Magnesium Sulfate for Subarachnoid Hemorrhage: A Piece of the Mosaic

To the Editor:

We congratulate Wong et al1 on the multicenter trial investigating magnesium sulfate for aneurysmal subarachnoid hemorrhage. After encouraging results from pilot trials,2–5 phase III trials are needed. Concerning outcome, the results showed no significant benefit of magnesium sulfate infusion over placebo.

However, the study misses considering some important characteristics. Wong et al describe only 1 case of hypocalcemia. The frequency of serum calcium measurements and values in both groups are not outlined. Slight to moderate hypocalcemia3,6 may abolish positive influences on outcome. Only systolic blood pressure values were analyzed at admission. Daily blood pressure measurements were not incorporated in the trial design. Other studies showed significant effects of magnesium sulfate infusion on blood pressure.5 Hypotension, in the present study, defined as persistent systolic blood pressure <90 mm Hg, occurred as frequently in the verum group as it did in the placebo group. The systolic blood pressure limit of 90 mm Hg, requiring inotropic support, may have been set too low in the investigating magnesium sulfate for aneurysmal subarachnoid hemorrhage trial and may have resulted in missing slight hypotensive episodes and adverse potential positive effects of magnesium sulfate therapy.

Other important treatment characteristics, such as type of rescue therapy with vasospasm, management of seizures, glucose, and fever, as well as hypocalcemia, are not defined. With subarachnoid hemorrhage, particularly, the importance of sustaining oxygenation, hemodynamic, temperature, and metabolic homeostasis is recognized.7 As the authors mention, a significant weakness of the study is the lack of on-site trial monitoring. Patients were enrolled over a period of 6.5 years. In most neurosurgical centers, standards in neurocritical care changed during this time. In the CONSCIOUS-1 study, the increased incidence of pulmonary complications and hypotension decreased beneficial effects of clazosentan on morbidity and mortality.8 An important lesson to be learned for all future studies with neuroprotective drugs is that standards for monitoring and treatment have to be established and controlled carefully.

Magnesium therapy may be an important piece of the mosaic regarding overall management of subarachnoid hemorrhage. Investigating magnesium sulfate for aneurysmal subarachnoid hemorrhage showed no mortality or difference in the incidence of severe complications like cardiac failure, renal failure, pneumonia, and sepsis related to study drug infusion. Pilot studies describe hypotension, bradycardia, muscular weakness, and hypocalcemia as possible side effects of high-dose magnesium therapy. Being aware of these side effects, future phase III studies should be performed before magnesium sulfate, because many neuroprotective agents before magnesium sulfate vanish into thin air prematurely. For further phase III studies, which are clearly required, standardized guidelines for monitoring and treatment should be defined and carefully analyzed with on-site trial monitoring.

The hypothesis that the low cerebrospinal fluid penetration of magnesium sulfate may explain the missing effect is interesting. In further studies, parallel performed measurements of cerebrospinal fluid concentration and serum level values of magnesium should be encouraged. They will help to gain more insights concerning dose optimization.

Disclosure

None.

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