Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: A randomized, placebo-controlled, clinical study*

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Objectives: To examine whether the maintenance of elevated magnesium serum concentrations by intravenous administration of magnesium sulfate can reduce the occurrence of cerebral ischemic events after aneurysmal subarachnoid hemorrhage.

Methods: Prospective, randomized, placebo-controlled study.

Setting: Neurosurgical intensive care unit of a University hospital.

Interventions: One hundred ten patients were randomized to receive intravenous magnesium sulfate or to serve as controls. Magnesium treatment was started with a bolus of 16 mmol, followed by continuous infusion of 8 mmol/hr. Serum concentrations were measured every 8 hrs, and infusion rates were adjusted to maintain target levels of 2.0–2.5 mmol/L. Intravenous administration was continued for 10 days or until signs of vasospasm had resolved. Thereafter, magnesium was administered orally and tapered over 12 days.

Measurements and Main Results: Delayed ischemic infarction (primary end point) was assessed by analyzing serial computed tomography scans. Transcranial Doppler sonography and digital subtraction angiography were used to detect vasospasm. Delayed ischemic neurologic deficit was determined by continuous detailed neurologic examinations; clinical outcome after 6 months was assessed using the Glasgow outcome scale. Good outcome was defined as Glasgow outcome scale score 4 and 5.

The incidence of delayed ischemic infarction was significantly lower in magnesium-treated patients (22% vs. 51%; \( p = .002 \)); 34 of 54 magnesium patients and 27 of 53 control patients reached good outcome (\( p = .209 \)). Delayed ischemic neurologic deficit was nonsignificantly reduced (9 of 54 vs. 15 of 53 patients; \( p = .149 \)) and transcranial Doppler-detected/angiographic vasospasm was significantly reduced in the magnesium group (36 of 54 vs. 45 of 53 patients; \( p = .028 \)). Fewer patients with signs of vasospasm had delayed cerebral infarction.

Conclusion: These data indicate that high-dose intravenous magnesium can reduce cerebral ischemic events after aneurysmal subarachnoid hemorrhage by attenuating vasospasm and increasing the ischemic tolerance during critical hypoperfusion.

Keywords: subarachnoid hemorrhage; magnesium; intravenous; delayed cerebral infarction; vasospasm

*See also p. 1382.

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DOI: 10.1097/CCM.0b013e3181d9da1e
improvement of outcome after aneurysmal subarachnoid hemorrhage (SAH) has been modest in the past decades. Recent studies still report a mortality of up to 50% (1, 2). Delayed cerebral ischemia attributable to cerebral vasospasm is the major cause of in-hospital morbidity and mortality (3). Its pathogenesis is still not fully understood. Attempts to prevent the occurrence of vasospasm and ischemic infarction have included hyperdynamic therapy to enhance cerebral blood flow, balloon angioplasty or chemical spasmolysis, and systemic administration of calcium antagonists.

Magnesium is a physiologic calcium antagonist with the potential to inhibit the pathophysiological processes of vasospasm and ischemic cell death. Under experimental conditions it prevents cellular calcium influx and excitatory amino acid release by the blockade of N-type and L-type calcium channels (4), prevents cellular calcium entry through N-methyl-D-aspartate receptor channels (5), reduces calcium-induced mitochondrial dysfunction (6), and preserves cellular energy metabolism (7). Magnesium has a vasodilatory effect and can enhance the deformability of red blood cells to improve cerebral perfusion in case of vascular narrowing.

Hypomagnesemia has been observed in 38% of SAH patients on hospital admission and correlated with the severity of SAH. Persistent hypomagnesemia during the first days after SAH predicted the occurrence of delayed cerebral ischemia (8). These data suggest that patients might profit from magnesium substitution.

Several studies have been published testing the efficacy of magnesium therapy after aneurysmal SAH (9–14). However, study designs, outcome parameters, co-medication, and dosing schedules varied markedly. The optimum dose is unknown because systematic dose-efficacy studies in SAH patients have not yet been performed. In an animal model of focal cerebral ischemia, the neuroprotective effect of intravenous magnesium was highest with serum levels of 2.0–2.5 mmol/L. Above 3 mmol/L, cardiodepressive effects limited neuroprotection (15). Because uptake, effects, and excretion in humans and mammals are similar, the present study was designed to investigate the benefit of continuously elevated serum magnesium concentrations to 2.0–2.5 mmol/L for patients with aneurysmal SAH.

### MATERIALS AND METHODS

The study was approved by the local ethics committee. Informed consent was obtained from the patient or a legal guardian. Inclusion criteria are depicted in Table 1.

### Standard Management

Patients were admitted to the intensive care unit and assessed by the Hunt/Hess and Glasgow Coma Scale. If intubated before admission, then the clinical state before intubation was used as documented. All patients were monitored with a central venous catheter, arterial line, and indwelling catheter. If Glasgow Coma Scale score was ≤8, patients were intubated to protect airways. External ventricular drainage was implanted if Glasgow Coma Scale score was ≤8 and computed tomography (CT) scans suggested elevated intracranial pressure, edema, or hydrocephalus. If external ventricular drainage placement was not possible, then an intracerebral probe was implanted for intracranial pressure measurement.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>Age older than 18 yrs</td>
<td>Serum creatinine &gt;1.5 mg/100 mL</td>
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<tr>
<td>Aneurysmal SAH</td>
<td>Atrialventricular block</td>
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<tr>
<td>Admission &lt;96 hrs after SAH</td>
<td>History of neuromuscular disease</td>
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<td></td>
<td>History of previous SAH</td>
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<td>Cancer</td>
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<td></td>
<td>Pregnancy</td>
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<tr>
<td></td>
<td>Treatment proposed to be continued elsewhere after aneurysm obliteration</td>
</tr>
<tr>
<td></td>
<td>Treatment discontinued at admission due to unpromising clinical condition</td>
</tr>
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</table>

SAH, subarachnoid hemorrhage.

Patients were excluded if electrocardiography on admission revealed an atrioventricular block of all grades (1–3) or were dependent on dialysis. If serum creatinine values were >1.5 mg/100 mL (133 μmol/L), then values were controlled 8 hrs later after fluid substitution with 1.5 L of Ringer’s solution. If serum creatinine had declined to <1.5 mmol/L, then the patient was included in the study.

Digital subtraction angiography and early aneurysm treatment were performed within 24 hrs whenever possible.

After aneurysm treatment, targets for hematocrit were 33% to 35%, targets for central venous pressure were 10–12 mm Hg, and targets for mean arterial blood pressure were 90–100 mm Hg to prevent episodes of hypotension. Targets were maintained using Ring-er’s solution, hydroxyethyl starch (6%), packed red cells, and catecholamines.

### Randomization

Randomization to one of the two treatment arms was performed in one block. A lot was drawn out of a box containing 55 enveloped lots for each treatment arm.

### Magnesium Dose

Patients in the magnesium group received a starting dose of 16 mmol magnesium sulfate over 30 mins (magnesium inresa 50%) followed by a continuous infusion of 8 mmol/hr. Serum electrolyte concentrations were measured 3 hrs after initiating the magnesium infusion and every 8 hrs thereafter (6:00 AM, 2:00 PM, and 10:00 PM). In patients with external ventricular drainage, cerebral spinal fluid concentrations were determined at 6:00 AM.

Infusion rates were adjusted to maintain serum concentrations of 2.0–2.5 mmol/L. Below 2.0 mmol/L, the infusion rate was increased by 1 mmol/hr; between 2.5–3.0 mmol/L, the infusion rate was reduced by 1 mmol/hr. Above 3.0 mmol/L, the infusion was paused and restarted at half the previous infusion rate if magnesium levels were within the target range 8 hrs later. Patients in the control group received an equal amount of normal saline. If the assessment of serum electrolytes on admission revealed hypomagnesemia, then it was not corrected by magnesium substitution in patients of the control group.

We analyzed records of our SAH patients of the previous 3 yrs and 83% of the patients who had delayed ischemic infarction experienced it within 10 days after admission. If infarction occurred later, then mean flow velocities in transcranial Doppler (TCD) sonography were >140 cm/sec in all patients. Therefore, we decided an intravenous magnesium administration for 10 days. Full intravenous administration was continued longer in patients with elevated flow velocities in TCD or whenever a detailed neurologic evaluation was possible and revealed clinical signs of vasospasm.

At day 11 or when clinical or Doppler sonographic signs of vasospasm had resolved, the infusion rate was reduced by half and oral administration of magnesium carbonate (90 mmol/day) was started to prevent a possible rebound effect. Patients who were able to drink received a tasteless solution of magnesium pow-
der (Loesniesium; Lilly Pharma, Bad Homburg, Germany) in 0.75 L of mineral water. To maintain patient blinding, control patients received an equal amount of mineral water. Intubated patients received the solution via nasogastric or percutaneous endoscopic gastrostomy tubes. Another 24 hrs later, intravenous treatment was stopped completely. Oral administration was continued and reduced by 15 mmol every other day.

**Data Acquisition and Outcome Parameters**

CT scans were obtained on days 3 or 4, on days 6 or 7, on days 9 or 10, before discharge and whenever otherwise necessary for diagnostic purposes. CT scans were analyzed by trained neuroradiologists (MP, LS) and a trained neurosurgeon (CS) not aware of the patients’ treatment allocation. Hypodensities were classified as: (1) preexisting; (2) exclusively resulting from intracerebral hematoma; (3) caused by operative procedures; or (4) delayed ischemic infarction defined as parenchymal hypodensity appearing between day 3 and the end of the observation period (16, 17). The latter was defined as the primary study end point (9, 16–18).

Neurologic examination was performed hourly by intensive care clinicians and findings documented in patients’ records. During ward rounds in the morning and evening and whenever the intensive care unit doctor reported delayed ischemic neurologic deficit (DIND), clinical findings were double-checked by the neurosurgeon on duty not aware of the patients’ treatment arm. DIND was defined as deterioration (new focal deficits or deteriorated level of consciousness) without other detectable reasons (rebleeding, seizure, electrolyte disturbance, and hydrocephalus). Delayed cerebral ischemia (DCI) was defined as symptomatic vasospasm or infarction on CT attributable to vasospasm (20).

TCD was performed daily by a trained medical technician blinded to the patients’ treatment allocation. Vasospasm was defined as mean flow velocity over 140 cm/sec in the anterior circulation and 90 cm/sec in the basilar artery.

The hyperdynamic therapy was intensified (mean arterial blood pressure, 110–125 mm Hg) by increasing the amount of pressor agents in awake patients in whom DIND developed and in comatose patients who presented sharp increases of flow velocities in TCD. Angiography was scheduled for awake patients when DIND remained refractory to hyperdynamic therapy. Comatose patients with increased flow velocities were transferred for angiography if they were cardiovasculary stable and showed controllable intracranial pressure values. Angiographic vasospasm was defined as narrowing of the arterial diameter of >30% with significant delay of circulation time. Balloon angioplasty or chemical vasospasmolysis was performed when possible. Angiographers were blinded to the patients’ treatment allocations. Clinical outcome, including the Glasgow outcome score was evaluated after 6 mos by a neurosurgeon blinded to the patients’ treatment arm.

**Data Analysis**

During the planning phase, data about magnesium treatment in SAH were scarce. Comparing data of an uncontrolled study by Boet et al (19), i.e., comparing 30% symptomatic vasospasm in magnesium-treated Fisher grade 3 patients to 60% in our own respective patients, a sample size of 87 patients was calculated to achieve sufficient test power (SigmaStat 2.01, Jandel Scientific, Erkrath, Germany). Considering a close relation between vasospasm and delayed infarction and a drop-out rate of 20%, we conceived a sample size of 110 patients. Outcome parameters were analyzed as a “per-protocol analysis.” GraphPad Prism 4 Statistical Software (GraphPad Software, San Diego, CA) was used. Parametric data were analyzed using an unpaired Student’s t test, nonparametric data by the Mann-Whitney U test, and incidences by a chi-square test. If multiple comparisons were indicated, then a Bonferroni correction was applied. Differences were considered significant at \( p < .05 \).

**RESULTS**

Two hundred one patients with SAH were admitted to our department between April 2003 and September 2006. Nineteen patients were not included because of admission later than 96 hrs after SAH. In 20 patients, therapy was discontinued after admission because of very poor clinical state and unpromising prognosis. In 32 patients, no aneurysm was detected, two had a history of SAH, and one was excluded because of leukemia. Ten patients were scheduled to return to the referring hospital after aneurysm treatment, four had atrioventricular block, one had neuromuscular disease, and one had renal failure. One patient was not included at his own request. The remaining 110 patients were randomized into one of the two treatment arms. Three patients were excluded after enrollment (Fig. 1). Data of the remaining 107 patients are presented in Table 2.
Physiologic Parameters

Magnesium serum levels in the first 10 days after admission are depicted in Figure 2. To maintain 2.0–2.5 mmol/L, daily administration of 140/11006 mmol magnesium sulfate was necessary. Apart from hypocalcemic tetany in one patient and facial flushing, no serious side effects were observed. Mean heart rate was lower under intravenous magnesium treat-

ment. The difference was significant on days 7 to 9. No episodes of profound hypotension or bradycardia were recorded (Fig. 3). After the infusion rate was halved, serum concentrations were 1.59 ± 0.22 in the magnesium group and 0.88 ± 0.07 in the control group. After intravenous administration had been stopped completely and only oral administration was continued, no patient showed an elevated serum concentration (0.89 ± 0.18 mmol/L in the magnesium group vs. 0.87 ± 0.07 in the control group). On admission, hypomagnesemia (<0.70 mmol/L) was found in six patients of each group. Although it was not corrected by magnesium substitution in patients of the control group, it normalized under measures of intensive care management. In no patient was hypomagnesemia found from day 2 after admission until the end of hospitalization. The course of magnesium serum concentrations in the first 10 days after admission is depicted in Figure 2. Mean calcium concentrations were significantly lower in magnesium-treated patients than in control patients (1.76 ± 0.21 vs. 2.06 ± 0.13 mmol/L) during intravenous treatment.

Delayed Ischemic Infarction and Clinical Outcome

Twelve patients (22%) in the magnesium group and 27 patients (51%) in the control group had delayed ischemic infarction (p = .0020; odds ration [OR], 0.28; 95% confidence interval [CI], 0.12–0.64). Data on delayed ischemic infarction and clinical outcome are summarized in Table 3.

DIND and DCI

Nine patients (17%) in the magnesium group and 15 patients (28%) in the control group had DIND (p = .1491; OR, 0.51; 95% CI, 0.20–1.29). Of nine patients in the magnesium group with DIND, one (11%) had delayed ischemic infarction. Of 15 patients in the control group with DIND, seven (47%) had delayed infarction (p = .0736; OR, 0.14; 95% CI, 0.014–1.45). The remaining 11 cases of delayed ischemic infarction in the magnesium group and 20 cases in the control group occurred in comatose patients.

Twenty patients (37%) in the magnesium group and 35 patients (66%) in the control group had DCI according to the definition of Frontera et al (20). This in-

Table 2. Patient data on computed tomography characteristics, neurologic state on admission, location of the aneurysm, and method of aneurysm treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Magnesium Group, n = 54</th>
<th>Control Group, n = 53</th>
<th>p</th>
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<tr>
<td>Age, yr†</td>
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<td>52 ± 13</td>
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</tr>
<tr>
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<td>33:21</td>
<td>33:20</td>
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<td>2</td>
<td>16</td>
<td>12</td>
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<tr>
<td>4</td>
<td>27</td>
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<td>Hunt/Hess grade</td>
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<td>12</td>
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</tr>
<tr>
<td>Coil</td>
<td>25</td>
<td>28</td>
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<tr>
<td>Conservative</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Location of aneurysm (anterior vs. poster circulation)</td>
<td>Anterior circulation, 44</td>
<td>Anterior circulation, 43</td>
<td>.9630</td>
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<tr>
<td></td>
<td>Posterior circulation, 10</td>
<td>Posterior circulation, 10</td>
<td></td>
</tr>
</tbody>
</table>

*aValues are expressed as mean ± sd.
Comparisons did not reveal significant differences.
includes patients who had delayed ischemic infarction and patients with DIND who did not have delayed ischemic infarction. \( (p/H11005.0027; \text{OR}, 0.30; 95\% \text{ CI, 0.1369 – 0.6684}). \)

**TCD-Detected and Angiographic Vasospasm**

Thirty-six patients (67\%) in the magnesium group and 45 patients (85\%) in the control group had TCD-detected/angiographic vasospasm \( (p/H11005.0279; \text{OR}, 0.36; 95\% \text{ CI, 0.14 – 0.91}). \) This includes 20 patients in the magnesium group and 22 patients in the control group not amenable to clinical evaluation because of a persistent Glasgow Coma Scale score of 3 with or without sedation.

Of 36 patients in the magnesium group with TCD-detected/angiographic vasospasm, 10 patients (28\%) had delayed ischemic infarction. Twenty-six of 45 patients (58\%) in the control group with TCD-detected/angiographic vasospasm had delayed ischemic infarction \( (p/H11005.0069; \text{OR}, 0.28; 95\% \text{ CI, 0.11– 0.72}). \) One patient in the magnesium group, analog-sedated because of elevated intracranial pressure, had left middle cerebral artery infarction on day 13 without elevated TCD readings. Territorial infarction was demarcated on CT. This case was registered as delayed ischemic infarction and magnesium infusion was not restarted.

**DISCUSSION**

The present data show beneficial effects of continuous high-dose intravenous magnesium administration for patients with aneurysmal SAH.

**Magnesium Dose and Serum Electrolytes**

In the present study, magnesium infusion was titrated to maintain elevated serum concentrations. In previous studies, in contrast, a preassigned daily amount of magnesium was administered. Target levels of 2.0–2.5 mmol/L proved to be safe. Although values of up to 3.5 mmol/L were observed after the initial loading dose, and although daily doses were higher than in previous studies, no complete cessation of magnesium treatment was necessary, as was reported by other authors (9–11, 14, 19, 21, 22). Because the dose required to maintain target levels varied markedly between the individual patients, and because bradycardia appeared to be the first sign of a magnesium overdose, a continuous cardiac monitoring and close surveillance of serum electrolytes are prerequisites of intravenous magnesium treatment. Patients with atrioventricular blocks were excluded from the present study. The negatively chronotropic and dromotropic effects of magnesium as a calcium antagonist might aggravate bradycardic arrhythmias or conduction disorders and, thus, its intravenous use might be dangerous.

We observed significant hypocalcemia with intravenous magnesium treatment. This was not treated because calcium antagonism most likely mediates beneficial effects of magnesium. Van de Water et al (23) found an inverse relation between magnesium and calcium concentrations during magnesium treatment in SAH patients and observed an increased frequency of DCI with more profound hypocalcemia. However, a more thorough analysis revealed that not hypocalcemia itself but rather higher levels of parathyroid hormone lead to a higher risk of DCI (24).
Antivasospastic Action and Neuroprotection

In previous trials, a lower rate of TCD-detected angiographic vasospasm and DIND (10, 14), improvement of outcome, and less delayed ischemic infarction were observed (11–13). Other studies, however, could not confirm these findings (10, 12). Magnesium might act as an antivasospastic and/or neuroprotective agent. We found a reduction of DIND that was not statistically significant. However, a large proportion of our patients were comatose and/or under analgesia. Therefore, the effect of magnesium on vasospasm-related clinical deterioration might be underestimated. The reduction of TCD-detected angiographic vasospasm was statistically significant. These findings suggest antivasospastic properties in accordance with other publications (9, 10, 12, 13). However, the results of the ‘Clazosentan to Overcome Neurological Ischaemia and Infarction Occurring after Subarachnoid Hemorrhage trial’ (CONSCIOUS-1) investigating the efficacy of Clazosentan (25) demonstrated that a significant reduction of cerebral vasospasm does not necessarily result in a distinct improvement of outcome because additional factors might be involved in the development of secondary ischemia and infarction.

However, we also observed that a lower percentage of patients with DIND and TCD-detected angiographic vasospasm had delayed ischemic infarction, suggesting an additional neuroprotective property. Despite these findings, we only registered a nonsignificant tendency toward improved neurologic outcome. One of the most decisive and predictive factors concerning outcome after aneurysmal SAH is the impact of the primary insult and the neurologic state on admission. Its effects cannot be treated by any specific form of therapy used to prevent secondary damage. Improvement of cardiopulmonary emergency measures in patients with poor-grade SAH and acceleration of diagnostic procedures are further key factors for the improvement of overall outcome after SAH (26).

Patient Characteristics and Trial Design

Single-center studies like the present one have significant limitations. Many procedures may be standardized. Still, each institution will have its own treatment and nursing standards. Patient characteristics also might not be representative of the whole population because of institutional and geographic differences. We recorded a high rate of intracerebral or intraventricular hematomas and larger numbers of patients in poor clinical condition than reported in previous trials and epidemiologic analyses (9, 11, 27, 28). This is probably attributable to the characteristics of the department as a tertiary care center with a large catchment area. Many patients are transferred from external departments for the evacuation of hematomas, ventriculostomy, or the treatment of complex aneurysms. Significant delay of diagnostics and treatment may occur causing a negative selection bias. Between the treatment arms, there was no marked difference concerning clinical state on admission and distribution of blood on CT scans allowing a comparison of groups and analysis of treatment effects. (Table 2).

Functional outcome after an adequate time span is the ideal end point for clinical studies but requires a large number of patients. In SAH trials, the incidence of DCI is frequently used as the primary end point because it correlates better with death and poor outcome than DIND or TCD-detected angiographic vasospasm (20). Definitions of DCI, however, are not unequivocal. Van den Bergh et al (11) defined it as “infarction on CT compatible with clinical features of DCI.” This does not well define secondary infarctions that occur in patients who are undergoing analog sedation or persistently comatose. Frontera et al (20) defined DCI as “symptomatic vasospasm or infarction on CT attributable to vasospasm.” However, this definition disregards the fact that not all patients presenting with symptomatic vasospasm will eventually have infarction (29). A large proportion of SAH patients admitted to our department cannot be assessed in detail through large parts of the treatment period. Therefore, delayed ischemic infarction on CT scans, a surrogate parameter, was chosen to be the primary end point.

Standard Therapy and Comedication

The use of calcium antagonists has been extensively studied in the past decades. A Cochrane review analyzed 20 trials investigating nimodipine treatment after SAH. Only one (30) showed a significant benefit of prophylactic oral treatment. Other studies found a trend toward better results but no significant improvement of outcome. Although the administration of oral nimodipine was basically recommended by the authors, they conclude that its prophylactic use is “not beyond any doubt” (31).

A high proportion of SAH patients are transferred from other hospitals under analgesia and mechanical ventilation and are not able to use oral nimodipine. We formerly administered nimodipine tablets but observed only incomplete uptake via gastric tubes. This became particularly obvious in the wake-up period of patients who had been undergoing analog sedation for several days because of elevated intracranial pressure or cardiopulmonary complications. This period frequently includes the time with the highest risk of hypotension and oxygenation complications. Therefore, the routine use of nimodipine was stopped and standard therapy was shifted toward a more aggressive hyperdynamic therapy in case of vasospasm and early re-angiography with the option of percutaneous transluminal angioplasty of spastic vessels.

Magnesium might be a useful adjunct or even alternative to nimodipine treatment. Pharmacologically, the two substances might interfere with each other at some point because both are calcium antagonists. If used together, then side effects like hypotension necessitating the discontinuation of magnesium treatment might occur at lower magnesium concentrations (18). Clinical trials investigating the combined use in SAH patients are underway (32, 33). Recent review articles discerned a tendency toward a lower incidence of DCI (31) and poor outcome (34), but no reduction of delayed ischemic infarction or mortality after SAH.

CONCLUSION

This study demonstrates a beneficial effect of intravenous magnesium to prevent secondary ischemic events after aneurysmal SAH. We observed a lower incidence of delayed cerebral vasospasm and, among patients who had vasospasm, a lower rate of delayed ischemic infarction or mortality after SAH.
REFERENCES


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