Plasma Magnesium Concentrations and Clinical Outcomes in Aneurysmal Subarachnoid Hemorrhage Patients

Post Hoc Analysis of Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage Trial

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Background and Purpose—Conflicting data have been obtained on optimal plasma magnesium concentrations for clinical outcomes in patients with aneurysmal subarachnoid hemorrhage.

Methods—Adults (aged 18 years or older) who had acute aneurysmal subarachnoid hemorrhage diagnosed were randomly assigned to receive either an intravenous MgSO4 infusion (80 mmol in 500 mL normal saline per day) or a placebo (500 mL normal saline per day) for up to 14 days. Post hoc multivariable binary logistic regression analyses were performed by dividing mean plasma magnesium concentrations into 4 quartiles according to treatment group and then comparing with the lowest quartiles.

Results—The worst clinical outcomes at 6 months were seen in MgSO4 group patients, with mean plasma magnesium concentrations in the fourth quartile, and in placebo group patients, with mean such concentrations in the third and fourth quartiles.

Conclusions—No evidence was found to suggest that a higher mean plasma magnesium concentration improves clinical outcomes. On the contrary, we found an association between high plasma magnesium concentration and worse clinical outcomes. (Stroke. 2010;41:1841-1844.)

Key Words: aneurysm ■ clinical vasospasm ■ delayed ischemic neurological deficit ■ magnesium ■ subarachnoid hemorrhage

Pilot clinical trials using magnesium sulfate in patients with acute aneurysmal subarachnoid hemorrhage have reported trends toward reduction in delayed cerebral ischemia and improvement in clinical outcomes.1–5 The recently completed Asian-Australasian Intravenous Magnesium Sulfate for Aneurysmal Subarachnoid Hemorrhage (IMASH) trial, a randomized, double-blinded, placebo-controlled, multicenter, phase III trial, however, did not demonstrate improvement in clinical outcomes with magnesium sulfate infusion.6 A Dutch multicenter, randomized, clinical trial, the Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH II) phase III clinical trial, is ongoing.7

Post hoc analysis of the Dutch pilot study data (MgSO4, 64 mmol/day) suggests that mean plasma magnesium concentrations of >1.61 mmol/L (fourth quartile) may have a negative effect on clinical outcomes.8 To further explore these conflicting results, we investigated the IMASH data to assess the relationships between plasma magnesium levels and clinical outcomes in patients with aneurysmal subarachnoid hemorrhage, with or without hypermagnesemic treatment.

Subjects and Methods

Under the IMASH protocol,6 adults (aged 18 years or older) who had acute aneurysmal subarachnoid hemorrhage diagnosed were randomly assigned to receive either an intravenous MgSO4 infusion (80 mmol in 500 mL normal saline per day) or a placebo infusion (500 mL normal saline per day) for up to 14 days. The exclusion criteria were significant renal impairment (plasma creatinine concentration >200 μmol/L) or preexisting neurological disability. The dosage was adjusted to target a plasma magnesium concentration of twice the baseline value and between 2.0 and 2.5 mmol/L. Patients were also administered oral nimodipine. The decision to clip or coil was at the discretion of the local neurosurgical team.

Outcomes were assessed by a research assistant or investigator who was blinded to the treatment allocation. The Extended Glasgow
Table 1. Patient Profiles and Clinical Outcomes in the Magnesium Sulphate Infusion and Placebo (Saline) Groups

<table>
<thead>
<tr>
<th></th>
<th>MgSO4 Group (n=169)</th>
<th>Saline Group (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>57.0 (12.5)</td>
<td>57.0 (12.5)</td>
</tr>
<tr>
<td>Male</td>
<td>61 (36)</td>
<td>58 (37)</td>
</tr>
<tr>
<td>Baseline plasma Mg conc.</td>
<td>0.79 (0.10)</td>
<td>0.80 (0.11)</td>
</tr>
<tr>
<td>Admission WFNS</td>
<td>4–5</td>
<td>56 (35)</td>
</tr>
<tr>
<td></td>
<td>1–3</td>
<td>107 (63)</td>
</tr>
<tr>
<td>Fisher CT grade</td>
<td>3–4</td>
<td>160 (95)</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>33 (20)</td>
<td>36 (23)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>73 (43)</td>
<td>71 (45)</td>
</tr>
<tr>
<td>GOSE</td>
<td>5–8</td>
<td>108 (64)</td>
</tr>
<tr>
<td></td>
<td>1–4</td>
<td>61 (36)</td>
</tr>
<tr>
<td>mRS</td>
<td>0–2</td>
<td>97 (57)</td>
</tr>
<tr>
<td></td>
<td>3–6</td>
<td>72 (43)</td>
</tr>
<tr>
<td>BI &gt;85</td>
<td>97 (57)</td>
<td>96 (61)</td>
</tr>
</tbody>
</table>

Data are in numbers (%), unless otherwise indicated. BI indicates Barthel Index; GOSE, Glasgow Outcome Scale Extended; mRS, modified Rankin Scale; WFNS, World Federation of Neurological Surgeons.

Outcome Scale (primary outcome at 6 months) was stratified into favorable (scores of 5–8) or unfavorable (scores ≤4) outcomes. The modified Rankin Scale (secondary outcome at 6 months) was similarly stratified into good (0–2) vs poor (3–6) and excellent (0–1) vs nonexcellent (2–6), as predefined in the protocol. The Barthel Index was stratified into scores of ≥85 (independent activity of daily living) or <85 (dependent activity of daily living).

Delayed ischemic neurological deficit was defined clinically as a new focal neurological deficit (motor or speech deficit) that had developed after subarachnoid hemorrhage, a decrease on the Glasgow Coma Scale of ≥2 points lasting ≥6 hours, or a new cerebral infarction not related to treatment (coiling or clipping) complications, rebleed, progressive hydrocephalus, electrolyte or metabolic disturbance, or infection. Hypertensive therapy, intra-arterial vasodilator treatment, or balloon angioplasty were applied only in patients with delayed ischemic neurological deficit.

Statistical Analysis
Statistical analyses were performed using SPSS for Windows Version 15.0 (SPSS). Statistical significance was set at \( P<0.05 \). Mean plasma magnesium concentrations were calculated for each patient over the entire period of study drug infusion. Crude estimates comparing mean plasma magnesium concentrations were performed using Mann-Whitney \( U \) tests. Multivariable binary logistic regression analysis was performed by dividing the mean plasma magnesium concentrations into 4 quartiles according to treatment group, using the lowest quartiles as the reference.

Results
The IMASH patient profiles are presented in Table 1. Three hundred twenty-seven patients in the 10 participating hospitals (Appendix) were enrolled between August 2004 and December 2008. Time from ictus to the start of study drug infusion was 31.7±15.5 hours. Mean serum magnesium concentrations were significantly higher in the MgSO4 group than in the saline group (1.67±0.27 mmol/L vs 0.91±0.16 mmol/L, respectively; \( P<0.001 \)).

Crude estimates of the mean plasma magnesium concentrations are presented in Table 2, from which it can be seen that in the MgSO4 group, patients with worse clinical outcome (Extended Glasgow Outcome Scale scores of 1–4, modified Rankin Scale scores of 3–6 or 2–6, or a Barthel Index <85) had higher mean plasma magnesium concentrations, whereas in the saline group, those with unfavorable outcome (Extended Glasgow Outcome Scale score 1–4) and delayed ischemic neurological deficit had higher mean plasma magnesium concentrations.

The results of the multivariable analyses of mean plasma magnesium concentrations by quartile are presented in Table 3. It can be seen that in the saline group, mean plasma concentrations >0.89 mmol/L were associated with worse clinical outcome (Extended Glasgow Outcome Scale score 1–4, modified Rankin Scale score 3–6 and 2–6, and a Barthel Index <85). Similarly, mean plasma concentrations >1.82 mmol/L were associated with worse clinical outcome (Extended Glasgow Outcome Scale score 1–4 and modified Rankin Scale score 3–6) in the MgSO4 group.

Discussion
This study found patients with worse clinical outcomes to also have high mean plasma magnesium concentrations. Data

Table 2. Mean Plasma Magnesium Concentrations and Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>MgSO4 Group</th>
<th>Placebo Saline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow Outcome Scale Extended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable (5–8) vs unfavorable (1–4)</td>
<td>1.62 (0.24) vs 1.77 (0.31)</td>
<td>0.90 (0.13) vs 0.93 (0.20)</td>
</tr>
<tr>
<td>Modified Rankin Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent (0–1) vs nonexcellent (2–6)</td>
<td>1.63 (0.24) vs 1.74 (0.30)</td>
<td>0.89 (0.13) vs 0.93 (0.20)</td>
</tr>
<tr>
<td>Good (0–2) vs poor (3–6)</td>
<td>1.62 (0.20) vs 1.72 (0.31)</td>
<td>0.89 (0.10) vs 0.92 (0.19)</td>
</tr>
<tr>
<td>Barthel Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent (&lt;85) vs independent (≥85)</td>
<td>1.63 (0.23) vs 1.73 (0.31)</td>
<td>0.89 (0.12) vs 0.92 (0.20)</td>
</tr>
<tr>
<td>Delayed ischemic neurological deficit</td>
<td>1.62 (0.28) vs 1.69 (0.27)</td>
<td>0.87 (0.13) vs 0.92 (0.16)</td>
</tr>
</tbody>
</table>

\*\( P<0.05 \), Mann-Whitney \( U \) tests.
on acute ischemic stroke suggest that acidosis may be linked to an increase in free magnesium because of the preferential binding of hydrogen ions to ATP and, hence, displacement of bound magnesium to free magnesium. Whether the same pathophysiology happened in aneurysmal subarachnoid hemorrhage patients remains to be explored.

According to the data of a previous study, 38% of aneurysmal subarachnoid hemorrhage patients had hypomagnesemia on admission, although it usually returned to within normal limits the next day and did not contribute to the outcome predictions in the multivariable model (OR, 1.3; 95% CI, 0.6–3.0). It is speculated that it may be related to transient intracellular shift and, hence, to a decrease in serum magnesium. Overall, hypomagnesemia on admission can be viewed as a normal bodily response to ischemia and thus has no prognostic significance.

A limitation in the current study is that no ionized serum magnesium concentrations were incorporated as routine in the protocol. To evaluate the effectiveness of treatment for aneurysmal subarachnoid hemorrhage more precisely, a future study should consider using composite outcome measures that include quality of life or cognition.

Conclusion
No evidence was found to suggest that a higher mean plasma magnesium concentration improves clinical outcomes. On the contrary, we found patients with worse clinical outcomes to have higher mean concentrations.

Appendix
IMASH investigators and participating hospitals
Steering Committee (CUHK, Hong Kong, China): W.S. Poon, G.K.C. Wong, R. Boet, J.M.K. Lam, X.L. Zhu, M.T.V. Chan, T. Gin Data Monitoring and Safety Committee: John Pickard (Cambridge, UK), Benny C.Y. Zee (Hong Kong, China) Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China (189 patients): G.K.C. Wong, R. Boet, W.S. Poon Pamela Youde Nethersole Eastern Hospital, Hong Kong China (34 patients): C.K. Wong, M.W.Y. Lee Hospital Universiti Sains Malaysia, Kubang Kerian, Malaysia (32 patients): J.M. Abdullah, R. Ghani Austin Health, Melbourne, Australia (17 patients): D. Cowie, S. Poultie Second Affiliated Hospital of Guangzhou Medical College, Guangzhou, China (15 patients): M.C. Li Alfred Hospital, Melbourne, Australia (14 patients): P.S. Myles, S. Wallace Tuen Mun Hospital, Hong Kong, China (12 patients): D.T.S. Fong, S.C. Yuen First Affiliated Hospital of Sun Yat Sen University, Guangzhou, China (10 patients): Z.S. Huang, Y.M. Sun Beijing Tiantan Hospital, Capital Medical University, Beijing, China (2 patients): J.Z. Zhao Kwong Wah Hospital, Hong Kong, China (2 patients): J.C.K. Kwok, K.Y. Chan

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Disclosures

None.

References


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