The effect of intravenous magnesium sulfate infusion on serum levels of sodium and potassium in patients with aneurysmal subarachnoid hemorrhage

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Abstract: Abnormal serum sodium levels are frequently observed among patients with aneurysmal subarachnoid hemorrhage (SAH) and may worsen cerebral edema or mass effect. Low serum potassium levels (hypokalemia) are also common among patients with aneurysmal SAH and are associated with prolonged QT interval and ventricular arrhythmia. Recent meta-analysis suggests that MgSO₄ infusion improves the clinical outcome in patients after aneurysmal SAH; however, MgSO₄ infusion may theoretically exacerbate electrolyte disturbance. We retrospectively reviewed the prospectively collected demographic and laboratory data of 100 patients after aneurysmal subarachnoid hemorrhage in a neurosurgical center in Hong Kong. Fifty patients had daily magnesium sulfate infusion for 14 days (Group 1) and 49 patients were managed similarly, without magnesium sulfate infusion (Group 2). Days of hypernatremia (mean±SD) were 2.0±2.7 for group 1 and 2.0±2.5 for group 2, p = 0.999; days of hyponatremia (mean±SD) were 2.7±3.1 for group 1 and 2.0±2.9 for group 2, p = 0.230; days of hypokalemia (mean±SD) were 4.5±3.1 for group 1 and 4.5±3.2 for group 2, p = 0.819. Hyperkalemia was uncommon in both groups. There was also no statistically significant difference between the two groups when the data were re-analyzed as severe hyponatremia, severe hypokalemia and severe hyperkalemia. Magnesium sulfate infusion was safe and did not seem to exacerbate the duration of electrolyte disturbance associated with aneurysmal subarachnoid hemorrhage.

Key words: subarachnoid hemorrhage, intracranial aneurysm, magnesium, sodium, potassium

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Abbreviations: SAH: subarachnoid hemorrhage, MgSO₄: magnesium sulfate, NMDA: N-methyl-D-aspartate, IMASH: intravenous magnesium sulfate in aneurysmal subarachnoid hemorrhage
Electrolyte disturbances such as hyponatremia, hypernatremia and hypokalemia are frequently observed during the first two weeks following aneurysmal SAH [1-6] and could be associated with poor outcome [7-10].

Delayed ischemic neurological deficit or clinical vasospasm remains a major cause of delayed neurological morbidity and mortality for patients with aneurysmal subarachnoid hemorrhage. Magnesium is a cerebral vasodilator [11-13] and voltage-dependent calcium channel blocker [14, 15]. Furthermore, its antagonistic action on NMDA receptors in the brain attenuates glutamate stimulation and decreases calcium influx during ischemic injury [14-18]. Though results in animal models on cerebral ischemia had been conflicting [19], initial experimental results in humans demonstrated its safety and effectiveness as compared to historical data [20-24].

MgSO\textsubscript{4} infusion is associated with disturbance in renal electrolyte excretion and may theoretically exacerbate electrolyte disturbance caused by aneurysmal SAH. We aimed to investigate the possible relationship between MgSO\textsubscript{4} infusion and electrolyte disturbance among patients with aneurysmal SAH.

**Patients and methods**

We retrospectively reviewed the prospectively collected clinical and laboratory data of 100 IMASH-recruited patients after aneurysmal SAH in a regional neurosurgical center in Hong Kong. Intravenous Magnesium Sulfate After Aneurysmal Subarachnoid hemorrhage (IMASH) trial is an ongoing multi-center double-blinded randomized controlled clinical trial to study the effects of MgSO\textsubscript{4} infusion in patients after aneurysmal SAH. The study protocol has been described previously [23]. The study recruited patients aged 18 years or above and within 48 hours after the onset of aneurysmal SAH. Patients were randomized to MgSO\textsubscript{4} infusion group and control group after obtaining informed consent from patients or next of kin. For patients assigned for MgSO\textsubscript{4} infusion, MgSO\textsubscript{4} 20mmol was administered over 30 minutes; this was followed by continuous infusion of magnesium sulfate 80mmol/day for 14 days. Infusion was adjusted so that the serum magnesium concentration was raised to approximately twice the baseline value and < 2.5 mmol/L. Serum magnesium concentration was measured by colorimetry using a dye-binding method on the Roche D & P Modular Analyzer (Roche Diagnostics GmBH, Mannheim, Germany). Patients in the control group received the equivalent volume of normal saline.

All patients were treated according to a standard protocol in the neurosurgical high dependency unit or intensive care unit if mechanical ventilation was required. Normotension, defined as systolic arterial pressure between 120 mmHg and 160 mmHg, was maintained except during episodes of vasospasm when hemodynamic therapy was induced. The intracranial aneurysm was either occluded by endovascular coils or clipped microsurgically. Endovascular coiling or microsurgical clipping was usually performed within 48 hours after admission. Patients also received nimodipine infusion 0.5 to 2 mg/hr and prophylactic anticonvulsant, sodium valproate 400 mg intravenously every 8 hours, switching to enteral administration later on. Patient characteristics, clinical and radiological severity of subarachnoid hemorrhage, as well as biochemical data were reviewed. Serum sodium and potassium concentrations were measured by ion-selective methods on the Roche D & P Modular Analyzer (Roche Diagnostics GmBH, Mannheim, Germany). Hyponatremia was defined as serum sodium below 134 mmol/L and severe hyponatremia was defined by serum sodium below 130 mmol/L. Hypernatremia was defined as serum sodium level above 145 mmol/L and severe hypernatremia was defined as serum sodium level above 150 mmol/L. Hypokalemia was defined by serum potassium level below 3.5 mmol/L and severe hypokalemia was defined by serum potassium level below 3.0 mmol/L.

The patient characteristics, incidence and duration of hyponatremia, hypernatremia, hypokalemia and hyperkalemia were compared using SPSS 14.0 for Windows. Proportions of categorical data were analyzed between groups using Chi-Square test or Fisher exact test. Continuous data were analyzed by unpaired t test. Two-sided P values less than 0.05 were considered statistically significant.

**Results**

Fifty-one patients had daily MgSO\textsubscript{4} infusion for 14 days (Group 1) and 49 patients were managed similarly without MgSO\textsubscript{4} infusion (Group 2). Demographic and clinical data are depicted in table 1. There was no statistically significant difference in age, sex, admitting WFNS (World Federation of Neurological Surgeons) grades, locations of aneurysm and treatment modalities.

Days of hyponatremia (mean+/SD) were 2.0+/2.7 for group 1 and 2.0+/2.5 for group 2, p = 0.999 (figure 1); days of hypernatremia (mean+/SD) were 2.7+/3.1 for group 1 and 2.0+/2.9 for group 2,
Table 1. Demographic and clinical data of the 100 IMASH-recruited patients.

<table>
<thead>
<tr>
<th>Group 1 (Magnesium)</th>
<th>Group 2 (Control)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Age (mean+/−SD)</td>
<td>57.1+/−13.4</td>
<td>58.7+/−11.8</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>14/37</td>
<td>17/32</td>
</tr>
<tr>
<td>WFNS</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>17</td>
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<tr>
<td>3</td>
<td>5</td>
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<td>16</td>
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<tr>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microsurgical clipping</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Embolization</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Severe hypernatremia occurred in 7.84% for group 1 and 22.4% for group 2, p = 0.029; severe hyponatremia occurred in 13.7% for group 1 and 10.2% for group 2, p = 0.211; severe hypokalemia occurred in 51% for group 1 and 40.8% for group 2, p = 0.056. The incidence of severe hypernatremia was significantly lowered in the MgSO4 infusion group while the incidences for severe hyponatremia or severe hypokalemia were not significantly different between the two groups.

Days of severe hypernatremia (mean+/−SD) were 0.3+/−1.1 for group 1 and 0.6+/−1.5 for group 2, p = 0.074 (figure 1); days of severe hyponatremia (mean+/−SD) were 0.4+/−1.4 for group 1 and 0.2+/−0.8 for group 2, p = 0.178 (figure 2); days of severe hypokalemia (mean+/−SD) were 0.9+/−1.3 for group 1 and 0.7+/−1.0 for group 2, p = 0.528 (figure 3). There was no statistically significant difference between group 1 and group 2 in terms of days of hypernatremia, hyponatremia and hypokalemia, as was the case for severe electrolyte disturbance. MgSO4 infusion did not exacerbate the duration of electrolyte disturbance associated with aneurysmal subarachnoid hemorrhage.

Discussion

When the blood-brain barrier becomes disrupted in the acute phase of aneurysmal SAH, sodium may accumulate in the interstitial space and promote the collection of interstitial fluid [1, 25, 26]. Thus, hyponatremia or hypernatremia may aggravate cerebral edema. Hypernatremia after aneurysmal SAH is associated with poor clinical outcome although it was uncertain whether hypernatremia per se accounts for the poor outcome or is a sign of severe brain damage [27]. Hyponatremia after SAH is commonly due to increased natriuresis from inappropriate elevation of atrial natriuretic peptide. In patients with cerebral infarction after aneurysmal SAH, hyponatremia is associated with increased mortality [28]. Hypokalemia in the acute phase of aneurysmal SAH might be related to a catecholamine surge or spontaneous diuresis. Hypokalemia could cause a prolongation in the QT interval and ventricular arrhythmias [29-31]. Thus, the commonly occurring electrolyte disturbances in the acute phase of aneurysmal SAH could have significant adverse effects to the patients if left unattended.

In the past three decades, early treatment of the aneurysm by either microsurgical clipping or endovascular embolization has largely prevented aneurysmal re-bleed. However, despite advancement in
neurointensive care, delayed ischemic neurological deficit or clinical vasospasm has remained a major reason for neurological morbidity and mortality in patients with aneurysmal SAH. On meta-analysis of the three available pilot randomized controlled clinical trials for MgSO4 infusion after aneurysmal SAH, favorable outcome was achieved in 71% of the magnesium-treated group and 61% of the placebo group, $p = 0.041$. Symptomatic vasospasm or delayed cerebral ischemia was noted in 19% of the magnesium-treated group and 28% of the placebo group, $p = 0.036$ [21-24]. Preliminary results were encouraging. Multi-center randomized controlled trials such as IMASH and MASH-2 are ongoing and should provide definitive guidelines regarding magnesium sulfate infusion after aneurysmal subarachnoid hemorrhage within the next two-three years.

Meanwhile, considering the obstetric experience, there is a concern that magnesium sulfate infusion would aggravate the electrolyte disturbances associated with aneurysmal SAH.

We were able to show that the incidence of severe hypernatremia was significantly lowered in the MgSO4 infusion group while the incidences for severe hyponatremia or severe hypokalemia were not significantly different between the two groups. There was no statistically significant difference between group 1 and group 2 in terms of days of hypernatremia, hyponatremia and hypokalemia. MgSO4 infusion did not seem to exacerbate the duration of electrolyte disturbance associated with aneurysmal subarachnoid hemorrhage and in fact lowered the duration of severe hypernatremia.
The limitation of the current study was that it only describes the data. No systemic collection of electrocardiographic data and cardiac status was carried out. The etiological basis of the electrolyte disturbances was also not systematically analyzed. The pathophysiology leading to a reduction in hypernatremia was not known from our study design of retrospective review of prospective collected data. It might be related to antidiuretic hormone action or a reflection of neuroprotection effects. Further study design incorporating measurement of diuresis and antidiuretic hormone as well as correlation to severity of brain injury could unfold the underlying pathophysiology. Background diabetes was only present in three patients, thus analysis of background diabetes in relationship to electrolyte disturbance was not carried out.

Nevertheless, we believe the current study provides data on the safety aspects of magnesium sulfate infusion with respect to electrolyte (sodium and potassium) disturbances.

**Conclusion**

Hypermagnesemic treatment with MgSO₄ infusion is safe in patients after aneurysmal SAH and does not exacerbate the occurrence and duration of electrolyte (sodium and potassium) disturbances associated with aneurysmal SAH.

**References**


![Figure 3. Distribution of days of hypokalemia and severe hypokalemia (Hypokalemia was defined by serum potassium level below 3.5 mmol/L and severe hypokalemia was defined by serum potassium level below 3.0 mmol/L). A) Magnesium Sulfate Group. B) Control Group.](image-url)


