

Potential Risk of Artificial Cerebrospinal Fluid Solution Without Magnesium Ion for Cerebral Irrigation and Perfusion in Neurosurgical Practice

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Abstract

The effect of irrigation with artificial cerebrospinal fluid (CSF) containing various magnesium ion (Mg^{2+}) concentrations on vasospastic arteries was investigated in the dog. Cerebral vasospasm was induced by the experimental subarachnoid hemorrhage model in 15 beagle dogs. Cisternal irrigation was performed for 1 hour via a microcatheter placed in the cisterna magna with commercially available artificial CSF (ARTCEREB®) with physiological concentration of Mg^{2+} (2.2 mEq/l) (ACM group, n = 5), ARTCEREB solution without Mg^{2+} (ACR group, n = 5), and ARTCEREB solution with higher Mg^{2+} concentration (5 mEq/l) (ACMM group, n = 5). CSF electrolyte concentrations and the diameters of the basilar and vertebral arteries were measured. In the ACM group, no changes were detected in either CSF Mg^{2+} concentration or arterial diameters. In the ACR group, the CSF Mg^{2+} decreased significantly to 0.8 ± 0.07 mEq/l from the baseline value of 1.4 ± 0.03 mEq/l, and both basilar and vertebral artery diameters were significantly decreased to 0.61 ± 0.18 mm and 0.57 ± 0.23 mm from their baseline values of 0.74 ± 0.22 mm and 0.68 ± 0.17 mm, respectively. In the ACMM group, the CSF Mg^{2+} significantly increased to 2.4 ± 0.15 mEq/l from the baseline value of 1.4 ± 0.05 mEq/l, and both basilar and vertebral artery diameters were significantly increased to 0.84 ± 0.19 mm and 0.90 ± 0.22 mm from their baseline values of 0.71 ± 0.21 mm and 0.69 ± 0.24 mm, respectively. Irrigation with artificial CSF solution without Mg^{2+} causes vasoconstriction of the cerebral artery. Irrigation with artificial CSF with appropriate Mg^{2+} concentration is essential, especially in patients with subarachnoid hemorrhage.

Key words: magnesiumion, artificial cerebrospinal fluid, vasoconstriction, vasospasm

Introduction

Vascular muscle tone is mainly regulated by extracellular calcium ion (Ca^{2+}) and magnesium ion (Mg^{2+}) concentrations. The extracellular Mg^{2+} acts as a vasodilator under both physiological and pathological conditions.^{7,15)} Recently, the extracellular Mg^{2+} concentration was shown to regulate the cerebral arteriole diameter that controls cerebral blood flow (CBF).¹¹⁾ Cisternal infusion of magnesium sulfate solution increased the cerebrospinal fluid (CSF) Mg^{2+} concentration, resulting in dilated spastic cerebral arteries and amelioration of the reduced CBF after experimental subarachnoid hemorrhage (SAH).^{8–10)} Therefore, maintenance of appropriate extracellular

and cisternal Mg^{2+} concentrations is considered to be clinically important under pathophysiological conditions.

Commercially available artificial CSF solution (ARTCEREB®; Otsuka Pharmaceutical Co., Ltd., Tokushima) is widely used to irrigate and perfuse the brain during cerebrospinal surgery. This artificial CSF has similar pH (7.3) and electrolyte concentrations to the human CSF.^{1,2)} ARTCEREB solution is characterized as containing the physiological level of Mg^{2+} (2.2 mEq/l). Recently, we reported that cisternal infusion of Ringer solution without magnesium worsens the cerebral arterial vasospasm induced in the canine SAH model, whereas infusion of Ringer solution containing magnesium resulting in CSF Mg^{2+} concentration of more than 3 mEq/l ameliorated such vasospasm.¹⁰⁾ Ringer solution's

electrolytes concentrations (130 mEq/l Na⁺, 4 mEq/l K⁺, 109 mEq/l Cl⁻, and 28 mEq/l lactate) are different from those of normal CSF. However, whether Mg²⁺ in the mock CSF solution acts as same as that in the Ringer solution has not been examined.

The present study investigated the effects of commercially available artificial CSF solutions with or without Mg²⁺ on the spastic cerebral arteries induced in the canine SAH model to assess the potential risks of using artificial CSF solution without Mg²⁺ for irrigation of the brain, and to provide the rationale for use of artificial CSF solution with appropriate Mg²⁺ concentrations for routine neurosurgical procedures including cisternal irrigation therapy in patients with SAH.

Materials and 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. Fifteen female beagle dogs (weighing 9–11 kg) were anesthetized with an intravenous bolus injection of 20 mg/kg of pentobarbital and subsequent continuous intravenous infusion of 1 ml/kg/hr of propofol. The dogs were intubated using a 6 Fr endotracheal tube and mechanically ventilated. On Days 1 and 2, the experimental SAH model was conducted to induce vasospasm by puncturing the cisterna magna with a 20-gauge needle and injecting autologous blood (0.5 ml/kg) after the removal of 0.3 ml/kg CSF (double hemorrhage SAH model). On Day 7, the animals were anesthetized and intubated as on Days 1 and 2. A 4 Fr double-lumen sheath catheter was placed in the femoral artery for cerebral angiography and blood gas sampling. End-tidal CO₂ was carefully monitored and the PaCO₂ was maintained between 35 mmHg and 45 mmHg.

The left vertebral artery was cannulated using a 4 Fr catheter under fluoroscopic control, and digital subtraction angiography was performed after injecting 2.5 ml iopamidol (Bayer AG, Leverkusen, Germany). Vertebral angiograms were obtained to measure the diameters of the vertebral artery and basilar artery, performed by radiological technicians unaware of the experimental protocols. The diameter of the basilar artery was measured at three points, the vertebro-basilar artery junction (lower point), basilar-superior cerebellar artery junction (upper point), and the midpoint between them. The mean value of the diameters at these three points was taken as the basilar artery diameter. The vertebral artery diameters were measured at both sides of the distal point of

the artery just proximal to the basilar artery, and the mean of the two diameters was taken as the vertebral artery diameter.

Immediately after the first angiography, the dogs were placed in the lateral position. Lumbar puncture was performed with a 17-gauge Tuohy needle. A microcatheter (Renegade™; Boston Scientific Corp., Natick, Massachusetts, USA) with a guide-wire (Transend™ EX; Boston Scientific Corp.) was introduced into the lumbar subarachnoid space under fluoroscopic observation, and the tip of the microcatheter was advanced and positioned in the cisterna magna. Three types of irrigation solution were prepared: commercially available artificial CSF solution with Mg²⁺ (2.2 mEq/l) (ARTCEREB, ACM), ARTCEREB without Mg²⁺ provided by Otsuka Pharmaceutical Co., Ltd. (ACR), and ARTCEREB with higher Mg²⁺ concentration (5 mEq/l) (ACMM). The compositions of these three artificial CSF solutions are listed in Table 1. The cisterna magna was punctured with a 20-gauge needle to obtain CSF samples for measurement of the CSF electrolyte concentrations. After CSF sampling, one of the three artificial CSF solutions was injected through the microcatheter as a bolus of 0.5 ml/kg and then infusion was continued at 5 ml/hr for 1 hour. The animals were divided into three groups (ACR group, ACM group, ACMM group) according to the artificial CSF solution, and each group contained five dogs.

After infusion was completed, vertebral angiography was repeated to measure the arterial diameters again, and CSF sampling was also repeated. The dogs were euthanized with overdose intravenous injection of pentobarbital. The CSF Na⁺, K⁺, Cl⁻, Ca²⁺, and Mg²⁺ ionized concentrations were measured with ion-selective electrodes (StatProfile CCX;

Table 1 Compositions of three kinds of artificial cerebro-spinal fluid

	ACR	ACM	ACMM
pH	≅7.3	≅7.3	≅7.3
Na ⁺ (mEq/l)	145	145	145
K ⁺ (mEq/l)	2.8	2.8	2.8
Cl ⁻ (mEq/l)	129	129	129
Ca ²⁺ (mEq/l)	2.3	2.3	2.3
Mg ²⁺ (mEq/l)	0	2.2	5.0
HCO ₃ ⁻ (mEq/l)	23.1	23.1	23.1
P (mEq/l)	1.1	1.1	1.1
Glucose (g/l)	0.61	0.61	0.61

ACM: artificial cerebro-spinal fluid solution with normal Mg²⁺ concentration (2.2 mEq/l), ACMM: artificial cerebro-spinal fluid solution with increased Mg²⁺ concentration (5 mEq/l), ACR: artificial cerebro-spinal fluid solution without Mg²⁺.

NOVA Biomedical, Waltham, Massachusetts, USA).

Data are presented as the means \pm SDs. The statistical significance of differences was analyzed with the paired t-test by using SPSS 7.5.1 J for Windows (SPSS Japan Inc., Tokyo). A p value < 0.05 was considered statistically significant.

Results

Table 2 shows the concentrations of arterial blood gases and CSF electrolytes before and after cisternal irrigation with the three types of artificial CSF solution. No changes in these data occurred except for the CSF Mg^{2+} concentration. In the ACR group, the Mg^{2+} concentration was 0.8 ± 0.07 mEq/l at 1 hour after irrigation, which was significantly ($p < 0.01$) decreased compared to 1.4 ± 0.03 mEq/l before the irrigation. In the ACM group, the Mg^{2+} concentration was 1.5 ± 0.08 mEq/l at 1 hour after irrigation, which was not significantly changed compared to 1.4 ± 0.10 mEq/l before irrigation.

Table 2 Arterial blood gas and CSF electrolytes before and after cisternal irrigation

	ACR	ACM	ACMM
Arterial blood gas			
pH			
before	7.37 ± 0.02	7.39 ± 0.01	7.36 ± 0.02
after	7.39 ± 0.03	7.37 ± 0.02	7.37 ± 0.02
pCO ₂			
before	37 ± 2	38 ± 2	39 ± 4
after	38 ± 3	39 ± 2	39 ± 2
pO ₂			
before	343 ± 43	379 ± 40	396 ± 23
after	384 ± 44	384 ± 35	376 ± 13
CSF electrolytes			
Na ⁺			
before	142 ± 2	143 ± 1	144 ± 1
after	139 ± 1	141 ± 1	140 ± 1
K ⁺			
before	2.7 ± 0.2	2.7 ± 0.1	2.7 ± 0.1
after	3.0 ± 0.2	2.9 ± 0.1	2.8 ± 0.1
Cl ⁻			
before	121 ± 4	123 ± 2	124 ± 1
after	121 ± 3	122 ± 2	125 ± 1
Ca ²⁺			
before	2.2 ± 0.1	2.1 ± 0.1	2.0 ± 0.1
after	2.2 ± 0.2	2.1 ± 0.1	2.0 ± 0.1
Mg ²⁺			
before	1.4 ± 0.03	1.4 ± 0.10	1.4 ± 0.05
after	$0.8 \pm 0.07^*$	1.5 ± 0.08	$2.4 \pm 0.15^*$

ACM: mock cerebrospinal fluid with normal magnesium concentration, ACMM: mock cerebrospinal fluid with higher magnesium concentration, ACR: mock cerebrospinal fluid without magnesium, CSF: cerebrospinal fluid. Data are means \pm standard deviation, * $p < 0.05$.

In the ACMM group, the Mg^{2+} concentration was 2.4 ± 0.15 mEq/l at 1 hour after irrigation, which was significantly ($p < 0.01$) increased compared to 1.4 ± 0.05 mEq/l before irrigation. In the ACMM group, the CSF Mg^{2+} significantly increased, but the vital signs (blood pressure, the heart rate, and the body temperature) were not significantly changed after irrigation (data were not shown).

Table 3 shows the arterial diameters of the basilar and vertebral arteries before and after cisternal irrigation with the three types of artificial CSF solution. In the ACR group, the diameters of the basilar artery and vertebral artery were 0.61 ± 0.18 mm and 0.57 ± 0.23 mm, respectively, at 1 hour after irrigation, which were significantly ($p < 0.05$) decreased compared to the diameters of 0.74 ± 0.22 mm and 0.68 ± 0.17 mm, respectively, before irrigation. Representative vertebral angiograms before and after cisternal irrigation with artificial CSF solution without Mg^{2+} are presented in Fig. 1. In the ACM group, the diameters of the basilar artery and vertebral artery were 0.75 ± 0.10 mm and 0.72 ± 0.19 mm, respectively, at 1 hour after irrigation, which were not significantly changed compared with the diameters of 0.73 ± 0.10 mm and 0.66 ± 0.11 mm, respectively, before irrigation. In the ACMM group, the diameters of the basilar artery and vertebral artery were 0.84 ± 0.19 mm and 0.90 ± 0.22 mm, respectively, at 1 hour after irrigation, which were significantly ($p < 0.05$) increased compared with the diameters of 0.71 ± 0.21 mm and 0.69 ± 0.24 mm, respectively, before irrigation. Representative vertebral angiograms before and after cisternal irrigation with artificial CSF solution containing higher Mg^{2+} concentration than that of the physiological state are presented in Fig. 2.

Table 3 Cerebral arterial diameters before and after cisternal irrigation

	ACR (n = 5)	ACM (n = 5)	ACMM (n = 5)
BA diameter (mm)			
before	0.74 ± 0.22	0.73 ± 0.10	0.71 ± 0.21
after	$0.61 \pm 0.18^*$	0.75 ± 0.10	$0.84 \pm 0.19^*$
VA diameter (mm)			
before	0.68 ± 0.17	0.66 ± 0.11	0.69 ± 0.24
after	$0.57 \pm 0.23^*$	0.72 ± 0.19	$0.90 \pm 0.22^*$

ACM: mock cerebrospinal fluid with normal magnesium concentration, ACMM: mock cerebrospinal fluid with higher magnesium concentration, ACR: mock cerebrospinal fluid without magnesium, BA: basilar artery, VA: vertebral artery. Data are means \pm standard deviation, * $p < 0.05$.

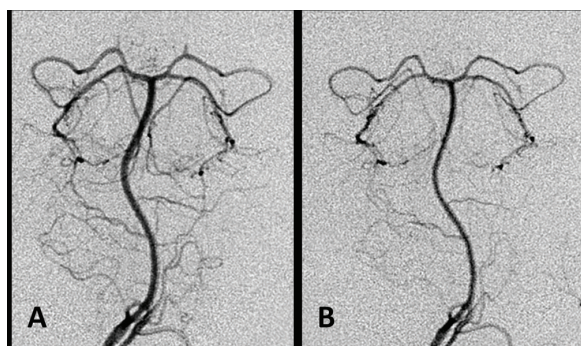


Fig. 1 Representative angiograms obtained before (A) and 1 hour after (B) cisternal irrigation with artificial cerebrospinal fluid (CSF) solution without Mg²⁺. Note the vasoconstriction after irrigation.

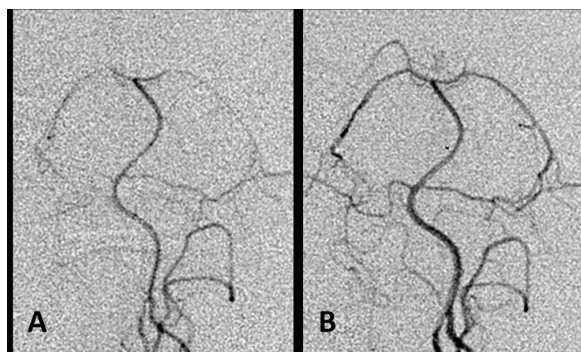


Fig. 2 Representative angiograms obtained before (A) and 1 hour after (B) cisternal irrigation with artificial cerebrospinal fluid (CSF) solution containing higher than physiological Mg²⁺ concentration (5 mEq/l). Note the vasodilation after irrigation.

Discussion

ARTCEREB solution is an artificial CSF with similar characteristics to physiological CSF.²⁾ The composition, pH, and concentrations of electrolytes including Mg²⁺ and glucose were determined based on the previously reported values for human physiological CSF.¹⁾ Generally, normal saline and lactated Ringer's solution have been used for irrigation and perfusion during neurosurgical procedures and post-operative continuous cisternal irrigation therapy to washout subarachnoid blood and prevent delayed vasospasm after SAH.^{4,5,12,14)} The main advantage of ARTCEREB solution is the physiological concentration of Mg²⁺ provided by neither normal saline nor lactated Ringer's solution. Cerebral irrigation with normal saline has been reported to cause adverse neurotoxicity effects such as neuronal cell death, seizure, high fever, and headache in both experimental animals and humans.^{3,13)} Moreover, irrigation by normal saline

and lactated Ringer's solution are known to cause worsening of brain edema surrounding the injured brain, whereas this adverse effect is less prominent using ARTCEREB.^{2,6)} Therefore, it is quite reasonable to irrigate and perfuse the brain by artificial CSF solution with the same composition of electrolytes and solutes as human CSF. However, the importance of appropriate Mg²⁺ concentration in the artificial CSF solution for the cerebral vasculature remains unclear.

The present study demonstrated that cisternal irrigation with artificial CSF without Mg²⁺ caused significant reduction in the diameters of spastic cerebral arteries after experimental SAH, artificial CSF with normal concentration of Mg²⁺ did not cause any change in the arterial diameter, and artificial CSF with increased concentration of Mg²⁺ caused vasodilation of the spastic cerebral arteries. Continuous cisternal irrigation therapy for washout of the blood clot in the subarachnoid space can prevent the vasospasm and subsequent delayed neurological deficits after aneurysmal SAH.^{4,5,12,14)} Such cisternal irrigation therapies use lactated Ringer's solution or normal saline as the vehicle for fibrinolytic agents such as urokinase and tissue typed plasminogen activator. The present findings suggest that use of irrigation solution without Mg²⁺ after SAH might potentially worsen vasospasm, and that artificial CSF solution with appropriate Mg²⁺ concentration would be better. Recently, investigation of the appropriate CSF Mg²⁺ concentration to dilate the spastic cerebral arteries in the experimental SAH models found that CSF Mg²⁺ concentration of more than 3 mEq/l caused dilation of all examined arterial diameters.¹⁰⁾ However, reanalysis of the same data using the χ^2 test showed that CSF Mg²⁺ concentration of more than 2.5 mEq/l significantly increased the spastic cerebral arterial diameter (data was not shown). The present study used artificial CSF solution with higher Mg²⁺ concentration (5 mEq/l) which resulted in CSF Mg²⁺ concentration of 2.4 ± 0.15 mEq/l after irrigation. Arterial diameter was slightly but significantly increased, and was well compatible with the previously reported data. CSF Mg²⁺ concentration of more than 2.5 mEq/l is supposed to be necessary for vasodilation therapy to treat and prevent vasospasm after SAH.

Adequate levels of Mg²⁺ in the irrigation solution during neurosurgical procedures are also important to maintain cerebral arterial and arteriolar diameters. Extracellular Mg²⁺ concentration controls the diameters of both cerebral arteries and the penetrating arterioles that act as resistance vessels to regulate CBF.^{11,15)} Mechanical spasm of cerebral blood vessels caused by direct touch, the spasmogenic property of irrigation fluid without Mg²⁺, and temporary

occlusion of the vasculature may all obstruct correct surgical manipulation of the blood vessels, and may cause CBF and metabolic disturbance.¹⁶⁾ Therefore, brain irrigation with artificial CSF solution with appropriate Mg²⁺ concentration is highly recommended in neurosurgical procedures. The use of commercially available artificial CSF (ARTCEREB) is the ideal solution for irrigation and perfusion of brain in routine neurosurgical practice.

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Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

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