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Revisão

Magnesium in subarachnoid hemorrhage. Useful with benefits?

Benefício terapêutico do Magnésio na fisiopatologia do vasoespasmo após hemorragia subaracnóide.

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ABSTRACT

Cerebral vasospasm is responsible for a great number of deaths and morbidity after acute subarachnoid hemorrhage. Beyond any doubt, it is related to physiopathology of endothelial cell contraction and relaxation. It has been proved as a therapeutic agent when administrated intravenously in patients after subarachnoid hemorrhage. A critical review of literature was accomplished by the authors in order to analyse all actions of vasospasm in SAH. The intravenous administration of magnesium is imperative and should be done immediately after the onset of SAH, as reccomended in the most important guidelines for the treatment of cerebral vasospasm.

Keywords: *subarachnoid hemorrhage, cerebral vasospasm, magnesium, cell membrane*

RESUMO

O vasoespasmo tem sido causador de grande numero de sequelas e óbitos após o evento da hemorragia subaracnóide. Várias hipóteses fisiopatológicas para seu desenvolvimento vêm sendo estudadas na literatura, todavia o envolvimento do magnésio na gênese e como substância terapêutica vem ganhando destaque cada vez maior. Os autores procuram identificar os pontos de relevância da cadeia de equilíbrio entre o cálcio e magnésio nas bombas de membrana endoteliais e o beneficio do mesmo na terapêutica, baseando-se na literatura revisada. A infusão de sulfato de magnésio endovenosa no período em que o vasoespasmo se instala parece ser um conduta extremamente útil e necessária no relaxamento da musculatura endotelial e faz parte hoje da maior parte dos protocolos de tratamento do vasoespasmo pós hemorragia subaracnóide.

Palavras-chave*: hemorragia meníngea; vasoespasmo cerebral; magnésio; membrana celular*

INTRODUCTION

Despite the publication of several randomized controlled studies, there is still much debate on whether magnesium sulfate improves outcome in patients with aneurysmal subarachnoid hemorrhage (SAH). Subarachnoid hemorrhage caused by a ruptured aneurysm accounts for only 5% of strokes, but occurs at a fairly young age and carries a worse prognosis. Delayed cerebral ischemia (DCI) is an important cause of death and dependence after SAH. The current mainstay of preventing DCI is nimodipine and maintenance of normovolemia but, even with this strategy, DCI occurs in a considerable proportion of patients. Magnesium is an inexpensive, easily available neuroprotective agent and has been shown to reduce cerebral vasospasm and infarct volume after experimental SAH. In a

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subgroup analysis in the Cochrane review of all randomized clinical trials of calcium antagonists in SAH, magnesium reduced the occurrence of DCI and poor outcome. Magnesium is a promising agent to prevent the occurrence of secondary ischemia and to improve outcome in patients with SAH. Currently two large phase II trials are being conducted that will hopefully provide definite evidence whether magnesium treatment is beneficial in SAH patients[6].

Review of Meta analysis

Sixteen trials, involving 3361 patients, were included in a review published by Dorhout Mees et al[2], 2005; three of the studies included magnesium sulphate in addition to nimodipine. Overall, calcium antagonists reduced the risk of poor outcome: the relative risk (RR) was 0.81 (95% confidence interval (CI) 0.72 to 0.92); the corresponding number of patients needed to treat was 19 (95% CI 1 to 51). For oral nimodipine alone, the RR was 0.67 (95% CI 0.55 to 0.81), for other calcium antagonists or intravenous administration of nimodipine, the results were not statistically significant. Calcium antagonists reduced the occurrence of secondary ischemia and showed a favorable trend for case fatality. For magnesium, in addition to standard treatment with nimodipine, the RR was 0.75 (95% CI 0.57 to 1.00) for a poor outcome and 0.66 (95% CI 0.45 to 0.96) for clinical signs of secondary ischemia.

In a well written study of 2006, according to Stippler et al[5], symptomatic vasospasm was present at a significantly lower frequency in patients who received MgSO4 infusion (18%) compared with patients who did not receive MgSO4 (42%) (p = 0.025). There was no significant difference in mortality rate at discharge (p = 0.328). A trend toward improved outcome as measured by the modified Rankin Scale (p = 0.084), but not the Glasgow Outcome Scale (p = 1.0), was seen in the MgSO4 treated group. They emphasized that MgSO4 infusion may have a role in cerebral vasospasm prophylaxis if therapy is initiated within 48 hours of aneurysm rupture.

Zhao et al, in an elegant study, searched the EMBASE and PubMed databases using the following terms: "magnesium sulfate" or "MgSO4 " with "subarachnoid hemorrhage" or "cerebral vasospasm". A manual search of the bibliographies of relevant articles was also conducted. They designed the metaanalysis of published randomized clinical trials and extracted the data, which were analysed by using Review Manager 4.2 from the Cochrane Collaboration (Oxford, UK). Five published manuscripts were identified according to the screening criteria. The occurrence of poor outcome (death, vegetative state, or dependency) in patients treated with magnesium sulfate was less likely than control group patients (odds ratio [OR] 0.54 [95% confidence interval, CI 0.36-0.81]). Mortality rates did not differ between magnesium sulfate (14%) and control treated (12%) patients (OR 1.16 [95% CI 0.51-2.65]). Their results indicate that although there was reduced likelihood of a poor outcome for patients treated with magnesium sulfate after SAH, patient mortality was not improved.

Intravenous treatment using magnesium

To evaluate the effect of magnesium sulfate (MgSO4) on the clinical course of patients with severe SAH, Boet & Mee[1] studied 10 patients with Fisher Grade 3 aneurysmal SAH. The patients were given a bolus as well as a constant infusion of intravenous MgSO4 up to 10 days postictus. Blood magnesium levels were obtained to adjust the daily requirement of MgSO4. Their goal was to raise the serum level to 2.0 to 2.5 mmol/L or twice the baseline serum level. Daily transcranial Doppler (TCD) ultrasonography was performed on each patient, insonating both anterior cerebral and middle cerebral arteries. Further management followed standard protocols, including the use of nimodipine and hypervolemic therapy. TCD ultrasonographic findings, as well as clinical evidence of cerebral vasospasm, were documented. All patients had a 3-month assessment using the Glasgow Outcome Scale. They observed that after administration of a 20 mmol MgSO4 bolus infusion and an average daily continuous infusion of 84.7 mmol, 8 of 10 patients achieved the predetermined serum magnesium levels. No adverse effects were noted during the infusions. Five patients exhibited evidence of vasospasm on TCD ultrasonography; vasospasm was severe in two patients (velocities, >200 cm/s). Three patients, including the two patients in whom TCD ultrasonography demonstrated severe vasospasm, exhibited clinical evidence of vasospasm. Two patients had a Glasgow Outcome Scale score of 3; the remainder had Glasgow Outcome Scale scores of 5 showing that the administration guidelines for the use of MgSO4 in aneurysmal SAH were established, however a prospective double-blind placebo-controlled trial should be required to establish the effectiveness of MgSO4 for treating vasospasm in aneurysmal SAH.

Yahia et al[7] studied patients with SAH receiving an intravenous infusion of 12 g of MgSO4 in a 500-mL solution of 0.9% NaCl administered at a rate of 4.06 mM (or 0.5 g) every hour over a 24-hour period for 10 days to achieve a target predetermined serum Mg range of more than 1.5 to less than 4.0 mM/L. They monitored the effect of MgSO4 on clinical examination, heart rate, and blood pressure was measured every 2 hours; serum glucose and phenytoin levels were monitored daily. Outcome mea-

sures included evidence of vasospasm on clinical examination, transcranial Doppler study ((TCD); velocity >or=100 cm/s), or repeat cerebral angiogram obtained within 10 days of SAH; and Glasgow Outcome Scale (GOS) score assessment and CT scan evidence of ischemic infarction at 30 days. They selected nineteen patients (mean age: 55 years; range: 39-84 years; 11 males, 8 females), and the patients should present Hunt Hess grade II or higher; mean Fisher grade 3. The authors observed vasospasm in nine patients (by clinical examination in two, TCD in five, and angiogram in nine). The mean serum Mg level was 2.7 mM/L (standard deviation: +/- 0.37) and was maintained during the infusion period. No clinical adverse effects, hemodynamic changes, or fluctuations in serum glucose or phenytoin levels were observed. None of the patients died; no CT evidence of ischemic infarction was present; and most had good outcomes (GOS 5 in 10 patients; GOS 4 in 8 patients).

Friedlich et al[3] studied a total of 85 patients with SAH: magnesium sulfate was infused in 43 patients. When compared with patients who did not receive MgSO4, there was a statistically significant lower incidence of clinical and radiological vasospasm in those who had the continuous infusion of magnesium sulfate ($p<0.01$). There was no statistically significant difference between patients who were submitted to coiling or clipping. They concluded that continuous magnesium sulfate infusion for the management of clinically significant cerebral vasospasm is safe and reduces its incidence . They did not mention the reduction of rate of ischemia as complication of vasospasm.

Physiopathology of vasoconstriction

Cerebral vasoconstriction is associated with increased cytosolic Ca(2+) concentration in vascular smooth muscle, presumably due to Ca(2+) influx and Ca(2+) release from intracellular stores. We tested the hypothesis that dantrolene (a blocker of Ca(2+)-induced Ca(2+) release from the ryanodine receptor channel on the sarco-endoplasmic reticulum) would potentiate the action of nimodipine (a voltage-dependent L-type Ca(2+) channel blocker, considered standard therapy for SAH) in inhibiting the vasoconstriction of isolated cerebral arteries[4] (Fig. 1). Dantrolene has synergistic effects with nimodipine against 5-HT-induced vasoconstriction in isolated cerebral arteries. Dantrolene-nimodipine interaction will require testing in a pathophysiological model but might provide treatment for reducing SAH-related vasospasm or other 5-HT-related vasospastic syndromes, such as Call-Fleming syndrome[4].

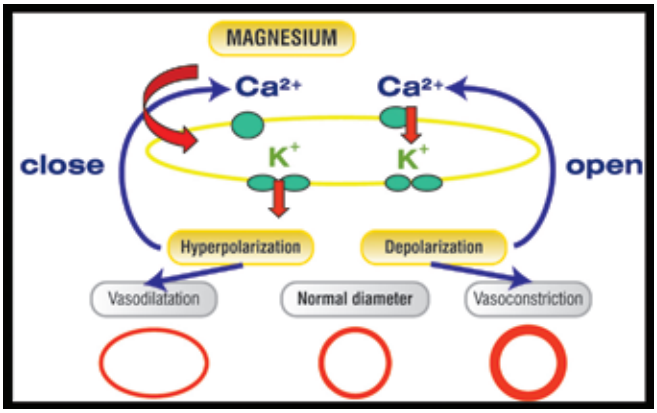

Figure 1. The schematic drawing shows the cell and the change in membrane surface between Calcium and Potassium. The intracellular calcium leads to depolarization, releasing potassium stored in the cell, leading to vasoconstriction. On the other hand, the misplacing of calcium due to its competition with magnesium may diminish the intracellular concentration of calcium and more potassium is delivered by the cell membrane causing the vasodilatation due to hyperpolarization.

Conclusion

According to the literature, the use of continuous magnesium sulfate infusion is safe and reduces the incidence of clinically cerebral vasospasm and the risk of poor outcomes.

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