Interaction Between Magnesium Sulfate and Acetylsalicylic Acid in the MASH Trial

To the Editor:

In the Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage (MASH) trial, van den Bergh and colleagues reported no significant difference in the incidence of delayed cerebral ischemia after magnesium sulfate or placebo in patients with aneurysmal subarachnoid hemorrhage. More recently, they reported similar findings with acetylsalicylic acid (ASA) in the same cohort of patients. Given that patients in this factorial study were randomized and assessed at the same time, it is somewhat puzzling to find that the results for the ASA part of the study were only available 14 months after the magnesium data were published. Nevertheless, we believe their analysis is incomplete.

Conceptually, the MASH trial consisted of 4 groups of patients. Group 1 received ASA alone, group 2 had magnesium and group 3 received both ASA and magnesium. Finally, there is a true placebo group, in that patients received neither aspirin nor magnesium (group 4). In its simplest form, the efficacy of ASA and magnesium can be evaluated by comparing outcomes in groups 1 with 4 and groups 2 with 4, respectively. A more powerful approach to evaluate the efficacy of ASA treatment would, however, compare all patients treated with ASA (ie, combining groups 1 and 3) with those who have not received ASA (including groups 2 and 4). Similarly, the magnesium effect can be evaluated by comparing outcomes in groups 2 and 3 with groups 1 and 4. Such analysis improves the power of the study considerably, and we believe this was performed in the MASH trial. But the approach is only valid if there was no interaction between ASA and magnesium treatment. In this regard, a positive (or synergistic) interaction overestimates the efficacy of individual treatment, whereas treatment effect is underestimated if the interaction is antagonistic in nature. Thus, a negative interaction may have explained the lack of effect for magnesium or ASA in patients with aneurysmal subarachnoid hemorrhage. Without details on the interaction effect, we believe it is inappropriate to carryout such analysis.

Disclosures

None.

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