Preventive effect of continuous cisternal irrigation with magnesium sulfate solution on angiographic cerebral vasospasms associated with aneurysmal subarachnoid hemorrhages: a randomized controlled trial

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OBJECTIVE Although cerebral vasospasm (CV) is one of the most important predictors for the outcome in patients with subarachnoid hemorrhage (SAH), no treatment has yet been established for this condition. This study investigated the efficacy of continuous direct infusion of magnesium sulfate (MgSO₄) solution into the intrathecal cistern in patients with an aneurysmal SAH.

METHODS An SAH caused by a ruptured aneurysm was identified on CT scans within 72 hours after SAH onset. All patients were treated by surgical clipping and randomized into 2 groups: a control group of patients undergoing a standard treatment and a magnesium (Mg) group of patients additionally undergoing continuous infusion of 5 mmol/L MgSO₄ solution for 14 days. The Mg²⁺ concentrations in serum and CSF were recorded daily. Neurological examinations were performed by intensive care clinicians. Delayed cerebral ischemia was monitored by CT or MRI. To assess the effect of the Mg treatment on CV, the CVs were graded on the basis of the relative degree of constriction visible on cerebral angiograms taken on Day 10 after the SAH, and transcranial Doppler ultrasonography was performed daily to measure blood flow velocity in the middle cerebral artery (MCA). Neurological outcomes and mortality rates were evaluated with the Glasgow Outcome Scale and modified Rankin Scale at 3 months after SAH onset.

RESULTS Seventy-three patients admitted during the period of April 2008 to March 2013 were eligible and enrolled in this study. Three patients were excluded because of violation of protocol requirements. The 2 groups did not significantly differ in age, sex, World Federation of Neurosurgical Societies grade, or Fisher grade. In the Mg group, the Mg²⁺ concentration in CSF gradually increased from Day 4 after initiation of the continuous MgSO₄ intrathecal administration. No such increase was observed in the control group. No significant changes in the serum Mg²⁺ levels were observed for 14 days, and no cardiovascular complications such as bradycardia or hypotension were observed in any of the patients. However, bradypnea was noted among patients in the Mg group. The Mg group had a significantly better CV grade than the control group ($p < 0.05$). Compared with the patients in the Mg group, those in the control group had a significantly elevated blood flow velocity in the MCA. Both groups were similar in the incidences of cerebral infarction, and the 2 groups also did not significantly differ in clinical outcomes.

CONCLUSIONS Continuous cisternal irrigation with MgSO₄ solution starting on Day 4 and continuing to Day 14 significantly inhibited CV in patients with aneurysmal SAH without severe cardiovascular complications. However, this improvement in CV neither reduced the incidence of delayed cerebral ischemia nor improved the functional outcomes in patients with SAH.

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KEY WORDS subarachnoid hemorrhage; magnesium; vasospasm; cisternal irrigation; vascular disorders

ABBREVIATIONS CV = cerebral vasospasm; DCI = delayed cerebral ischemia; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; IQR = interquartile range; MCA = middle cerebral artery; Mg = magnesium; MgSO₄ = magnesium sulfate; Mg²⁺_{CSF} = Mg²⁺ concentration in the CSF; Mg²⁺_{serum} = Mg²⁺ concentration in the serum; PaCO₂ = partial pressure of carbon dioxide; SAH = subarachnoid hemorrhage; TCD = transcranial Doppler; WFNS = World Federation of Neurosurgical Societies.

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CEREBRAL vasospasm (CV) remains one of the major causes of high morbidity rates after an aneurysmal subarachnoid hemorrhage (SAH).^{7,15} Moreover, delayed cerebral ischemia (DCI) attributable to CV might be associated with the poor functional outcomes in patients with SAH.³² Many clinical approaches to treating CV have been investigated, but the interpretations of their results are varied and controversial.^{1,9} Consequently, no standard treatment for CV has yet been established.

Calcium-antagonist agents such as nimodipine, which produce vasodilation, may effectively treat patients with CV.^{7,16} Recently, magnesium (Mg), which physiologically acts as a calcium antagonist, has also been suggested as a potential therapeutic agent for CV.^{16,18,19,32} Several groups have reported the efficacy of high-dose intravenous Mg administration after an aneurysmal SAH.^{3,29,40} High-dose intravenous Mg therapy has a vasodilatory effect, but increases the risk for exposure hypotension or hypoperfusion in patients with a CV. The Mg^{2+} levels in serum must be strictly maintained at 2.0–2.5 mmol/L to avoid cardiac complications.^{35,36} Intravenous Mg therapy did not affect functional outcomes after aneurysmal SAHs in Phase III trials, although several other clinical studies have demonstrated a benefit after an SAH. Results from the MASH (magnesium in aneurysmal subarachnoid hemorrhage) trial 2, a study of the effect of intravenous Mg infusion in patients with SAH, and from an updated meta-analysis of 7 randomized control trials have shown that intravenous Mg therapy did not improve clinical outcomes after an SAH.^{5,6}

Previously, we reported a new administration method in which magnesium sulfate ($MgSO_4$) solution is directly infused into the cistern and the CSF space.²⁴ Intracisternal $MgSO_4$ solution infusion has a vasodilatory effect on spastic cerebral arteries in animal models and improves reduced cerebral blood flow in an experimental model.^{23–27} Moreover, this infusion method was effective in a small group of patients with aneurysmal SAH.²⁸ Direct Mg infusion into the CSF (Mg^{2+}_{CSF}) with a minimum required dosage of Mg, but does not increase Mg^{2+} concentration in the serum (Mg^{2+}_{serum}). Such an approach has the potential for dilating the cerebral vessels in SAH patients while avoiding the cardiac and systemic hypoperfusion complications associated with intravenous Mg infusion.

The present prospective randomized pilot study examined the effect of continuous intracisternal administration of Mg in patients with an aneurysmal SAH. We used transcranial Doppler (TCD) ultrasonography and cerebral angiography to assess the efficacy of intrathecal Mg infusion for preventing CV and monitored both Mg^{2+}_{serum} and Mg^{2+}_{CSF} to assess the safety of this treatment. We also examined improvements in functional outcome in the patients undergoing this treatment relative to a control group of patients receiving standard treatment.

Methods

Patient Selection

The clinical trial protocol was reviewed and approved by the Juntendo University Shizuoka Hospital ethical

committee. All patients or their legally authorized representatives provided written informed consent. This trial (no. UMIN000015760) is registered with the University Hospital Medical Information Network Clinical Trials Registry (<http://www.umin.ac.jp/ctr/index.htm>).

This study included data from 70 consecutive patients presenting with SAH from April 2008 to March 2013. The diagnosis of SAH was established on the basis of CT performed on admission within 72 hours after SAH onset. The etiology of the SAH was a ruptured aneurysm in all cases included here, because patients whose SAH was diagnosed as resulting from trauma, arteriovenous malformation, or other causes were excluded. All of the included patients underwent surgical clipping because patients treated with coil embolization were excluded. Other exclusion criteria included age older than 80 years, World Federation of Neurosurgical Societies (WFNS) Grade V SAH, and major surgical complications identified by CT after surgery. Because patients with an SAH with a Fisher grade of 1 have a low incidence of CV, which is not suitable for evaluating the preventive effects of a treatment on CV, and because an intracerebral hematoma in patients with a Fisher Grade 4 SAH has a strong influence on functional outcome, patients having an SAH with Grade 1 or Grade 4 were also excluded. Patients with pathological serum Mg levels, defined as less than 3.5 mmol/L or more than 7.0 mmol/L measured as ionized Mg, were also excluded.¹⁴

The patients were randomized into 2 groups by a stratified block randomization method with the following factors: age, sex, and WFNS grade and Fisher grade and location of the SAH. The control group received a standard treatment with cisternal irrigation therapy,⁴⁹ and the Mg group received continuous infusion of $MgSO_4$ solution in addition to the standard treatment.

Surgical Treatment and $MgSO_4$ Infusion

Patients were surgically treated within 72 hours after SAH onset and then received care under normovolemic and normotensive conditions. During direct clipping surgery, the Liliequist membrane was opened to allow CSF circulation between the supratentorial and infratentorial cisterns, and the cisternal drainage tube was placed into the basal cistern. A spinal drainage tube was also inserted through the lumbar spine immediately after the surgery. As a clot-lysis agent under our standard cisternal irrigation protocol, alteplase, 0.2 mg (that is, recombinant tissue-type plasminogen activator; Mitsubishi Tanabe Pharma), was directly administered into the basal cistern via the cisternal drainage tube every 8 hours for 2 days.⁴⁹ During administration of the clot-lysis agent, absence of hemorrhagic complications was confirmed by daily CT examinations. Normovolemia was maintained in all patients using Mg-free transfusions. Mild hypervolemia and induced hypertension was attempted in patients with deteriorating neurological status due to CV. Fasudil hydrochloride, 90 mg (Eril S; Asahi Kasei Pharma), was administered daily for 14 days.^{36,37}

Continuous infusion of $MgSO_4$ solution containing 5 mmol/L of Mg^{2+} was performed at 20 ml/hr from Day 4

until Day 14 through the cisternal to spinal drainage. The cisternal drainage tube was connected to the pressure-control system via a T connector as a safety outlet. The overflow route was set at a height of 15 cm H₂O to avoid excessive infusion. All drainage catheters were carefully maintained to avoid complications such as overdrainage or increased intracranial pressure during the irrigation (Fig. 1).²⁸

The patients' basic vital signs were recorded daily or continuously during administration of the MgSO₄ solution and included the following: blood pressure, heart rate, body temperature, oxygen saturation, arrhythmia, and blood gas levels. Partial pressure of oxygen and partial pressure of carbon dioxide (PaCO₂) were monitored daily by arterial gas analysis, and tracheal intubation was considered in the presence of bradypnea with a PaCO₂ of over 60 mm Hg. Blood samples were routinely taken for biochemical examination. Mg²⁺_{serum} and Mg²⁺_{CSF} were monitored daily before, during, and after infusion of the MgSO₄ solution with ion-selective electrodes (Critical Care Xpress; Nova Biomedical) for 14 days.

Neurological examination was performed by intensive care clinicians. Symptomatic CV was defined as clinical neurological deterioration attributable to a CV, after exclusion of hydrocephalus, seizures, surgical invasion, or other causes. However, symptomatic CV was difficult to define only on the basis of clinical deterioration, particularly in

comatose patients or in patients under sedation. Therefore, we defined low-density areas on CT images as symptomatic CV after other causes had been excluded by repeated postoperative CT examinations.^{11,12} The CV was diagnosed jointly with a neurosurgeon unaware of the clinical details who confirmed that a low-density area might be caused by a DCI after an SAH.

Angiography was repeated on Day 10 after the SAH to obtain data on the location and degree of CV during treatments in both control and Mg groups. The degree of CV constriction was assessed by comparing the CV findings on the Day 10 cerebral angiogram with those on the angiogram obtained on admission for the SAH. The CV on Day 10 was graded on a scale of 1 to 5 by a neurosurgeon unaware of the patient's clinical status as follows: Grade 1, mild constriction ($\leq 20\%$); Grade 2, mild-to-moderate constriction (21%–40%); Grade 3, moderate constriction (41%–60%); Grade 4, moderate-to-severe constriction (61%–80%); and Grade 5, severe constriction ($\geq 81\%$).¹⁶ Angioplasty treatment by the balloon technique and chemical vasodilator agents were not used in any of the patients.

Transcranial Doppler ultrasonography was performed daily for 14 days after the surgery. Mean velocity was measured in the M₁ segment of the middle cerebral artery (MCA) on the surgical side. The average of the velocity in the M₁ MCA segment for the first 4 days was calculated

FIG. 1. Schematic of the cisternal Mg irrigation system used in this study. Through the cisternal drainage tube, MgSO₄ solution (5 mmol/L) was continuously infused at 20 ml/hr into the subarachnoid space for 14 days. The overflow was set at a height of 15 cm H₂O to avoid excessive infusion (indicated by the blue drainage bag). The irrigation fluid was mainly drained via a spinal drainage route. A ventricular drainage route acted as a safety outlet (indicated by the orange drainage bag) for emergencies when the intracranial pressure suddenly increased. The level of the drainage (indicated by the red drainage bag) was adjusted according to the drainage volume, which was recorded hourly. The 2 scale bars on both sides indicate the height of the drainage points measured from the external auditory meatus at 0 cm H₂O.

as the baseline velocity for each patient. For both groups, any changes in the MCA velocity measured on Days 5–14 was calculated as the percentage of the baseline velocity.

Statistical Analysis

Neurological outcomes and mortality rates were evaluated with scores on the Glasgow Outcome Scale (GOS) and modified Rankin Scale at 3 months after SAH onset. Average values for groups are given as mean $\pm$ SD or as median and interquartile range (IQR). The data were analyzed with the chi-square test, Fisher exact test, or Mann-Whitney U-test. Statistical significance was defined as $p < 0.05$.

Results

From April 2008 to March 2013, 263 patients with SAH caused by a ruptured aneurysm were treated at Jun-tendo University Shizuoka Hospital. Of these patients, 73 were eligible and enrolled in this study. However, 3 patients were later excluded, because of violation of protocol requirements in 1 case in the control group and because of an injection failure of the MgSO_4 solution in 2 patients in the Mg group. The clinical data of the remaining 70 patients (35 patients in the control group and 35 patients in Mg group) are summarized in Table 1. No significant differences were detected between the 2 groups in age, sex, WFNS grade, or Fisher grade. All 70 patients were treated by surgical clipping, and the patients in the 2 groups had aneurysms in similar locations.

The temporal changes in $\text{Mg}^{2+}_{\text{serum}}$ and $\text{Mg}^{2+}_{\text{CSF}}$ are shown in Fig. 2. In the control group, both $\text{Mg}^{2+}_{\text{CSF}}$ and $\text{Mg}^{2+}_{\text{serum}}$ tended to decrease in the first 4 days, but no statistically significant changes in these 2 concentrations were observed during the 14-day measurement period in this group. In contrast, $\text{Mg}^{2+}_{\text{CSF}}$ in the Mg group gradually increased from Day 4 after the start of continuous MgSO_4 intrathecal administration, reached a plateau level on Day 6, and remained at similarly high levels until Day 14. $\text{Mg}^{2+}_{\text{serum}}$ in the Mg group also slightly increased from the baseline level, but was not significantly different from $\text{Mg}^{2+}_{\text{serum}}$ in the control group. No patient in either group required supplementation of Mg because of Mg deficiency.

No cardiovascular complications associated with Mg administration, such as bradycardia or hypotension, were observed in the Mg patients. However, a decline in consciousness and bradypnea possibly caused by the sedative effect of Mg were observed in this group. The Glasgow Coma Scale (GCS) score in the Mg group decreased with the rise in $\text{Mg}^{2+}_{\text{CSF}}$. The median GCS score in the Mg group of 7 (IQR 7–13) was significantly lower than in the control group (median GCS score 15, IQR 14–15, $p < 0.05$) on Day 10. Tracheal intubation was necessary in 23 patients (65.7%) of the Mg group and in 11 patients (31.4%) of the control group. Strict maintenance of the PaCO_2 level in patients with increasing intracranial pressure resulted in no worsening of outcomes related to the bradypnea.

Angiographic examinations for CV after surgery were performed in 32 patients (91.4%) in the Mg group and in 33 patients (94.3%) in the control group. An angiography could not be performed in the other patients because of

TABLE 1. Characteristics of the patients in the Mg and control groups*

Characteristic	Group		p Value
	Mg	Control	
No. of patients	35	35	
Mean age in yrs	59.1	59.5	0.859†
Women, %	68.6	65.7	0.799‡
Median WFNS grade	2	2	
WFNS grade			0.500§
I	8 (22.9)	9 (25.7)	
II	18 (51.4)	20 (57.1)	
III	2 (5.7)	1 (2.9)	
IV	7 (20.0)	5 (14.3)	
V	0 (0.0)	0 (0.0)	
Fisher grade of SAH			0.680§
1	0 (0.0)	0 (0.0)	
2	12 (34.3)	12 (34.3)	
3	23 (65.7)	23 (65.7)	
4	0 (0.0)	0 (0.0)	
SAH location			0.416‡
ACA	19 (54.3)	14 (40.0)	
ICA	10 (28.6)	15 (42.9)	
MCA	6 (17.1)	5 (14.3)	
Other	0 (0.0)	1 (2.9)	
Side of SAH			0.075‡
Left	16 (45.7)	12 (34.3)	
Midline	15 (42.9)	11 (31.4)	
Right	4 (11.4)	12 (34.3)	

ACA = anterior cerebral artery; ICA = internal carotid artery.

* The values in this table represent number of patients (%) unless indicated otherwise.

† The p value was calculated with an unpaired t-test.

‡ The p value was calculated with a chi-square test.

§ The p value was calculated with a Mann-Whitney U-test.

renal dysfunction, allergy, or systemic conditions. The CV grade was significantly better in the Mg group (median grade of 2) than in the control group (median grade of 3) ($p < 0.05$). None of the patients in the Mg group had a severe CV with a grade of 4 or 5 (Fig. 3).

Twenty-one patients (60.0%) in the Mg group and 23 patients (65.7%) in the control group underwent a TCD examination. Detection of the MCA or recording of continuous blood flow velocity in the MCA was difficult in some patients. The TCD ultrasonography results indicated that the velocity in the MCA increased more in the control group. In particular, the velocity was significantly higher in the control group than in the Mg group from Day 10 onward (Fig. 4).

A DCI identified on CT or MRI scans was observed in 9 patients (25.7%) in the control group and in 5 patients (14.3%) in the Mg group. Ischemic lesions attributable to a CV might be more common in the control group, and a more severe cerebral infarction might have occurred this group, but no significant differences were observed between the 2 groups.

FIG. 2. Changes in Mg^{2+} concentration in both serum and CSF over time. The Mg^{2+}_{CSF} in the Mg group significantly increased from the Mg^{2+}_{CSF} at baseline after Day 4 and had plateaued by Day 6 (Mg^{2+}_{CSF} marked by asterisks were statistically significantly different from the baseline concentration, $p < 0.05$). The Mg^{2+}_{CSF} in the patients in the Mg group was also significantly different from the Mg^{2+}_{CSF} in the patients in the control group on Days 4–14 ($p < 0.05$, repeated-measure ANOVA). The 2 patient groups did not significantly differ in Mg^{2+}_{serum} ($p > 0.05$). Ctrl CSF = Mg^{2+}_{CSF} in the control group; Ctrl serum = Mg^{2+}_{serum} in the control group; Mg CSF = Mg^{2+}_{CSF} in the Mg group; Mg serum = Mg^{2+}_{serum} in the Mg group.

The clinical outcomes at the 3-month follow-up examination are shown in Table 2. Overall, the 2 groups did not significantly differ in these outcomes. Favorable outcomes indicated by modified Rankin Scale scores of 0–2 were observed for 28 patients (80.0%) in the control group and for 27 patients (77.1%) in the Mg group. A good outcome (scored as good recovery or moderate disability according to the GOS) was noted for 32 patients (91.4%) in the control group and for 30 patients (85.7%) in the Mg group. The 2 groups also had a similar rate of permanent shunt placement for hydrocephalus. The mortality rate was 2.9% in both 2 groups, with 1 patient dying in each group.

Discussion

The results of this study suggest that continuous cister-

nal infusion with $MgSO_4$ solution reduces the incidence of angiographic CV in patients with aneurysmal SAH, particularly of severe CVs with grades of 4 or 5 on our angiographic CV scale. Such findings might suggest a lower incidence of infarction in the Mg group; however, we note that our study protocol did not reduce the incidence of DCI and did not improve clinical outcomes among the patients.

Many experimental and clinical studies have demonstrated the vasodilatory effect of Mg^{2+} .^{22,23,26,31,42} For example, results from a meta-analysis have indicated that intravenous Mg administration exerts a vasodilatory effect on CV.⁴⁶ However, the recently conducted randomized controlled MASH-2 study failed to confirm that Mg infusion improves functional outcomes.^{5,6,46,48} Nonetheless, the physiological actions of Mg are probably important.³⁰ To reach a CV via the blood route, Mg^{2+}_{serum} needs to be

FIG. 3. The angiographic CV grades in the Mg and control groups on Day 10. The angiographic CV grades in the control group were on average significantly higher than those in the Mg group ($p < 0.05$, Mann-Whitney U-test). Severe CVs (that is, those of Grade 4 or 5 on our angiographic CV scale) were not observed in the Mg group.

FIG. 4. Changes in MCA velocity over time in the Mg and control groups. The velocities were measured by TCD ultrasonography and are presented as percentages of the velocity at baseline (that is, the mean MCA velocity during the first 4 days after surgery determined for each patient). Compared with the MCA velocity in the Mg group, the MCA velocity in the control group increased significantly during the 10-day period assessed, peaking at Day 13. Statistically significant differences at the various time points between the 2 patient groups are indicated by asterisks above the velocity data for the control group.

TABLE 2. Summary of the clinical outcomes of the patients in this study at the 3-month follow-up*

Variable	Group		p Value
	Mg	Control	
mRS score			0.322†
0	12 (34.3)	17 (48.6)	
1	10 (28.6)	7 (20.0)	
2	5 (14.3)	4 (11.4)	
3	3 (8.6)	3 (8.6)	
4	2 (5.7)	3 (8.6)	
5	2 (5.7)	0 (0.0)	
6	1 (2.9)	1 (2.9)	
GOS category			0.411†
GR	22 (62.9)	25 (71.4)	
MD	8 (22.9)	7 (20.0)	
SD	3 (8.6)	2 (5.7)	
VS	1 (2.9)	0 (0.0)	
D	1 (2.9)	1 (2.9)	
Favorable outcome, %			
mRS score of 0, 1, or 2	77.1	80.0	0.771‡
GOS score of GR or MD	85.7	91.4	0.452‡
Patients requiring VPS/LPS, %	45.7	42.3	0.810‡
Mortality rate, %	2.9	2.9	1.000‡
Mean hospital LOS, days	47.9	46.1	0.710§

D = death; GR = good recovery; LOS = length of stay; LPS = lumboperitoneal shunt; MD = moderately disabled; mRS = modified Rankin Scale; SD = severely disabled; VPS = ventriculoperitoneal shunt; VS = vegetative state.

* The values in this table represent number (%) of patients unless indicated otherwise.

† The p value was calculated with a Mann-Whitney U-test.

‡ The p value was calculated with a chi-square test.

§ The p value was calculated with an unpaired t-test.

maintained at high levels, because Mg translocates poorly across the blood-brain barrier. Any ensuing toxic effects of high Mg^{2+}_{serum} can lead to various systemic complications such as arrhythmia, hypotension, or bradypnea. Accordingly, maintaining a Mg^{2+}_{serum} optimal for the therapeutic window is extremely difficult because of the high risk for cardiovascular events.^{30,45}

We have previously reported that the vasodilatory effect in intracranial arterial vessels may depend on Mg^{2+}_{CSF} .²⁵ In contrast to intravenous $MgSO_4$ injection, the direct cisternal infusion method used in the present study readily increases Mg^{2+}_{CSF} with a relatively small volume of $MgSO_4$ solution. The findings in this study thus have demonstrated a safe infusion rate of $MgSO_4$ solution for achieving a Mg^{2+}_{CSF} that results in optimal vasodilation.⁴⁵ No adverse effect of Mg^{2+} on the cardiovascular system was observed, even though the intrathecal $MgSO_4$ infusion slightly increased Mg^{2+}_{serum} . This infusion method is relatively safe if the total infusion volume is adjusted such that it maintains a balance of the CSF drainage volume with that of the perfusion solution. Cisternal drainage is more invasive, but is one of the standard techniques in the surgical treatment of ruptured aneurysms.^{17,33,49} We propose that continuous cisternal infusion is no more invasive than conventional treatment of patients with SAH.

Recently, several studies have shown that DCI is not closely associated with CV, suggesting that CV is not the only cause of DCI in patients with SAH.^{4,9} On the other hand, the occurrence of cerebral infarction is clearly associated with DCI, and cerebral infarction identifiable on CT or MRI scans is clearly associated with poor functional outcomes.¹⁰ A DCI might be caused by several factors, including early brain injury, microthromboembolism, cortical spreading ischemia, cerebrovascular autoregulation dysfunction, and delayed effects of SAH-induced brain injury.^{2,8,9,13,35,44} Clinically, the infarction caused by severe CV is well known to occur in patients with SAH. The severity of CV is one of the independent predictors of a poor functional outcome. Therefore, preventing CV occurrence is important for patients with SAH.^{10,21}

The results of the present study show that intracisternal Mg therapy significantly ameliorates angiographic CV but fails to improve clinical outcomes. Recently, despite indicating decreased occurrence of CV after treatment with clazosentan, a potent vasodilator acting as a selective endothelin A receptor antagonist, a Phase 3 clinical study (that is, the CONSCIOUS-2 trial) failed to show any effect of vasodilation on CV-related morbidity rates or on functional outcomes.²⁰ The results in this and other studies suggest that vasodilatory treatment alone may not sufficiently improve the clinical outcomes in SAH patients, so any new treatment modality should have both vasodilatory and neuroprotective effects.^{19,47} Mg²⁺ not only acts as a vasodilator by blocking Ca²⁺ influx via the voltage-dependent calcium channels in the vascular smooth muscle but also acts as a neuroprotector by inhibiting glutamate and N-methyl-D-aspartate receptors.^{18,27,39,41} We started intracisternal Mg infusion on Day 4 after the ictus, and Mg²⁺CSF reached a plateau on Day 6. We therefore hypothesize that our intracisternal Mg infusion protocol might not have been initiated early enough to prevent DCI-related brain injuries such as early brain injury and cortical spreading ischemia. On the basis of these results, we are planning to conduct another randomized controlled trial of intracisternal Mg therapy starting immediately after clipping surgery.³⁸

In this study, the level of observed sedation depended on Mg²⁺CSF, and respiratory depression also emerged. The sedative effect of Mg²⁺ might improve the cerebral metabolic rate of oxygen and may provide neuroprotection.^{27,43} Although respiratory depression might not worsen a CV if airway conductivity and oxygenation levels remain normal, it is not a safe clinical sign. Moreover, respiratory depression requiring tracheal intubation might provoke systemic complications such as pneumonia, cardiac failure, or malnutrition. We considered that these negative effects would offset the potential benefits of our intracisternal Mg therapy.

Although the present study failed to indicate that the Mg treatment statistically significantly improved functional outcomes, we note the favorable outcomes in 80% of the patients in the control group, a rate that was higher than the rates reported from other randomized controlled trials.^{5,30,34,45} A selection bias that arose from our exclusion of patients with an SAH with a Fisher grade of 4, a WFNS grade of V, or with severe surgical complications should also be considered in the interpretation of our results. We also note that continuous irrigation with MgSO₄ solution has been previously shown not to improve functional outcomes compared with several treatments including administration of fasudil hydrochloride (a Rho kinase antagonist), cisternal irrigation therapy with tissue-plasminogen activator, and others.^{30,38} Last, the present study was a single-center trial, with too few cases to evaluate the functional outcome in SAH attributed to multifactorial etiologies.

Conclusions

The results of the present study demonstrated that continuous cisternal irrigation with MgSO₄ solution decreases the rate of occurrence of CV in patients with SAH. How-

ever, this improvement in CV onset did not reduce the incidence of DCI, and it also did not improve functional outcomes in our patients. Despite the observed reduction in CV, which is the likely cause of DCI, the vasodilatory effect of Mg²⁺ on CV did not appear to improve the functional outcomes in this study. Prevention and aggressive treatment of pathological CV are certainly beneficial for patients with SAH, so both require further clinical research. We propose that a prospective multicenter trial should be conducted to address this need for additional clinical data on CV in patients with SAH.

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