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Intravenous magnesium therapy in adult patients with an aneurysmal subarachnoid haemorrhage: A systematic review and meta-analysis☆

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ABSTRACT

Background: The value of magnesium for the prevention of cerebral arterial vasospasm in patients with aneurysmal subarachnoid haemorrhage (SAH) is debatable. We performed a systematic review to collate the available evidence to evaluate the effects of intravenous magnesium for the prevention of cerebral arterial vasospasm.
Materials and methods: An electronic search of MEDLINE (Ovid), ProQuest, CINAHL and the Cochrane Database of Systematic Reviews was undertaken up to 1st October 2012 for randomised controlled trials (RCTs) of intravenous magnesium for the prevention of vasospasm in adult patients with aneurysmal SAH. Primary outcome measures were risk of vasospasm, functional outcomes and mortality. Results are presented as risk ratios (RR) and 95% confidence intervals (CI).
Results: Nine of 38 trials were included in this review. Not all trials could be combined for analyses due to differences in reported outcomes and outcome definitions. Of the trials that could be combined we found a statistically significant reduction on the incidence of vasospasm with magnesium (RR 0.83; 95% CI 0.71, 0.98; $P=0.03$). No statistical difference for the last reported favourable functional outcome (RR 1.00; 95% CI 0.96, 1.05; $P=0.84$); or mortality (RR 0.95; 95% CI 0.77, 1.18; $P=0.67$) between magnesium treated and standard care/control groups was found.
Conclusion: We identified a benefit in the role of magnesium to reduce the incidence of cerebral vasospasm in patients with an aneurysmal SAH. However no benefit was found regarding improved favourable functional outcome or a reduction of mortality.

Introduction

Of all stroke-related years of life lost before age 65, subarachnoid haemorrhage (SAH) accounts for 27%.[1] Subarachnoid haemorrhage affects a younger cohort of people compared with other types of stroke (ischaemic stroke and intracranial haemorrhage), with an average age of 57 years (range 45–64 years).[2] Of all types of strokes, SAH accounts for 1 in 20 strokes, with approximately 85% caused by the rupture of a cerebral aneurysm. Mortality rate from an aneurysmal SAH is approximately 50%, one third dying before reaching hospital.[3,4] Survivors of an aneurysmal SAH can go on to have mental and physical disabilities, some needing lifelong care.[4,5] Recent reviews of the incidence of SAH in Australia and internationally have reported that the incidence of SAH has not reduced over time. There is a need to review the progress of medical management in this relatively young patient group, whom have a high mortality rate.[2,6]

Cerebral arterial vasospasm (referred to as "vasospasm" from here onwards) is one of the complications affecting neurological outcome after aneurysmal SAH.[3] Vasospasm is the narrowing of arterial lumens causing reduced cerebral blood flow that results in delayed cerebral ischaemia (DCI) and delayed cerebral ischaemic infarction (DCII).[7] DCII occurs in 40%[8] of aneurysmal SAH patients in part due to vasospasm.[3] Vasospasm generally begins 3–5 days after the haemorrhage where peak DCI occurs between days 5 and 14.[3] As the onset of vasospasm after haemorrhage is delayed there is an opportunity to initiate preventative therapies such as treatment with the calcium channel blocker nimodipine plus other interventions to improve cerebral blood flow.[3,9,10]

There is a growing trend in clinical practice to add a magnesium sulphate infusion as a vasodilator because it is thought to have

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neuroprotective properties.[10,11] After an aneurysmal SAH, calcium floods smooth muscle and neuronal cells inducing vessel wall contraction.[7] Surrounding red blood cells break down triggering leucocyte production and inhibition of nitric oxide, a vasodilator.[7] Magnesium sulphate is a calcium antagonist; inhibits leucocyte production of endothelin-1 – a potent vasoconstrictor; inhibits free radical production; and platelet aggregation, all resulting in potential vasospasm prevention.[7]

On review of the literature five meta-analyses of trials have been conducted regarding the role of magnesium sulphate in vasospasm after aneurysmal subarachnoid haemorrhage.[7,12–15] Dorhourt Mees et al.[12] in a Cochrane Collaboration review of calcium antagonists found a benefit to hypermagnesia, reducing poor functional outcome, DCI and the risk of mortality. However, due to the small sample size the recommendation was to wait for the results of the IMASH and MASH-2 trial findings. In a meta-analysis by Zhao et al.,[15] they combined the results of five trials and concluded that there was a reduced risk of poor outcome in those treated with magnesium and no difference in the risk of mortality. However two of the five trials combined in their meta-analysis were not prospective, randomised controlled trials (RCTs) rather matched historical control cohorts.[15] In another meta-analysis by Ma et al.,[13] five trials were combined for analysis and then two trials were removed which were thought to be of low quality. When combining the three remaining trials Ma concluded that magnesium significantly reduced the risk of poor functional outcome and DCI, based on 401 participants.[13] Chen and Carter[7] added to the meta analysis of Zhao[15] which included four new trials where 936 participant results were analysed. Chen and Carter[7] also concluded that those treated with magnesium had a reduced risk of poor functional outcome and no change to the risk of mortality, however the results of two non-RCTs remained in the analysis. Wong[16] removed the two non-RCTs from those analysed by Chen and Carter[7] concluding that an infusion of magnesium sulphate did not have a beneficial effect on DCI or neurological outcomes in the 875 participants analysed. In publishing clinical recommendations, The American Neurocritical Care Society[9] advise against the use of hypermagnesia therapy until the results of MASH-2 were available, but to definitely avoid hypomagnesia.

With the availability of new evidence, including the largest RCT to date on magnesium therapy in SAH,[17] and the continued uncertainty surrounding the benefit of magnesium therapy,[9] the authors of this review believed an up to date systematic review and meta-analysis of the literature was required. There is a need to reconsider the evidence of patient benefit regarding the use of magnesium therapy on the development of DCI, favourable functional outcome, the risk of mortality, and for the first time, to investigate the potential of magnesium therapy on the incidence of vasospasm following aneurysmal SAH.

Objectives

To undertake a systematic review of randomised controlled trials (RCTs) of magnesium sulphate infusion compared to placebo/standard care in adult patients who have had a SAH due to an aneurysm. The outcome measures of the review were the presence of cerebral artery vasospasm and delayed cerebral ischaemic deficits (DCID), as measured by favourable functional outcome and mortality.

Methods

Study types

Publications selected for review were RCTs of patients with aneurysmal SAH receiving intravenous magnesium for the prevention of vasospasm. To be included trials needed to have assessed the development of cerebral vasospasm or the functional outcome of the participant.

Participants

This review searched for adult patients who were 18 years or older with an aneurysmal SAH and who were cared for in a medical facility.

Interventions

Any use of intravenous magnesium versus a placebo/standard treatment control group for the prevention of vasospasm in aneurysmal SAH. Trials comparing standard treatment/placebo control groups with a magnesium treatment group were expected to include Nimodipine as this is a part of the current standard of care and has been shown to have neuroprotective mechanisms.[12]

Outcome measures

The primary outcome measure for this review is the effect of intravenous magnesium on the presence of vasospasm as detected by cerebral blood flow velocity during digital subtraction angiography and/or transcranial Doppler (TCD). Also, if possible, the presence of DCI which can be described as delayed ischaemic neurological deficit (DIND) and confirmed DCII, will be reported.

A secondary outcome measure of interest in this review is the patient's favourable functional recovery as measured by scales such as, but not limited to, the Glasgow Outcome Scale (GOS) or Extended Glasgow Outcome Scale (GOSE). The GOS, originally designed for use in those with severe head injuries, is a five point scale where 5 is a good recovery (GR), 4 moderate disability (MD), 3 severe disability (SD), 2 vegetative state, 1 dead.[18] In response to concerns that the five point scale did not adequately describe functional outcome, the scale was extended. The GOSE is an eight-point scale where the GR, MD and SD groups are divided into upper or lower bands to obtain a more sensitive result. Where 8 is an upper GR, 7 lower GR, 6 upper MD, 5 lower MD, 4 upper SD and 3 lower SD, 2 and 1 remain as described by the GOS.[18]

The risk of mortality will also be assessed as a secondary outcome measure. If mortality is not reported then it will be derived from a GOS or GOSE score of 1.[18]

Search methods

Electronic search

The following databases were searched for relevant trials: MEDLINE (Ovid) 1946 to February 1st, 2013 (see Appendix A for full search details); ProQuest (1970 to February 1st, 2013); CINAHL (1981 to February 1st, 2013); and the Cochrane Database of Systematic Reviews (1991 to February 1st, 2013).

The search terms can be found in Appendix A and followed the PICO format (population, intervention, comparison and measurable outcome) of a focused clinical question. The P and I were used initially to search so not to overly limit the search findings which could result in missed articles. The search limits that were applied include only studies in humans and in English.

Search of other sources

All article reference lists on the review topic, were searched for further relevant articles. Authors were not individually contacted