A randomised controlled trial of induced hypermagnesaemia following aneurysmal subarachnoid haemorrhage

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Clinically apparent cerebral arterial vasospasm is common following aneurysmal subarachnoid haemorrhage (SAH), and angiographic evidence of vasospasm may be evident in 70% of patients. The incidence of vasospasm peaks at 4–12 days and may cause cerebral ischaemia and neurological deficits. Clinical trials examining the effect of magnesium administration on the occurrence of vasospasm and functional outcomes have produced conflicting results. Magnesium is relatively cheap but can cause hypotension, hypocalcaemia and bradycardia. We conducted the Magnesium in Aneurysmal Subarachnoid Haemorrhage (MASH) trial to test the hypothesis that inducing hypermagnesaemia would reduce the incidence of cerebral arterial vasospasm detected by blinded review of digital subtraction angiograms.

Methods

Participants

Patients admitted to two tertiary hospitals (Royal North Shore Hospital and Royal Hobart Hospital) in Australia from 1 April 2005 who had a clinical history consistent with aneurysmal SAH occurring within the previous 72 hours and for whom aneurysmal SAH had been confirmed by cerebral computed tomography (CT) were eligible for the study. Patients were excluded if they were younger than 18 years, if they had a serum creatinine concentration that exceeded 200 μmol/L, if death was thought to be imminent within 72 hours, if they were known to have myasthenia gravis, if they were pregnant, or if cerebral vasospasm was present before inclusion in the study. The study was approved by the Northern Sydney Health Human Research Ethics Committee (protocol number 0405112M) and the Tasmanian Human Research Ethics Committee (protocol number H0008298). Written informed consent was obtained from each patient or a legal surrogate before commencing any study activity.

Randomisation and masking

Participants were randomly assigned by the clinicians treating them or by local research coordinators using variable block sizes to one of two target ranges for serum magnesium concentration: normal range (0.65–1.05 mmol/L) or high range (1.60–2.50 mmol/L). Randomisation was stratified by study site and aneurysm location.

Results

Of 162 patients, 81 were assigned to the normal range group and 81 to the high-range group; the primary outcome was available for 78 and 79 patients, respectively. The groups had similar baseline characteristics. Vasospasm occurred in 40 patients (50.6%) and 50 patients (64.1%) assigned to high-range and normal-range groups, respectively (adjusted OR, 0.51; 95% CI, 0.26–1.02; P = 0.06). At 90 days, neurological recovery between the groups was not significantly different (adjusted OR for worse outcome, 0.71; 95% CI, 0.39–1.32; P = 0.28). Patients in the high-range group were treated with more noradrenaline to support arterial blood pressure (79 [16–218] mg) v 59 [14–129] mg; P = 0.03) and had lower mean (SD) serum calcium concentration (1.9 [0.2] mmol/L v 2.1 [0.2] mmol/L, P < 0.001).

Conclusion

Patients assigned a higher serum magnesium concentration had a reduced incidence of vasospasm as seen by angiography, but the difference was not statistically significant. Clinically significant outcomes were not different between groups. A firm recommendation for induced hypermagnesaemia cannot be made from this study.

Trial registration number: ACTRN12605000058673.
fied by World Federation of Neurosurgical Societies grade of SAH (grade I–III v grade IV–V) and by hospital. Allocation was concealed by enclosing the code for treatment assignment in sealed opaque envelopes, but clinical staff in the intensive care unit were subsequently made aware of treatment assignment. Neurosurgical staff responsible for requesting non-routine cerebral angiography, the patients and the outcome assessors remained blind to the treatment assignments.

Procedures

Patients received an intravenous infusion of magnesium sulfate at a constant rate of 20 mL per hour; the concentration of magnesium in the infusion was adjusted to achieve the assigned serum magnesium concentration. The trial intervention was discontinued 12 days after the original haemorrhage or on discharge from the ICU if this occurred earlier; the intervention was also discontinued if death was thought to be imminent or if the focus of a patient’s management was changed to palliative care.

Patient care was directed by the same protocol for both groups. Wherever possible, ruptured aneurysms were secured by surgical or endovascular treatment within 48 hours and all patients received intravenous or oral nimodipine. Blood pressure was supported by noradrenaline infusion, aiming for a systolic blood pressure of 120–160 mmHg once the aneurysm was secure. Patients underwent cerebral angiography on Day 5, or earlier if they developed clinical signs suggestive of vasospasm. Clinically relevant vasospasm was treated with chemical or balloon angioplasty and angiography was repeated daily until vasospasm resolved.

The primary outcome measure was the incidence of cerebral arterial vasospasm diagnosed by digital subtraction angiography and adjusted for baseline characteristics. Cerebral arterial vasospasm was defined as nil (no change in calibre of any of the cerebral arteries compared with baseline), mild (<25% vessel narrowing), moderate (25%–50% vessel narrowing) or severe (>50% vessel narrowing). The presence and severity of vasospasm on angiography was determined by two neuroradiologists who were unaware of treatment assignments. Secondary outcome measures included neurological function assessed by Glasgow outcome score (GOS) and modified Rankin score (mRS) 90 days after randomisation, duration of vasospasm, proportion of patients receiving endovascular treatment for vasospasm, duration of mechanical ventilation, and duration of ICU and hospital stay. All functional outcomes were assessed by research assistants who were unaware of treatment assignments. Tertiary outcomes included total dose of noradrenaline received and serum calcium concentration.

Sample size and interim analysis

We planned to recruit 190 patients to provide 80% power to detect a 20 percentage point reduction in the incidence of vasospasm — from 60% to 40%. An independent data monitoring committee conducted an interim analysis after the first 90 patients had completed study follow-up.

Baseline assessment and data collection

At baseline, we collected demographic data and clinical characteristics, including the Acute Physiology and Chronic Health Evaluation (APACHE) II score (a severity of illness score on a scale of 0 to 71, with higher scores indicating more severe illness). The grade of SAH was assessed at

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**Figure 1. Flow of patients through the study**

- **386 patients eligible**
- **162 patients randomly assigned**
  - 81 assigned to high-range magnesium
  - 81 assigned to normal-range magnesium
- **224 patients excluded**
  - 187 met exclusion criteria
  - 30 consents refused or unavailable
  - 7 objections from treating physician

- Follow-up
  - Cerebral angiography in 78 patients
  - Discharge and Day 90 data in 81 patients
- Analysis by intention to treat

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* Exclusion criteria (number of patients): traumatic subarachnoid haemorrhage (31), death imminent (21), vasospasm on presentation (6), aged <18 years (2), presented >72 hours after symptom onset (73), returning to another hospital after intervention (19), perimesencephalic venous bleed (31), met criteria but not picked up in the screening process so were not randomised (4). † Unavailable refers to no next of kin being present or contactable in cases where the patient could not provide consent for themselves.
hospital presentation using the World Federation of Neurological Societies grading system. The location and size of the aneurysm detected by angiography and presence of hydrocephalus detected by CT were recorded. Other pre-morbid conditions recorded were diagnosed hypertension, history of smoking, previous SAH or other cerebrovascular accident, and prior use of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins).

From randomisation to ICU discharge, the first serum magnesium and calcium concentrations measured each day were recorded. Treatment with mechanical ventilation and noradrenaline was also recorded.

**Statistical analysis**

Statistical analysis was conducted according to a predefined statistical analysis plan and was by intention to

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**Table 1. Baseline characteristics of patients in the study**

<table>
<thead>
<tr>
<th></th>
<th>High-range magnesium (n=81)*</th>
<th>Normal-range magnesium (n=81)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29/81 (35.8%)</td>
<td>29/81 (35.8%)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n; mean (SD)</td>
<td>79; 55.8 (12.7)</td>
<td>81; 56.6 (14.4)</td>
</tr>
<tr>
<td><strong>Time from bleed to randomisation, hours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n; mean (SD)</td>
<td>81; 46.9 (17.9)</td>
<td>81; 44.5 (17.7)</td>
</tr>
<tr>
<td><strong>Location before hospital admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>17/81 (21.0%)</td>
<td>16/81 (19.8%)</td>
</tr>
<tr>
<td>Other hospital</td>
<td>64/81 (79.0%)</td>
<td>65/81 (80.2%)</td>
</tr>
<tr>
<td><strong>History of hypertension</strong></td>
<td></td>
<td></td>
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<tr>
<td>n; mean (SD)</td>
<td>30/81 (37.0%)</td>
<td>30/81 (37.0%)</td>
</tr>
<tr>
<td><strong>History of smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n; mean (SD)</td>
<td>34/81 (42.0%)</td>
<td>25/81 (30.9%)</td>
</tr>
<tr>
<td><strong>History of subarachnoid haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n; mean (SD)</td>
<td>2/81 (2.5%)</td>
<td>1/81 (1.2%)</td>
</tr>
<tr>
<td><strong>History of cerebrovascular accident</strong></td>
<td></td>
<td></td>
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<tr>
<td>n; mean (SD)</td>
<td>3/81 (3.7%)</td>
<td>4/81 (4.9%)</td>
</tr>
<tr>
<td><strong>History of statin use</strong></td>
<td></td>
<td></td>
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<tr>
<td>n; mean (SD)</td>
<td>13/81 (16.0%)</td>
<td>19/81 (23.5%)</td>
</tr>
<tr>
<td><strong>Aneurysm location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown†</td>
<td>6/81 (7.4%)</td>
<td>13/81 (16.0%)</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>63/81 (77.8%)</td>
<td>53/81 (65.4%)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>12/81 (14.8%)</td>
<td>15/81 (18.5%)</td>
</tr>
<tr>
<td><strong>Aneurysm size‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small &lt; 5mm</td>
<td>16/59 (27.1%)</td>
<td>17/50 (34.0%)</td>
</tr>
<tr>
<td>Medium 5–10 mm</td>
<td>30/59 (50.8%)</td>
<td>29/50 (58.0%)</td>
</tr>
<tr>
<td>Large &gt; 10 mm</td>
<td>13/59 (22.0%)</td>
<td>4/50 (8.0%)</td>
</tr>
<tr>
<td><strong>GCS on admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n; mean (SD)</td>
<td>81; 12.3 (4.2)</td>
<td>81; 12.4 (3.8)</td>
</tr>
<tr>
<td><strong>WFNS grade</strong></td>
<td></td>
<td></td>
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<tr>
<td>GCS 15; motor deficit absent except cranial nerve palsy</td>
<td>39/81 (48.1%)</td>
<td>34/81 (42.0%)</td>
</tr>
<tr>
<td>GCS 13–14; motor deficit absent</td>
<td>19/81 (23.5%)</td>
<td>23/81 (28.4%)</td>
</tr>
<tr>
<td>GCS 13–14; motor deficit present</td>
<td>2/81 (2.5%)</td>
<td>3/81 (3.7%)</td>
</tr>
<tr>
<td>GCS 7–12; motor deficit present or absent</td>
<td>9/81 (11.1%)</td>
<td>11/81 (13.6%)</td>
</tr>
<tr>
<td>GCS 3–6; motor deficit present or absent</td>
<td>12/81 (14.8%)</td>
<td>10/81 (12.3%)</td>
</tr>
<tr>
<td>Hydrocephalus present</td>
<td>35/78 (44.9%)</td>
<td>47/81 (58.0%)</td>
</tr>
<tr>
<td>APACHE II score§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n; mean (SD)</td>
<td>81; 14.2 (7.1)</td>
<td>80; 13.4 (6.2)</td>
</tr>
</tbody>
</table>

GCS = Glasgow coma score. WFNS = World Federation of Neurological Societies. APACHE = Acute Physiology and Chronic Health Evaluation. * Data are number/denominator (percentage) unless otherwise indicated. † Aneurysm not seen in six and 13 patients in the high-range and normal-range groups, respectively. ‡ Aneurysm size not recorded in 16 and 18 patients in the high-range and normal-range groups, respectively.
The primary outcome was vasospasm severity analysed as a binary outcome (nil v any), with a sensitivity analysis using all four categories (nil, mild, moderate or severe). Secondary categorical outcomes included the GOS and mRS at 90 days after randomisation. Secondary continuous outcomes included duration of ICU and hospital stay, duration of mechanical ventilation and duration of vasospasm.

The primary analysis comparing vasospasm as a binary outcome was conducted using the Pearson $\chi^2$ test. Analyses using the four categories of vasospasm severity as well as categorical analyses of the GOS and mRS used ordinal
logistic regression after confirming the validity of the proportional odds assumption. Secondary continuous outcomes were analysed using analysis of variance (t test). All primary and secondary outcomes were analysed with and without adjustment for baseline grade of SAH and age, sex and smoking history. For binary outcomes, adjusted analyses were conducted using logistic regression.

Results

For logistic reasons, we determined in January 2009 that recruitment of patients would cease on 31 December 2009. Between 1 April 2005 and 31 December 2009, 162 participants were recruited; 81 were assigned to normal-range magnesium and 81 to high-range magnesium. Consent to continue the trial intervention was withdrawn by one patient in the normal-range group but consent for data use was granted; thus baseline data were available for all patients. One hundred and fifty-seven of 162 patients (96.9%) had cerebral angiography on Day 5. Reasons for not undertaking angiography included death and previous radiological contrast reaction. At completion of the trial, vital status 90 days after randomisation (ie, GOS and mRS) was unavaiable for two patients, both of whom were in the normal-range group. The flow of patients through the study is shown in Figure 1, and the baseline characteristics of the two patient groups, which were similar, are summarised in Table 1.

Study treatment was discontinued before Day 10 for 11 patients in the normal-range group (13.5%) and in 15 patients in the high-range group (18.5%). Reasons for discontinuation of study treatment are given in Table 2. One patient allocated to the normal-range group inadvertently received high-dose magnesium for several days. Serum magnesium concentrations of patients in the study are shown by day and group in Figure 2. The mean (SD) serum magnesium concentration was 1.70 (0.2) mmol/L in the high-range group and 0.87 (0.1) mmol/L in the normal-range group (P<0.001) (Table 3).

Primary outcome — incidence and severity of vasospasm

Vasospasm occurred in 40 of 79 patients (50.6%) assigned to high-range magnesium and 50 of 78 patients (64.1%) assigned to normal-range magnesium (odds ratio [OR], 0.57; 95% CI, 0.30–1.09; P = 0.09); the result was similar after adjusting for baseline characteristics (OR, 0.51; 95% CI, 0.26–1.02; P = 0.06). The mean (SD) duration of vasospasm was 5.2 (7.0) days and 3.4 (3.2) days in the high-range and normal-range groups, respectively (P = 0.2) (Table 3). The severity of vasospasm did not differ significantly between groups (OR, 0.63; 95% CI, 0.35–1.12; P = 0.12), even after adjusting for baseline characteristics (P = 0.12).

Secondary outcomes

GOS and mRS values were similar in the two groups at hospital discharge (P = 0.12 and P = 0.14, respectively), and at 90 days (P = 0.32 and 0.38, respectively) (Table 3, Figure 3). After adjustment for baseline characteristics, GOS and mRS values for the two groups at 90 days were similar (OR
for GOS, 0.71 [95% CI, 0.39–1.32; \( P = 0.28 \)] v OR for mRS, 0.79 [95% CI, 0.44–1.40; \( P = 0.41 \)].

The duration of mechanical ventilation, duration of ICU stay and duration of hospital stay did not differ significantly between the groups (Table 3). Nineteen of 78 patients (24.4%) in the high-range group and 26 of 76 patients (34.2%) in the normal-range group underwent endovascular treatment of vasospasm (adjusted OR, 0.54; 95% CI, 0.24–1.19; \( P = 0.13 \)) (Table 3).

Tertiary outcomes

The median (IQR) amount of noradrenaline administered was significantly higher in the high-range group (79 [16–218] v 59 [14–129] mg; \( P = 0.03 \)). The mean (SD) serum calcium concentration was lower in the high-range group (1.9 [0.2] v 2.1 [0.2] mmol/L; \( P < 0.001 \)).

Discussion

We found that inducing a higher serum magnesium concentration in patients with aneurysmal SAH reduced the risk of vasospasm, but the difference was not statistically significant. In addition, more patients in the high-range group had favourable neurological function at 90 days, but again this difference was not statistically significant. The amount of noradrenaline required to support blood pressure was significantly higher in the high-range magnesium group.

In conducting our trial, we sought to ensure a high degree of internal and external validity by concealing treatment allocation before randomisation, evaluating a number of clinically important outcomes and achieving near complete follow-up. Ascertainment of the primary and clinical outcomes was performed by blinded assessors. The primary outcome was diagnosis of vasospasm by digital subtraction angiography, which is the gold standard for assessment of cerebral arterial vasospasm and has a strong association with the development of clinically significant cerebral infarction.\(^{13}\) The management of serum magnesium concentration was standardised — a high proportion of patients received their assigned treatment, and magnesium concentration differed significantly between the groups. Limitations of our trial include the relatively small sample size, having to terminate recruitment at 85% of the planned sample size and the inability to blind treating nursing staff and study personnel to treatment allocation. In addition, we did not record the participants’ arterial blood pressure during the trial and although the same blood pressure management protocol was applied to the two groups it is possible that the results were influenced by a difference in arterial blood pressure between the groups.

The role of magnesium in the management of aneurysmal SAH remains unclear. Recent guidelines recommend against inducing hypermagnesaemia, pending the conclusion of further randomised controlled trials.\(^{14}\) The results we report here are one such trial. Interpretation of the current evidence base is hampered by inconsistent trial methodology, with trials using different regimens for the administration of magnesium and assessing different end points.\(^{15}\) A number of trials have examined the effect of targeting a predetermined plasma magnesium concentration with a variable-dose intravenous infusion.\(^{5,6}\) Other trials have used fixed-dose magnesium without targeting a particular serum magnesium concentration.\(^{6,9-11}\) This approach may allow considerable overlap in magnesium concentration between the treated and control groups. We hypothesised that if magnesium is an effective treatment, the beneficial effect would come from inducing and maintaining a set level of hypermagnesaemia, and we therefore targeted a specific magnesium concentration in each group. Our results demonstrate good separation of the magnesium concentration between groups. All our patients were treated in an ICU with invasive vascular monitoring and a protocol that sought to support arterial blood pressure and to induce moderate hypertension if cerebral arterial vasospasm was detected. The potential of magnesium to cause hypotension is evident from the increased dose of noradrenaline administered to our patients assigned to the higher magnesium concentration. In addition, inducing hypermagnesaemia may lower serum calcium concentration and this is confirmed by our results. In clinical practice, we have elected to allow hypocalcaemia unless we observe adverse effects that are attributable to hypocalcaemia or made worse by hypocalcaemia. The effect of magnesium administration on systemic arterial pressure and serum calcium concentration has been inconsistently reported in previous trials and, as both may be important modifiers of the effect of magnesium on recovery following SAH, this adds to the difficulty of interpreting the different trial results.

Previous trials have reported a wide variety of outcome measures. Most trials report a measure of functional recovery at 3 or 6 months.\(^{4,8,11-13}\) Methods for diagnosing cerebral arterial vasospasm have included transcranial Doppler ultrasound,\(^{9,16}\) CT angiography and digital subtraction angiography.\(^{16,17}\) Previous trials have used inconsistent definitions for delayed cerebral ischaemia and infarction — CT has been used in some trials\(^{7,9}\) and clinical assessment has been used in others.\(^{9}\)

Our data confirm the conclusion of earlier trials that the administration of magnesium to induce moderate hypermagnesaemia is safe in patients with aneurysmal SAH. Our data further suggest but cannot confirm that the administration of magnesium to induce moderate hypermagnesaemia may be beneficial in patients with aneurysmal SAH; these results may only apply if patients are closely monitored, blood pressure is carefully maintained and moderate...
hypocalcaemia is tolerated. Our patients were treated in specialist centres where endovascular treatment of established vasospasm is practised routinely; our findings may not apply in centres where such treatment is not available.

The effect of magnesium administration on clinically important outcomes such as mortality and degree of neurological recovery following aneurysmal SAH requires further study in large high-quality randomised controlled trials. Future trial protocols should standardise the management of arterial blood pressure, serum calcium concentrations and the management of vasospasm, recognising the potential for such concomitant treatments to modify the effect of hypermagnesaemia on clinically important outcomes. These variables should also be reported in detail so that the external validity of trial results can be assessed. Until such trials are conducted and reported, it may be premature to make firm recommendations for or against induced hypermagnesaemia in this setting.

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Statistical analysis: Severine Bompoint, Jayanthi Mysore and Laurent Billot (George Institute for Global Health, University of Sydney).

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Competing interests

None declared.

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References


