Magnesium in subarachnoid haemorrhage: proven beneficial?

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Abstract. Subarachnoid haemorrhage (SAH) 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 ischaemia (DCI) is an important cause of death and dependence after aneurysmal subarachnoid haemorrhage. 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 subgroup analysis in the Cochrane review of all randomized clinical trials of calcium antagonists in SAH, magnesium reduced the occurrence of DCI and that of poor outcome. Magnesium is a promising agent to prevent the occurrence of secondary ischaemia and to improve outcome in patients with SAH. Currently two large phase III trials are being conducted that will hopefully provide definite evidence whether magnesium treatment is beneficial in SAH patients.

Key words: controlled clinical trial, subarachnoid haemorrhage, magnesium, meta-analysis

Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) caused by a ruptured aneurysm accounts for only 5% of strokes, but occurs at a fairly young age and carries a worse prognosis than other types of stroke [1]. The incidence of subarachnoid haemorrhage in most populations is 6-7 per 100 000 person-years [2]. About one in eight patients die before reaching the hospital. The in-hospital case fatality is about one-third. Of patients who survive the SAH approximately one-third remain dependent. Because of the young age SAH occurs and its poor prognosis, the loss of productive life years from SAH is as large as that from ischaemic stroke, the most frequent subtype of stroke.

Aneurysms arise at sites of arterial branching, usually at the base of the brain, either on the circle of Willis itself or at a nearby branching point. Most intracranial aneurysms will never rupture. Risk factors for subarachnoid haemorrhage are hypertension, smoking, and excessive alcohol intake, all of which more-or-less double the risk [3].

Severe sudden headache is the cardinal feature, but patients frequent deteriorate into unconsciousness shortly after onset. On admission two-thirds of all patients have depressed consciousness, of whom half are in coma [4].

Diagnosis is made by CT brain scanning. Rebleeding is the most imminent danger; a first aim is therefore occlusion of the aneurysm. Endovascular obliteration by means of platinum spirals (coiling) is the preferred mode of treatment, but some patients require a direct neurosurgical approach (clipping) [5].

For those patients who survive the first 24 hours after the haemorrhage, delayed cerebral ischaemia is consistently the leading cause of poor outcome and death, adversely affecting more than one in five of all patients who have suffered SAH and survived [6, 7].
Delayed cerebral ischaemia

Unlike thromboembolic stroke, cerebral ischaemia after subarachnoid haemorrhage has a gradual onset and often involves more than the territory of a single cerebral artery or one of its branches. The clinical manifestations evolve gradually, over several hours, and consist of hemispheric focal deficits, a reduction in the level of consciousness, or both. It is mainly a diagnosis of exclusion, when clinical deterioration occurs and hydrocephalus, rebleeding, hypoxia, and metabolic abnormalities have been ruled out. The peak frequency of cerebral ischaemia is from 5 to 14 days after subarachnoid haemorrhage. A simplistic explanation is vasospasm, but arterial narrowing – a complex process in itself – is neither a necessary nor a sufficient condition [8]. The time course for delayed cerebral ischaemia (DCI) parallels that of angiographic vasospasm [9], but, although about 70% of patients may develop arterial narrowing, only 20-30% will manifest neurological deficits [6].

The precise underlying pathogenic mechanisms remain obscure [10, 11], but it seems that endothelial mechanisms provide the most prominent contribution to this process and there is growing evidence that the constituents of a subarachnoid blood clot, especially oxyhaemoglobin, seem to be the principle initiating factor [12].

The current mainstay of preventing and treat DCI include neuroprotection with the dihydropyridine calcium channel antagonist nimodipine and maintenance of normovolemia, but even with this strategy DCI still occurs in up to 30% of patients and improvement in clinical outcome has been modest [4, 13-16]. Reducing the consequences of ischemia through neuroprotection may therefore improve outcome after SAH. Because DCI occurs mostly more than 4 days after the initial bleeding, the interval between the bleeding and the onset of ischemia provides an opportunity for preventive treatment.

Magnesium

In several experimental models of cerebral ischaemia a significant neuroprotective effect of magnesium is demonstrated, with reported infarct reduction of 25 to 61% [17-19]. Putative modes of action include inhibition of the excitatory amino acid glutamate release, and blockade of the NMDA-glutamate receptor and voltage dependent calcium channels [20]. Magnesium reduces the production of endothelin and completely attenuates the vasoconstrictive effect of endothelin, possibly by voltage-dependent blocking of calcium channels [21, 22].

Animal studies

Magnesium has a vasorelaxing effect in oxyhaemoglobin-induced vasospasm and it ameliorates vasospasm in experimental SAH [23-25]. Magnesium induces a dose-dependent vasodilatation, reduces cerebrovascular tone, increases CBF and protects the metabolism [26-29].

We have demonstrated in an experimental model that the duration of ischaemic depolarisations after SAH is substantially reduced after pre-treatment with magnesium sulphate [30]. Magnesium also postpones anoxic depolarisation [31]. This maintenance of the membrane potential may at least partly explain the neuroprotective properties of magnesium in SAH. We have shown in a rat model of SAH that pre-treatment with magnesium sulphate reduces acute cerebral lesion volume with more than 60% [30].

Observational clinical studies

Low magnesium serum levels occur frequently after SAH and is most likely caused by intracellular shift of magnesium ions [29, 32]. The diminished availability and subsequent decreased extracellular Mg²⁺ after SAH results in significantly increased intracellular free Ca²⁺ in cerebral vascular muscle cells. This may cause cerebral microvascular constriction, followed by a proinflammatory response, inducing vascular smooth muscle, endothelial and neuronal cell damage [33]. Hypomagnesaemia also results in a reduced endothelial NO release by which means hypomagnesaemia can induce vasoconstriction as well [34, 35].

Thus, there might be a causal relation between the decreased availability of magnesium in SAH and the deterioration of the acute cerebral damage and the development of vasospasm and DCI. In our study in 107 consecutive patients the majority had hypomagnesaemia at some time within three weeks after SAH, which increased the risk for DCI threefold [29].

MASH-1

Between November 2000 and January 2004, we enrolled 283 patients in the clinical controlled “Magnesium and Acetylsalicylic acid in Subarachnoid
Haemorrhage” (MASH-I) trial. Magnesium sulphate therapy consisted of a continuous intravenous dose of 64 mmol/day per day, to be started within 4 days after SAH and continued until 14 days after occlusion of the aneurysm. An intention to treat analysis of the primary outcome measure DCI resulted in a hazard ratio for magnesium treatment of 0.61. The risk reduction for poor outcome at three months was 23% [36]. The mean magnesium level in the treatment period was $1.47 \pm 0.32$ mmol/L, side effects were mild and sparse [37].

A post-hoc analysis suggests that the treatment effect of magnesium is larger after endovascular occlusion than after neurosurgical clipping, which underlines the conclusion that further trials are not at risk to be underpowered if the proportion of endovascular treated patients increases [38].

Meta-analysis

The results of the MASH-I study suggest that magnesium reduces DCI and subsequent poor outcome, but the results are not yet definitive. Besides the MASH-I study, there are several small clinical studies that demonstrate the safety and possible improvement in clinical outcome of magnesium therapy in subarachnoid haemorrhage. We assessed in a systematic review whether magnesium decreases the occurrence of secondary ischemia and poor outcome after aneurysmal subarachnoid haemorrhage. We sought to identify all unconfounded clinical controlled trials with magnesium in patients with aneurysmal SAH. Trials were identified in the Stroke Group Trials Register of the Cochrane Library, PUBMED and MEDLINE. Outcome measures were DCI and poor outcome. An estimate of the treatment effect across trials was calculated with the Mantel-Haenszel method according to the intention-to-treat principle.

Four trials totalling 437 patients were included in the review [36, 39-41]. All used magnesium sulphate in addition to nimodipine. The overall relative risk for DCI was 0.67 (95% CI 0.47-0.96) (figure 1), and for poor outcome 0.74 (95% CI 0.57-0.96) (figure 2).

Phase 3 clinical controlled trials; iMASH and MASH-II

There are two on-going phase 3 clinical controlled trials evaluating the effect of magnesium in SAH.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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<td>Total (95% CI)</td>
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<td>0.67 [0.47, 0.96]</td>
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</table>

![Figure 1. Studies with magnesium in addition to nimodine – effect on delayed cerebral ischaemia.](image1)

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</table>

![Figure 2. Studies with magnesium in addition to nimodine – effect on poor outcome.](image2)
The Hong Kong based Intravenous Magnesium sulphate in Aneurysmal Subarachnoid Haemorrhage (iMASH) trial is a phase III randomized, clinical international multicentre trial that evaluate the effect of magnesium sulphate on the clinical outcome of patients with aneurysmal SAH [NCT00124150]. After randomisation 20 mmol of magnesium sulphate is given over 30 minutes, followed by infusion of 80 mmol/day or equivalent volume of saline within 48 h after onset of symptom and continued for 14 days from the day of haemorrhage. This is a single-blind trial. The study aims for a plasma magnesium concentration in the treatment group of 2.0-2.5 mmol/L or twice the serum baseline level. The primary outcome is the extended Glasgow Outcome Scale at six months. Secondary outcome measurements are the incidence of clinical vasospasm, Barthel Index, modified Rankin score, modified National Institute of Health Stroke Score, and MCA velocities as measured by transcranial Doppler. Sample size was based on the assumption that 55% of patients in the control group reach GOSE \( \geq 5 \) and that the difference between treatment groups is 15-20%. With a power of 80%, the total number of patients required would be 348. The trial is closed to recruitment as of 12/31/08 and analysis of the results are awaiting the 6 month follow-up period.

The Magnesium in Aneurysmal Subarachnoid Haemorrhage (MASH-II) study is a phase III randomized, clinical international multicentre trial that studies the effect of magnesium sulphate after aneurysmal SAH [ISRCTN68742385] [42]. Study medication (magnesium sulphate 64 mmol/day or placebo) is given via continuous infusion within 4 days and until 20 days after the haemorrhage. Outcome is determined with the modified Rankin scale three months after the haemorrhage. Analysis will be according to the intention-to-treat principle. So far, in May 2009 over 700 patients have been included in 6 Dutch, 1 UK, and 1 Chilean hospital. Based on the results of the MASH-1 study sample size calculations indicate that 1 200 patients are needed to give a statistically significant result (with \( \alpha = 5\% \) and a power of 80%). We aim to include these patients before 2011. A first interim analysis was performed after 300 patients and a second interim analysis will be performed after recruitment and follow-up of 750 patients.

In conclusion, magnesium is a promising agent to prevent the occurrence of delayed cerebral ischaemia and to improve outcome in patients with SAH. Currently 2 large phase III trials are being conducted that will hopefully provide definite evidence whether magnesium treatment is beneficial in SAH patients.

Acknowledgments

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References


