the spinal drainage (outlet). The cerebrospinal fluid magnesium ion concentration (1.2 ± 0.2 mEq/l) significantly increased after the infusion therapy (6.0 ± 1.7 mEq/l, $p < 0.001$). Repeat angiography showed vasodilatory effect on the spastic cerebral arteries at 3 hours after the infusion, especially in the arteries near to the site of cisternal drainage placement. The magnesium infusion also caused decreased mean arterial blood velocity in the spastic arteries in 6 of the 7 measured patients (162 ± 38 cm/sec to 114 ± 42 cm/sec, $p < 0.001$). Finally, 5 of the 10 patients achieved good recovery, 1 patient had moderate disability, 1 patient became severely disabled due to meningitis, and 3 patients were vegetative or dead, due to failure of magnesium irrigation in 1 patient and advanced age in the other 2 (more than 80 years old). This preliminary study indicates that intra-cisternal infusion of magnesium sulfate solution has vasodilatory effect on the spastic cerebral arteries after aneurysmal SAH.

Key words: subarachnoid hemorrhage, vasospasm, magnesium, cerebrospinal fluid

Introduction

Delayed cerebral vasospasm remains a common cause of morbidity and mortality despite advances in microsurgical or endovascular treatments of aneurysmal subarachnoid hemorrhage (SAH). One-third of the patients with symptomatic vasospasm die and another one-third suffer permanent neurological deficit.[3,10] Various prophylactic strategies against cerebral vasospasm have been advocated, such as intra-oral intake of calcium blocker (nimodipine),[1] nicardipine prolonged-release implant,[6] rho-kinase inhibitor (fasudil hydrochloride),[22] cisternal irrigation with urokinase or tissue plasminogen activator,[8,12] and cisternal irrigation with milrinone.[2] However, after the onset of symptomatic vasospasm, only a few therapies are available, such as hypertensive-hypervolemic-hemodilution (triple-H) therapy,[18] intra-arterial injection of papaverin,[5] and transluminal balloon angioplasty.[15] Therefore, a new therapeutic modality to dilate the spastic cerebral arteries during symptomatic vasospasm is needed.

Pilot clinical studies have demonstrated the safety and efficacy of intravenous magnesium therapy for SAH.[24,26] However, recent prospective studies of continuous intravenous administration of magnesium sulfate in patients with aneurysmal SAH failed to show any vasodilatory effect on vasospasm detected by angiography and transcranial Doppler ultrasonography.[20,23] The blood-brain barrier is relatively impermeable to magnesium ion (Mg^{2+}), so increased blood concentration of Mg^{2+} may not affect

Received April 28, 2008; Accepted November 18, 2008

the spastic cerebral arteries.[21] In contrast, in vitro studies clearly show that increased extracellular Mg^{2+} concentration definitely causes vasodilation of both normal and contracted cerebral vessels in the presence of vasospasm-inducing agents.[11,17] Therefore, intra-cisternal administration of Mg^{2+} is expected to reverse delayed cerebral vasospasm. Recently, we showed that intra-cisternal infusion of Mg^{2+} solution improved reduced cerebral blood flow (CBF) induced by experimental SAH in the rat.[14] Furthermore, we demonstrated the vasodilatory effect of intra-cisternal injection of Mg^{2+} solution on spastic cerebral arteries in the dog model of SAH.[13]

The present study examined the vasodilatory effect of intra-cisternal infusion of magnesium sulfate solution on the spastic cerebral arteries of patients who developed symptomatic vasospasm after aneurysmal SAH.

Materials and Methods

The clinical trial protocol was reviewed and approved by Juntendo University Shizuoka Hospital ethics committee (#073). Informed consent for this protocol was obtained from each patient or legally authorized representative.

Intra-cisternal infusion of magnesium sulfate solution was performed in 10 patents with aneurysmal SAH who underwent direct clipping surgery within 24 hours of onset, and with computed tomography (CT) findings classified as Fisher group[4] 3 or 4. A cisternal drainage tube was placed in the prepontine cistern after opening of the Liliequist membrane, and an additional drainage tube in the sylvian fissure because of thick SAH in the sylvian fissure in Case 7. A spinal drainage tube was placed in the lumber spine immediately after the clipping surgery. Fasudil hydrochloride (90 mg/day, 14 days) was administered to all patients but not triple-H therapy.

The diagnosis of symptomatic vasospasm was based on reduced level of consciousness (more than 2 points lower on the Glasgow Coma Scale) and/or focal neurological deficits in the absence of other potential causes. Immediately after the onset of symptomatic vasospasm, if CT detected no low density area due to vasospasm, a 4F sheath catheter was placed in the femoral artery and carotid angiography was performed on the operated side. After the angiography, 10 ml of 15 mmol/l magnesium sulfate in Ringer solution (Na^+ 130 mEq/l, K^+ 4 mEq/l, Cl^- 109 mEq/l, lactate 28 mEq/l) was administered through the cisternal catheter followed by clamping for 1 hour. Continuous infusion of 15 mmol/l magnesium sulfate solution at 20 ml/hr was started and continued until day 14. Irrigation was performed through the cisternal to spinal drainage. The cisternal tube and the pressure control system at 15 cmH_2O were connected by a T-connector for safe irrigation. Three hours after the start of intra-cisternal infusion of magnesium sulfate, carotid angiography was repeated through the same femoral sheath catheter.

The arterial diameter before and after the intra-cisternal infusion of magnesium sulfate solution was measured and the percentage increase calculated by a radiological technician unaware of the details of the clinical protocol. The arterial diameters were measured at the narrowest points in each arterial segment (C_1 or C_2 segment of the internal carotid artery, M_1 and M_2 segments of the middle cerebral artery, A_1 and A_2 segments of the anterior cerebral artery, and the posterior communicating artery). The cerebrospinal fluid (CSF) and serum Mg^{2+} concentrations were monitored before and after the intra-cisternal infusion of magnesium sulfate solution using ion-selective electrodes (StatProfile CCX; NOVA Biomedical, Boston, Mass., U.S.A.). Transcranial Doppler ultrasonography was performed to measure the mean blood flow velocity in the middle cerebral artery on the onset day of symptomatic vasospasm and the next day in 7 patients. The significance of differences was analyzed by the paired t-test using SPSS 7.5.1 J for Windows (SPSS Japan Inc., Tokyo). P values < 0.05 were considered statistically significant.

Results

Table 1 summarizes the characteristics and outcomes of the 10 patients with symptomatic vasospasm treated by intra-cisternal infusion of magnesium sulfate solution. Table 2 shows the percentage increase in spastic arterial diameter at 3 hours after infusion. The duration of intra-cisternal infusion of magnesium sulfate solution ranged from 4 to 9 days (mean 6.7 $\pm$ 1.6 days). CSF Mg^{2+} concentration before infusion was 1.2 $\pm$ 0.2 mEq/l and significantly increased to 6.0 $\pm$ 1.7 mEq/l after infusion ($p < 0.001$), except in Case 8 who did not show any increase in CSF Mg^{2+} up to day 14. The Mg^{2+} concentration in the spinal CSF became stable at 2 days after starting the irrigation, so we took the CSF Mg^{2+} concentration at 2 days after the irrigation as the representative value. The pre- and postinfusion serum Mg^{2+} concentrations were 0.8 $\pm$ 0.1 and 0.9 $\pm$ 0.1 mEq/l, respectively, and were not significantly different. All patients except for Case 8, who did not respond to magnesium infusion, showed vasodilatory effect on the spastic cerebral arteries at

Table 1 Characteristics and outcome of patients with symptomatic vasospasm

Case No.	Age (yrs)/ Sex	HK grade	Fischer group	Aneurysm location	DIND	Pre/Post CSF Mg^{2+} concentration (mEq/l)	Pre/Post flow velocity (cm/sec)	Mg infusion (days)	CT low density	GOS (mRS)
1	59/F	V	3	MCA	+	1.4/4.0	221/183	5	none	GR(0)
2	56/M	II	3	AcomA	+	1.1/5.1	186/119	7	none	GR(0)
3	67/F	II	3	MCA	+	1.0/5.0	NE	9	watershed	GR(0)
4	59/M	V	4	AcomA	+	1.2/3.9	NE	4	none	GR(1)
5	43/M	IV	3	AcomA	+	1.3/5.2	131/64	8	none	GR(1)
6	61/M	V	4	MCA	+	1.1/7.0	118/81	6	none	MD(3)
7	52/F	II	3	MCA	+	0.9/7.8	172/131	8	none	SD(4)
8	65/F	III	3	AcomA	+	1.4/1.1	126/213	7	MCA	VS(5)
9	81/F	II	3	AcomA	+	1.2/7.8	145/105	8	MCA	VS(5)
10	81/F	III	3	AcomA	+	1.2/8.2	NE	5	MCA, ACA, PCA	D(6)

ACA: anterior cerebral artery, AcomA: anterior communicating artery, CSF: cerebrospinal fluid, CT: computed tomography, D: death, DIND: delayed ischemic neurologic deficits, GOS: Glasgow Outcome Scale, GR: good recovery, HK: Hunt and Kosnik, MCA: middle cerebral artery, MD: moderate disability, mRS: modified Rankin scale, NE: not examined, PCA: posterior cerebral artery, SD: severe disability, VS: vegetative state.

Table 2 Percentage increase in arterial diameter after intra-cisternal magnesium infusion

Case No.	ICA	M_1	M_2	A_1	A_2	PcomA
1	17	20	43	33	33	50
2	17	0	0	0	0	20
3	21	15	8	10	36	28
4	0	38	7	33	0	30
5	0	0	0	0	0	8
6	0	0	10	14	23	33
7	6	100	80	18	17	33
8	0	0	0	0	0	0
9	3	12	0	0	0	90
10	0	19	13	0	13	64
Mean ± SD	7 ± 9	23 ± 32	18 ± 27	12 ± 14	14 ± 15	40 ± 25

A_1 and A_2: A_1 and A_2 segments of the anterior cerebral artery, ICA: internal carotid artery, M_1 and M_2: M_1 and M_2 segments of the middle cerebral artery, PcomA: posterior communicating artery, SD: standard deviation.

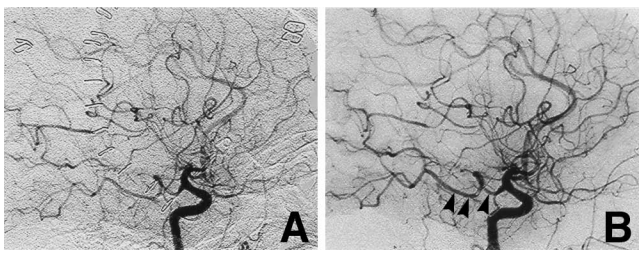

Fig. 1 Case 1. Right carotid angiograms showing symptomatic vasospasm before (A) and 3 hours after intra-cisternal infusion of magnesium sulfate solution (B). The cisternal drainage tube for magnesium infusion was placed in the prepontine cistern, and the posterior communicating artery and the posterior cerebral artery showed remarkable dilation (*arrowheads*).

3 hours after the intra-cisternal infusion of magnesium sulfate solution. The posterior communicating artery was the most commonly dilated artery (40 ± 25%) because of its close location to the cisternal tube placement (Fig. 1). Case 7 who had the cisternal tube in the sylvian fissure showed prominent dilation of the M_1 and M_2 segments (Fig. 2). The mean flow velocity in the middle cerebral artery at the onset of symptomatic vasospasm (162 ± 38 cm/sec) decreased significantly on the day after the intra-cisternal infusion (114 ± 42 cm/sec, $p < 0.001$), except in Case 8. Case 8 showed a further increase in mean flow velocity, and subsequently developed cerebral infarct in the middle cerebral artery territory on CT resulting in vegetative state. The angiographic vasodilatory effects appeared immediately after starting the magnesium irrigation therapy, whereas the neurological symptoms showed gradual resolution in patients without severe infarction on CT. Complications of magnesium cisternal irrigation therapy induced meningitis in one patient, and respiratory suppression in two patients who completely recovered after the irrigation. The cause of

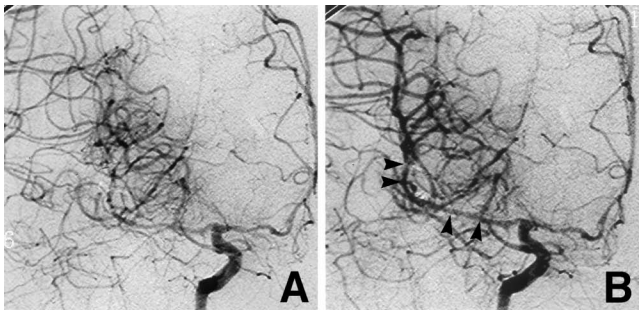

Fig. 2 Case 7. Right carotid angiograms showing symptomatic vasospasm before (A) and 3 hours after intra-cisternal infusion of magnesium sulfate solution (B). The cisternal drainage tube for magnesium infusion was placed in the sylvian fissure, and the M_1 and M_2 segments of the middle cerebral arteries showed remarkable dilation (*arrowheads*).

the respiratory suppression could not be clarified in this limited study.

The outcome was evaluated at 6 months postoperatively. Five patients had good recovery, 1 patient had moderate disability, 1 patient had severe disability due to meningitis, 2 patients developed vegetative state, and 1 patient died. Cases 9 and 10 aged more than 80 years old had cerebral infarcts on CT which resulted in vegetative state or death despite the increased CSF Mg^{2+} concentration.

Discussion

Mg^{2+} has a vasodilation effect mediated through blocking of Ca^{2+} influx and competitive inhibition of Ca^{2+} binding at the calmodulin sites which affect the myosin light chain kinase active form in the smooth muscles of cerebral blood vessels.[25] Mg^{2+} also attenuates the effects on the cerebral arteries of endothelin-1 and oxyhemoglobin, which are considered to be important potent vasoconstrictors after SAH.[7,11]

The present study demonstrated that intra-cisternal infusion of magnesium sulfate solution has a vasodilatory effect on the spastic cerebral arteries of patients with symptomatic vasospasm following aneurysmal SAH. The effect of magnesium infusion was most prominent in the arteries near to the cisternal drainage placement because the repeated angiography was performed shortly after the start of infusion (3 hours). This finding suggests the importance of the location of the cisternal tube that is used for magnesium infusion. The cisternal tube should be placed in the cistern containing the thick SAH blood clot.

The present study used 15 mmol/l magnesium sulfate in Ringer solution. The optimal concentration for the infusion is not clear. Recently, cisternal irrigation with 3 mEq/l Mg^{2+} and 4 mg/ml ascorbic acid was reported to prevent the occurrence of cerebral vasospasm after aneurysmal SAH.[19] Our preclinical study demonstrated that intra-cisternal infusion of 10 mmol/l magnesium sulfate solution improved the CBF reduced by experimental SAH in the rat.[13,21] The optimal concentration may be 10 mmol/l magnesium sulfate solution. The vasodilatory effect of magnesium infusion therapy may depend on maintaining the CSF Mg^{2+} concentration at 3 mEq/l more than the concentration of the infusate.[13,19] Further study is needed to settle this issue.

Magnesium infusion failed to increase the CSF Mg^{2+} concentration in one of our patients. In this series, the cisternal tube was connected to the pressure control system at 15 cmH_2O by a T-connector. The cisternal tube in Case 8 may have been obstructed, thus preventing flow of magnesium infusate into the cerebral cisterns. This patient developed cerebral infarct resulting in vegetative state. We have to develop a more effective and safe intracisternal infusion system. Our two patients aged more than 80 years old did not respond to the magnesium infusion therapy, and developed cerebral infarcts resulting in poor outcomes. Elderly patients may suffer other conditions such as thromboembolism and cortical spreading depression rather than cerebral vasospasm of the large vessels.[9,16]

Milrinone irrigation and prolonged-release nicardipine implant in the cerebral cisterns are also potent methods to dilate the spastic cerebral arteries after SAH.[2,6] However, Mg^{2+} is a physiological component of the CSF, and the magnesium concentration in the infusate can be controlled by monitoring the CSF Mg^{2+} concentration.

This preliminary clinical study included a limited number of patients, so we cannot conclude whether the vasodilatory effect of intra-cisternal magnesium infusion therapy is related to the improvement of the clinical outcome. Further study is needed to assess the optimal concentration of magnesium sulfate, optimal start timing and duration of the infusion, location of the cisternal drainage placement, infusion system, and the neurotoxicity of intra-cisternal injection. However, this study does indicate that intracisternal injection of magnesium sulfate is a promising treatment to ameliorate cerebral vasospasm in patients with SAH.

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Commentary

The authors present a new therapy for cerebral vasospasm using an intra-cisternal infusion method of Mg sulfate. Mg^{2+} has a vasodilatory effect mediated through blocking of Ca^{2+} channels and inhibition of myosin light chain kinase. However, recent prospective studies of continuous intravenous administration of Mg sulfate in patients with SAH did not show any vasodilatory effect on vasospasm. The blood-brain barrier is relatively impermeable to Mg^{2+}, so intravenous administration of Mg sulfate may not affect the spastic arteries. In these in vitro studies, the authors showed the effectiveness of intra-cisternal infusion of Mg sulfate for experimental vasospasm in the rat and dog. As a result of these experiments, the authors devised a new therapy for cerebral vasospasm using intra-cisternal infusion of Mg sulfate. This new therapy showed good results for cerebral vasospasm as 50% of cases in this study were good outcome. However, 40% of cases in this study were poor outcome due to vasospasm and other complications. For this reason, as the authors described, further study is needed to assess the dosage of Mg sulfate, optimal start timing, and infusion system in order to carefully evaluate the efficacy of this therapy.

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Magnesium ion can block cellular calcium ion influx and competitively inhibit calcium binding at the calmodulin site. It may also attenuate the effects of blood degradation products such as endothelin-1 or oxyhemoglobin on cerebral vessels, thereby assisting in the reduction of cerebral vasospasm. Thus, administration of magnesium sulfate is considered to be a possible treatment for cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH). In recent years, many investigations in both experimental and clinical studies have been conducted to elucidate the efficacy of magnesium on cerebral vasospasm.

In this preliminary clinical trial, the authors tried to demonstrate that continuous intra-cisternal infusion of magnesium sulfate solution on a small group of patients with poor grade SAH up to 14 days after the bleeding decreases the severity of cerebral vasospasm. Their results revealed a local vasodilatation effect of major cerebral vessels on the angiographic study as well as decreased mean arterial blood velocity on a transcranial Doppler ultrasonographic study after intra-cisternal infusion of this agent. Half of their patients achieved good recovery at 6-month follow up after this treatment.

While these results suggest that the magnesium sulfate may be a promising treatment for SAH, these results must first be validated in a multicenter, large-scale clinical trial before it can be applied in daily clinical practice.

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Cerebral vasospasm remains an important problem for aneurysmal SAH patients. Although various prophylactic agents, such as calcium blocker (nimodipine) and rho-kinase inhibitor (fasudil hydrochloride) are clinically used, few of them will be efficient after the onset of symptomatic vasospasm. Promising new therapies are critically needed and encouraged. Based on their experimental work on canines, the authors clinically tried a novel method with continuous intracisternal infusion of magnesium sulfate solution after the onset of symptomatic vasospasm. The magnesium infusion correlated with decreased mean arterial blood velocity, increased arterial diameter and good recovery in non-aged patients. Except for one patient suffering from meningitis, this method could be relatively safe. Compared with intravenous magnesium sulfate therapy, local delivery of magnesium sulfate avoids the interference of the blood-brain barrier and the interaction of the whole body systems. Compared to local implant of nicardipine, intra-cisternal infusion of magnesium can be given continuously and widely distributed to all vascular territories. Therefore, from the results of this pilot study, intra-cisternal infusion of magnesium sulfate could be a potent therapy for the symptomatic vasospasm caused by aneurysmal SAH. However, aged patients did not respond to this treatment.

Besides the limitations of this study mentioned by the authors, however, there was inadequate selection of patients in the study, two cases belonged to Fisher Group 4, which refers to intracerebral or intraventricular clot with diffuse or no SAH.[1] The modified

Fisher Scale proposed by Zervas and Ogilvy[2] is more accurate than the Fisher Scale for defining and predicting patients with potential risk of vasospasm. Continuous injection of magnesium sulfate may cause higher ICP. The authors infused the solution with the pressure of 15 cmH_2O, so how to treat the patients when the ICP is beyond this level? Therefore, a prospective randomized controlled trial should be carried out before the conclusion that intra-cisternal infusion of magnesium sulfate ameliorates cerebral vasospasm in SAH patients is made.

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