Magnesium sulfate ineffective following aneurysmal subarachnoid hemorrhage

Intravenous magnesium sulfate did not improve clinical outcome following aneurysmal subarachnoid hemorrhage

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February 24, 2013 – Intravenous Magnesium Sulfate ($MgSO_4$) did not improve clinical outcome in patients admitted to hospital with aneurysmal subarachnoid haemorrhage, according to the results of the MASH-2 study, a randomized, placebo-controlled, phase 3 trial.

Sanne M. Dorhout Mees, MD, of the Utrecht Stroke Center, Rudolf Magnus Institute of Neurosciences, Utrecht, The Netherlands, and colleagues, published their findings in the *Lancet* on July 7, 2012.

According the researchers, “delayed cerebral ischemia occurs usually between 4 to 10 days after aneurysmal subarachnoid hemorrhage, and is an important cause of poor outcome.” Treatment with $MgSO_4$, a neuroprotective agent of benefit in the treatment of eclampsia, showed promise in an earlier randomized, placebo-controlled, phase 2 trial.

In this prior phase 2 trial, encouraging, but not significant, improvement with intravenous $MgSO_4$ plus nimodipine versus placebo plus nimodipine was observed. Further evidence, from a Cochrane review, demonstrated that $MgSO_4$ plus nimodipine was superior to placebo plus nimodipine in preventing both delayed cerebral ischemia and poor outcome. Following these positive findings the researchers determined that a phase 3 trial was warranted.

In the MASH-2 study, patients admitted to centres in the Netherlands, Scotland or Chile, within 4 days of an aneurysmal subarachnoid hemorrhage, were eligible for inclusion; 604 were randomized to the treatment arm and 596 to the placebo arm (4 were lost to follow-up). Treatment was 64 mmol $MgSO_4$ delivered by continuous intravenous infusion for 20 days; controls received saline as placebo. All patients received oral nimodipine 360 mg/day.

Outcome measures were assessed three months after hemorrhage; the primary outcome was death or dependence (modified Rankin Scale score ≥4) and the secondary outcome was symptom free survival (modified Rankin Scale score of 0).

The primary outcome did not differ between $MgSO_4$ and placebo groups (26.2% vs. 25.3%; risk ratio [RR] 1.03; 95% CI 0.85 – 1.25) nor did the secondary outcome (7.6% vs. 7.7%; RR 0.99; 95% CI 0.67 – 1.46). Furthermore, an updated meta-analysis of 2,047 patients and showed no significant difference between groups (RR 0.96)

Only unexpected serious adverse events were reported; four patients, all in the $MgSO_4$ group, were withdrawn from the study due to asymptomatic hypocalcemia or hypermagnesemia.

“The MASH-2 trial is the first adequately powered randomized controlled trial that shows no beneficial effect of magnesium on outcome,” the researchers commented, adding, “we do not recommend routine use of intravenous magnesium 64 mmol/day for the improvement of outcome after aneurysmal subarachnoid hemorrhage.”

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