Optimal cerebrospinal fluid magnesium ion concentration for vasodilatory effect and duration after intracisternal injection of magnesium sulfate solution in a canine subarachnoid hemorrhage model

Laboratory investigation

Kentarō Mori, M.D., Ph.D.,¹ Takaji Yamamoto, M.D., Ph.D.,¹ Masahiro Miyazaki,¹ Yasukazu Hara,² Yasuhisa Aiko,² Nobuhiko Koike,² Shinsuke Sakamoto,² Yasuki Nakao, M.D., Ph.D.,¹ and Takanori Esaki, M.D., Ph.D.¹

Departments of ¹Neurosurgery and ²Radiology, Juntendo University, Shizuoka Hospital; and ³Juntendo Casualty Center, Izunokuni, Shizuoka, Japan

Object. The optimal CSF Mg²⁺ concentration for vasodilation of spastic cerebral arteries after subarachnoid hemorrhage (SAH) and its duration are unknown. The temporal profile of the vasodilatory effect and optimal CSF Mg²⁺ concentration after the intracisternal injection of MgSO₄ solution were investigated in an SAH model in canines.

Methods. Cerebral vasospasm was induced by experimental SAH using a 2-hemorrhage model in 26 female beagles. On Day 7, 0.5 ml/kg of 15, 10, 5, or 0 mmol/L MgSO₄ in Ringer solution was injected into the cerebellomedullary cistern. Angiography was performed on Day 1 (before SAH) and before and 1, 3, and 6 hours after the intracisternal injection on Day 7 to measure arterial diameters of the basilar artery (BA), superior cerebellar artery (SCA), and vertebral artery (VA). Cerebrospinal fluid Mg²⁺ was also measured at the same time.

Results. Arterial diameters of the BA, SCA, and VA were significantly decreased by vasospasm on Day 7. Arterial diameter ratios (ratio of arterial diameter after MgSO₄ injection to diameter before injection on Day 7) of the BA and SCA at 1 and 3 hours after and the VA at 1 hour after intracisternal injection of the MgSO₄ solution were positively correlated with the CSF Mg²⁺ concentration. All arterial diameter ratios, except 1 point of the SCA, exceeded 1 if the CSF Mg²⁺ concentration was > 3 mEq/L at 1 hour after injection. Animals with CSF Mg²⁺ concentrations > 3 mEq/L at 1 hour after injection (11 dogs) showed significantly increased arterial diameters of the BA at 1 and 3 hours after and of the SCA and VA at 1, 3, and 6 hours after injection, as compared with the diameters before injection. The CSF Mg²⁺ concentration significantly increased at 1 hour (3.73 ± 0.69 mEq/L, p < 0.01) and 3 hours (2.05 ± 0.35 mEq/L, p < 0.01) after the intracisternal injection as compared with the baseline value (1.41 ± 0.20 mEq/L).

Conclusions. The reversible effect of an intracisternal injection of MgSO₄ solution on the spastic artery requires CSF Mg²⁺ concentrations > 3 mEq/L. The vasodilatory effect continues for 3–6 hours after injection. These results suggest that the continuous infusion or intermittent intracisternal injection of MgSO₄ is needed to maintain the optimal CSF Mg²⁺ concentration and constantly ameliorate cerebral vasospasm. (DOI: 10.3171/2010.10.JNS10866)

Key Words • cerebrospinal fluid • magnesium ion • vasospasm • subarachnoid hemorrhage

Abbreviations used in this paper: BA = basilar artery; SAH = subarachnoid hemorrhage; SCA = superior cerebellar artery; VA = vertebral artery.
In the present study we followed the changes in the diameters of spastic cerebral arteries by using canine SAH models to elucidate the optimal CSF Mg$^{++}$ concentration for and the temporal profile of this vasodilatory effect after intracisternal injection of different concentrations of MgSO$_4$ solution.

Methods

All animal experiments were performed in accordance with the Institutional Guidelines and Rules of Animal Experimentation and the Guidelines for the Care and Use of Laboratory Animals of Juntendo University, Shizuoka Hospital. Cerebral vasospasm was induced using a 2-hemorrhage model in 26 female beagle dogs weighing 9–11 kg and anesthetized with an intravenous bolus injection of 20 mg/kg of pentobarbital. Anesthesia was maintained by continuous intravenous injection of 1 ml/kg/hr of propofol until the end of the procedure. The dogs were intubated using a 6 Fr endotracheal tube, and respiration was controlled with an MR imaging–compatible mobile respirator (paraPAC 2000 MR imaging, Smiths Medical). A 4 Fr, double-lumen sheath catheter was placed in the femoral artery for cerebral angiography, blood pressure monitoring, and arterial gas sampling. End-tidal CO$_2$ was carefully monitored, and the PaCO$_2$ was maintained between 35 and 45 mm Hg.

Both T1- and T2-weighted MR imaging were performed using a 1.5-T Gyroscan (Philips Medical Systems). The Evans index ([maximum bifrontal horn distance/maximum inner diameter of skull] × 100, expressed in %) was calculated. After MR imaging, the left VA was cannulated using a 4 Fr catheter under fluoroscopic control, and digital subtraction angiography was performed after injecting 2.5 ml of iopamidol (Bayer) via an automatic injector (1.2 ml/second). After control baseline images of the VA, BA, and SCA were obtained, the cisterna magna was punctured with a 20-gauge needle, 0.3 ml/kg of CSF was removed by gravity flow, and 0.5 ml/kg of autologous blood was injected into the cerebellomedullary cistern (first SAH). The Mg$^{++}$ and Ca$^{++}$ concentrations in the CSF and serum were measured via ion-selective electrodes (StatProfile CCX, NOVA Biomedical). After the blood injection, the dog’s head was tilted downward at 30° for 15 minutes. The animals were then allowed to recover from anesthesia.

The second SAH was induced on Day 3 using the same procedure. On Day 7 the dogs were anesthetized and a tracheal cannula was inserted. A 4 Fr double-lumen sheath was also placed in the femoral artery. Again, T1- and T2-weighted MR imaging were performed to assess any pathological changes including ischemic ones. At 1.5 hours after inducing anesthesia, left VA angiography was performed to assess any changes in the VA, BA, and SCA following experimental SAH. Immediately after angiography, the cisterna magna was punctured with a 20-gauge needle to remove 0.3 ml/kg of CSF and to inject 0.5 ml/kg of 15 (8 animals), 10 (6 animals), 5 (6 animals), or 0 mmol/L (6 animals) MgSO$_4$ solution in Ringer solution (130 mEq/L Na$^+$, 4 mEq/L K$^+$, 109 mEq/L Cl$^-$, and 28 mEq/L lactate) into the cerebellomedullary cistern. Each dog’s head was then tilted downward at 30° for 15 minutes.

Left VA angiography was repeated to assess the changes in arterial diameters at 1, 3, and 6 hours after injection of the MgSO$_4$ solution. The PaCO$_2$ was meticulously maintained between 35 and 45 mm Hg during the experiment. Magnetic resonance imaging was also repeated to evaluate any changes at 5 hours after MgSO$_4$ administration. Cerebrospinal fluid and serum samples were collected to measure Mg$^{++}$ and Ca$^{++}$ concentrations before MgSO$_4$ administration and after each angiography. Immediately after the final angiography and CSF and serum samples, the dogs were humanely killed via intravenous injection of pentobarbital overdose, and their brains were removed and immersed in 10% formalin. The fixed brain was sliced coronally and then stained with H & E and elastica van Gieson for histological examination of the BA.

Arterial diameters were measured using digital subtraction angiography (Infinix Celeve-i, Toshiba Medical Systems) with a matrix of 1024 × 1024 and automatically calibrated for conversion between millimeters and pixels to measure the arterial vessel diameter. Angiograms were recorded in real time, and the images were captured at peak arterial contrast opacification. A radiological technician unaware of the details of the experimental protocol measured the arterial diameters of the bilateral VAs at the junction with the BA. The mean of the 2 measured diameters was taken as the diameter of the VA. The arterial diameters of the BA were measured at 3 equidistant points between the junctions with the VA and the SCA. The mean of the 3 measured diameters was taken as the arterial diameter of the BA. The arterial diameters of the bilateral SCAs were measured at both sides of the junction with the BA. The mean of the 2 measured diameters was taken as the diameter of the SCA.

Data are presented as the means ± SDs. The statistical significance of differences was analyzed with 1-way ANOVA, the paired t-test, the Wilcoxon signed-rank test, linear regression, and the chi-square test by using SPSS 7.5.1 J for Windows (SPSS Japan, Inc.). A p value < 0.05 was considered statistically significant.

Results

Physiological Parameters and Morphological Changes

Table 1 lists the physiological parameters and serum concentrations of Mg$^{++}$ and Ca$^{++}$ on Day 1 and before and after the intracisternal injection of the MgSO$_4$ solution on Day 7. The mean arterial blood pressure, hemoglobin concentration, hematocrit, arterial blood gas parameters, and serum Mg$^{++}$ and Ca$^{++}$ concentrations did not change throughout the experimental procedures. Body temperature was significantly increased on Day 7 as compared with that on Day 1 (p < 0.001) but did not show significant changes before and after the intracisternal injection of the MgSO$_4$ solution. The animals showed hydrocephalus on Day 7. The Evans indexes before (26.2 ± 2.2%) and after (26.2 ± 1.9%) intracisternal injection of the MgSO$_4$ solution on Day 7 were significantly increased as compared with that on Day 1 (19.7 ± 1.5%), but were not significantly different from one another. No other pathological changes, including ischemia, were noted on MR imaging (data not shown). Photomicrographs of the coronal sections of the
Intracisternal injection of MgSO₄ solution on the vasodilation of spastic cerebral arteries and CSF Mg⁺⁺ and Ca⁺⁺ concentrations

Correlation Between Change in Arterial Diameter and CSF Mg⁺⁺ Concentration

To examine the effects of the CSF Mg⁺⁺ concentration on arterial diameter, the ratios of the arterial diameter before intracisternal injection of the MgSO₄ solution to the diameter after injection (arterial diameter ratio) were calculated on Day 7. The arterial diameter ratios of the BA were positively correlated with the CSF Mg⁺⁺ concentration at 1 hour (R = 0.554, p < 0.01), but not at 3 hours (R = 0.258, p = 0.204) after injection (Fig. 1). The arterial diameter ratios of the SCA were positively correlated with the CSF Mg⁺⁺ concentration at 1 hour (R = 0.608, p < 0.01) and 3 hours (R = 0.586, p < 0.01) after injection, but not at 6 hours (R = 0.204, p = 0.600) after intracisternal injection (Fig. 2). The arterial diameter ratios of the VA were positively correlated with the CSF Mg⁺⁺ concentration at 1 hour after injection (R = 0.554, p < 0.01), but not at 3 hours (R = 0.204, p = 0.318) and 6 hours (R = 0.108, p = 0.600) after intracisternal injection (Fig. 3). The arterial diameter ratios, except 1 point in the SCA, exceeded 1 in all animals with CSF Mg⁺⁺ concentrations > 3 mEq/L at 1 hour after intracisternal injection of MgSO₄ solution. To determine the effective concentration of Mg⁺⁺, a chi-square test was performed with 2 categorized Mg⁺⁺ concentrations, more or less than 3 mEq/L, and 2 categorized vasodilator ratios of the artery, more or less than 1.0. Given that the statistical p values of the chi-square tests for the BA, SCA, and VA were 0.024, 0.024, and 0.046, respectively, the 3 mEq/L level caused a significant vasodilatory effect.

Temporal Profile of the Effects of the Intracisternal Injection of MgSO₄ Solution on the Vasodilation of Spastic Cerebral Arteries and CSF Mg⁺⁺ and Ca⁺⁺ Concentrations

Changes in CSF Mg⁺⁺ and Ca⁺⁺ concentrations and cerebral arterial diameters were analyzed in the 11 animals with a > 3 mEq/L CSF Mg⁺⁺ concentration at 1 hour after intracisternal injection of the MgSO₄ solution. Figure 4 upper shows the temporal profile of changes in CSF Mg⁺⁺ and Ca⁺⁺ concentrations on Day 1 and before and 1, 3, and 6 hours after injection of the MgSO₄ solution on Day 7. The Mg⁺⁺ concentration before injection on Day 7 (1.41 ± 0.20 mEq/L) did not change compared with that on Day 1 (1.36 ± 0.14 mEq/L). The Mg⁺⁺ concentration of 3.73 ± 0.69 mEq/L at 1 hour after and 2.05 ± 0.35 mEq/L at 3 hours after injection represented significant increases (p < 0.01), as compared with the value before MgSO₄ injection. The Ca⁺⁺ concentration returned to the baseline value at 6 hours after MgSO₄ injection (1.54 ± 0.21 mEq/L). The Ca⁺⁺ concentration before injection on Day 7 (2.24 ± 0.12 mEq/L) was slightly but significantly increased (p < 0.01), as compared with that on Day 1 (2.11 ± 0.11 mEq/L). The Ca⁺⁺ concentration was 2.34 ± 0.07 mEq/L (p < 0.01) at 1 hour, 2.37 ± 0.12 mEq/L (p < 0.01) at 3 hours, and 2.34 ± 0.14 mEq/L (p < 0.05) at 6 hours after the injection on Day 7, a significant increase as compared with the value before MgSO₄ injection.

Figure 4 lower shows the temporal changes in the cerebral arterial diameters on Day 1 and before and 1, 3, and 6 hours after intracisternal injection of MgSO₄ on Day 7. The diameters of the BA, SCA, and VA before SAH on Day 1 were 1.21 ± 0.19, 0.88 ± 0.19, and 1.02 ± 0.25 mm, respectively. The BA, SCA, and VA showed significant decreases (p < 0.01) in diameter to 0.66 ± 0.13, 0.41 ± 0.07, and 0.54 ± 0.18 mm, respectively, before the injection of MgSO₄ on Day 7 as compared with their values on Day 1. The arterial diameter of the BA was significantly increased to 0.79 ± 0.16 mm (p < 0.01) at 1 hour and 0.77 ± 0.14 mm (p < 0.05) at 3 hours after injection, as compared with before injection. The arterial diameter of the SCA was significantly increased to 0.53 ± 0.09 mm (p < 0.01) at 1 hour, 0.56 ± 0.11 mm (p < 0.01) at 3 hours, and 0.49 ± 0.09 mm (p < 0.05) at 6 hours after injection, as compared with before injection. The arterial diameter of the VA was significantly increased to 0.70 ± 0.21 mm (p < 0.01) at 1 hour, 0.65 ± 0.19 mm (p < 0.05) at 3 hours, and 0.62 ± 0.16 mm (p < 0.05) at 6 hours after injection, as compared with before injection.

BAs stained with H & E and elastica van Gieson showed SAH mainly in the ventral surface of the brainstem. The adventitia of the BA demonstrated edematous change with inflammatory cell infiltration. The internal elastic lamina showed folding and corrugation. These histological findings are typical of cerebral vasospasm (data not shown).

### TABLE 1: Summary of physiological parameters*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>(Pre-MgSO₄)</th>
<th>(Post-MgSO₄)</th>
<th>p Value(Pre-MgSO₄) (Post-MgSO₄)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean blood pressure (mm Hg)</td>
<td>100 ± 12</td>
<td>93 ± 12</td>
<td>96 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>body temperature (°C)</td>
<td>37.6 ± 0.3</td>
<td>38.2 ± 0.4</td>
<td>38.2 ± 0.5</td>
<td>&lt;0.001</td>
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<tr>
<td>hemoglobin (g/dl)</td>
<td>12.4 ± 1.0</td>
<td>11.8 ± 1.0</td>
<td>12.1 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>37 ± 3</td>
<td>35 ± 3</td>
<td>36 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.03</td>
<td>7.39 ± 0.02</td>
<td>7.38 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>38 ± 3</td>
<td>38 ± 2</td>
<td>38 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>398 ± 34</td>
<td>407 ± 26</td>
<td>400 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>serum Mg⁺⁺ concentration (mEq/L)</td>
<td>1.10 ± 0.09</td>
<td>1.15 ± 0.10</td>
<td>1.11 ± 0.11</td>
<td>NS</td>
</tr>
<tr>
<td>serum Ca⁺⁺ concentration (mEq/L)</td>
<td>2.84 ± 0.19</td>
<td>2.88 ± 0.17</td>
<td>2.82 ± 0.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data are presented as the means ± SDs. Abbreviation: NS = not significant.

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The changes in CSF Mg\textsuperscript{2+} and Ca\textsuperscript{2+} concentrations and cerebral arterial diameters were analyzed in the 15 animals with CSF Mg\textsuperscript{2+} concentrations < 3 mEq/L at 1 hour after the intracisternal injection of MgSO\textsubscript{4} or Ringer solution. Figure 5 upper shows the temporal profile of changes in CSF Mg\textsuperscript{2+} and Ca\textsuperscript{2+} concentrations on Day 1 and before and 1, 3, and 6 hours after intracisternal injection of the MgSO\textsubscript{4} or Ringer solution on Day 7. The Mg\textsuperscript{2+} concentration was 1.78 mEq/L at 1 hour after injection.

Fig. 1. Relationships between arterial diameter ratios of the BA and CSF Mg\textsuperscript{2+} concentrations at 1 (A), 3 (B), and 6 (C) hours after intracisternal injection of MgSO\textsubscript{4} solution. The arterial diameter ratios were positively correlated with the CSF Mg\textsuperscript{2+} concentration at 1 and 3 hours after injection. Note that all arterial diameter ratios exceeded 1 in the animals with CSF Mg\textsuperscript{2+} concentrations > 3 mEq/L at 1 hour after injection. Black circles indicate animals that received 15 mmol/L MgSO\textsubscript{4}; white squares, 10 mmol/L MgSO\textsubscript{4}; black triangles, 5 mmol/L MgSO\textsubscript{4}; and white circles, 0 mmol/L MgSO\textsubscript{4}.

Fig. 2. Relationships between arterial diameter ratios of the SCA and CSF Mg\textsuperscript{2+} concentrations at 1 (A), 3 (B), and 6 (C) hours after intracisternal injection of MgSO\textsubscript{4} solution. The arterial diameter ratios were positively correlated with the CSF Mg\textsuperscript{2+} concentration at 1 and 3 hours after injection. Note that all arterial diameter ratios, except for 1 point, exceeded 1 in the animals with CSF Mg\textsuperscript{2+} concentrations > 3 mEq/L at 1 hour after injection.
tion, which was significantly increased (p < 0.05) compared with the value before injection (1.41 ± 0.09 mEq/L). The Mg²⁺ concentration had returned to the baseline value at 3 hours (1.51 ± 0.18 mEq/L) and 6 hours (1.36 ± 0.11 mEq/L) after the MgSO₄ injection. The CSF Ca²⁺ concentration before injection on Day 7 (2.21 ± 0.23 mEq/L) was slightly but significantly increased (p < 0.05) compared with that on Day 1 (2.03 ± 0.19 mEq/L). The CSF Ca²⁺ concentrations after the injection did not change significantly.

Figure 5 lower shows the temporal changes in the cerebral arterial diameters on Day 1 and before and 1, 3, and 6 hours after intracisternal injection of the MgSO₄ or Ringer solution on Day 7. The diameters of the BA, SCA, and VA on Day 7 before injection were significantly decreased, as compared with those on Day 1. The arterial diameters of the BA at 1 and 3 hours after injection were significantly increased, compared with before injection. The arterial diameters of the SCA and VA at 1, 3, and 6 hours after injection were significantly increased, as compared with before injection.
Data in the present study showed that the arterial diameter ratios of the BA and SCA at 1 and 3 hours and of the VA at 1 hour after the intracisternal injection of MgSO₄ solution were significantly correlated with the CSF Mg⁺⁺ concentration. We also demonstrated that animals with a CSF Mg⁺⁺ concentration > 3 mEq/L at 1 hour after intracisternal injection of the MgSO₄ solution had increased diameters of spastic cerebral arteries. The present findings suggest that the CSF Mg⁺⁺ concentration should be increased to > 3 mEq/L to dilate spastic cerebral arteries after SAH. Despite a decline in the CSF Mg⁺⁺ concentration to below 3 mEq/L at 3 hours after and a return to baseline at 6 hours after intracisternal injection of the MgSO₄ solution, the diameter of spastic arteries continued to be significantly dilated for 3–6 hours. Our results suggest that continuous intracisternal infusion or intermittent injection of MgSO₄ solution would be necessary to maintain the optimal CSF Mg⁺⁺ concentration and constantly ameliorate cerebral vasospasm.

Results in the present study also indicated a slight but significantly increased CSF Ca⁺⁺ concentration at 1–6 hours after intracisternal injection of MgSO₄ solution in the animals with dilated spastic cerebral arteries. The increased CSF Ca⁺⁺ concentration may result from the inhibition of extracellular Ca⁺⁺ influx due to the Ca⁺⁺ blocker effect of the increased extracellular Mg⁺⁺ concentration. Therefore, the mechanism of the vasodilatory effect of the intracisternal injection of MgSO₄ solution on spastic cerebral arteries following SAH might be mediated by the Ca⁺⁺ channel blocker effect of the increased extracellular Mg⁺⁺ concentration.

Several clinical trials have reported that the intravenous infusion of MgSO₄ reduces the occurrence of delayed neurological ischemia and improves outcome after aneurysmal SAH, presumably mediated by the neuroprotective effects of Mg such as the inhibition of excitatory amino acid (glutamate) and the blockage of voltage-dependent calcium channels and N-methyl-D-aspartic acid receptors.³⁰,¹⁵–²⁰ But 2 prospective randomized controlled trials on the continuous intravenous administration of MgSO₄ in patients with SAH failed to show any vasodilatory effect on vasospastic vessels according to angiography and transcranial Doppler ultrasonography.¹⁰,¹² Continuous intravenous infusion of MgSO₄ also failed to reverse spastic cerebral arteries in an in vivo SAH model in monkeys.¹ The absence of expected vasodilatory effects on the spastic cerebral arteries after the intravenous infusion of MgSO₄, despite the increased blood concentration of Mg⁺⁺, is considered to result from the relative impermeability of the blood-brain barrier to Mg⁺⁺ in the blood. Extracellular Mg⁺⁺ concentration is key to the regulation of vascular smooth muscle tone.²,¹⁴ An increased extracellular Mg⁺⁺ concentration definitely causes vaso-dilation of both normal and contracted cerebral arteries in the presence of vasospasm-inducing agents in vitro.¹,⁵ Cerebrospinal fluid Mg⁺⁺ concentrations in the range of 2.4–9.6 mEq/L have caused the dilation of normal arteries in the cat.¹¹ Therefore, the intravenous infusion of MgSO₄ cannot increase the extracellular Mg⁺⁺ concentration in the brain to a level adequate to dilate spastic cerebral arteries.

**Discussion**

Data in a previous study demonstrated the vasodilatory effect of the intracisternal injection of MgSO₄ solution on spastic cerebral arteries in a canine SAH model utilizing angiography.⁹ Using a quantitative autoradiographic technique, we have also shown that the intracisternal infusion of MgSO₄ solution improves reduced cerebral blood flow after experimental SAH in the rat.⁷ Note, however, that the optimal CSF concentration of Mg⁺⁺ to dilate spastic cerebral arteries and the duration of its vasodilatory effect were not investigated.

**Fig. 5.** Time profiles of CSF Mg⁺⁺ and Ca⁺⁺ concentrations (upper) and cerebral arterial diameters (lower) in the 15 animals with CSF Mg⁺⁺ concentrations < 3 mEq/L at 1 hour after intracisternal injection of MgSO₄ or Ringer solution. The CSF Mg⁺⁺ concentration at 1 hour after injection was significantly increased compared with before injection and returned to the baseline value at 3 and 6 hours after. The CSF Ca⁺⁺ concentrations after injection were not significantly increased compared with before injection. The diameters of the BA, SCA, and VA on Day 7 before injection were significantly decreased compared with those of Day 1. The arterial diameter of the BA at 6 hours was significantly decreased compared with before injection. The arterial diameters of the VA at 3 and 6 hours after injection were significantly decreased compared with before injection.

The arterial diameter of the SCA did not change significantly after the MgSO₄ injection.

Representative angiograms illustrating the development of vasospasm on Day 7 and the reversal effects at 1–6 hours after the intracisternal injection of the MgSO₄ solution (15 mmol/L) are presented in Fig. 6.
Data in the present study also revealed that animals with CSF Mg\textsuperscript{++} concentrations < 3 mEq/L at 1 hour after the intracisternal injection of MgSO\textsubscript{4} or Ringer solution demonstrated further decreases in the diameters of the spastic cerebral arteries of the VA and BA. The decreased arterial diameters were observed mainly in the animals treated with the intracisternal injection of Ringer solution without MgSO\textsubscript{4} (Figs. 1–3). This finding suggests that cisternal irrigation therapy without Mg\textsuperscript{++} may worsen cerebral vasospasm in patients with SAH.

Several clinical studies on the intracisternal infusion of MgSO\textsubscript{4} therapy in patients with aneurysmal SAH have shown a reduction in the incidence of symptomatic vasospasm and the reversible effect on angiographic vasospasm.\textsuperscript{8,13} Data in the present study demonstrated that the injection of an intracisternal MgSO\textsubscript{4} solution had a positive but moderate vasodilatory effect. Therefore, this therapy may require combination with some other adjunct treatment, such as hemolytic irrigation to wash out the subarachnoid blood clot. A preliminary clinical study of the intracisternal infusion of MgSO\textsubscript{4} solution has documented some unfavorable effects, such as anesthesia and respiratory suppression in patients who required admission to the intensive care unit.\textsuperscript{8} Based on the results of our experimental studies, a randomized controlled clinical study of intracisternal infusion therapy in patients with aneurysmal SAH is currently underway at our institution.

Conclusions

The reversible effect of the intracisternal injection of MgSO\textsubscript{4} solution on the spastic artery required CSF Mg\textsuperscript{++} concentrations > 3 mEq/L. The vasodilatory effect continued for 3–6 hours after the intracisternal MgSO\textsubscript{4} injection. These results suggest that the continuous infusion or intermittent intracisternal injection of MgSO\textsubscript{4} is needed to maintain the optimal CSF Mg\textsuperscript{++} concentration and constantly ameliorate cerebral vasospasm.
Optimal cerebrospinal fluid magnesium concentration and duration

Disclosure

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Author contributions to the study and manuscript preparation include the following. Concept and design: Mori. Acquisition of data: Mori, Yamamoto, Miyazaki, Nakao, Esaki. Analysis and interpretation of data: Mori. Drafting the article: Mori. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Yamamoto. Administrative/technical/material support: Miyazaki, Hara, Aiko, Koike, Sakamoto.

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Address correspondence to: Kentaro Mori, M.D., Ph.D., Department of Neurosurgery, Juntendo University, Shizuoka Hospital, 1129 Nagaoka, Izunokuni, Shizuoka 410-2295. Japan. email: kmori@med-juntendo.jp.