



Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial

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Summary

Background Magnesium sulphate is a neuroprotective agent that might improve outcome after aneurysmal subarachnoid haemorrhage by reducing the occurrence or improving the outcome of delayed cerebral ischaemia. We did a trial to test whether magnesium therapy improves outcome after aneurysmal subarachnoid haemorrhage.

Methods We did this phase 3 randomised, placebo-controlled trial in eight centres in Europe and South America. We randomly assigned (with computer-generated random numbers, with permuted blocks of four, stratified by centre) patients aged 18 years or older with an aneurysmal pattern of subarachnoid haemorrhage on brain imaging who were admitted to hospital within 4 days of haemorrhage, to receive intravenous magnesium sulphate, 64 mmol/day, or placebo. We excluded patients with renal failure or bodyweight lower than 50 kg. Patients, treating physicians, and investigators assessing outcomes and analysing data were masked to the allocation. The primary outcome was poor outcome—defined as a score of 4–5 on the modified Rankin Scale—3 months after subarachnoid haemorrhage, or death. We analysed results by intention to treat. We also updated a previous meta-analysis of trials of magnesium treatment for aneurysmal subarachnoid haemorrhage. This study is registered with controlled-trials.com (ISRCTN 68742385) and the EU Clinical Trials Register (EudraCT 2006-003523-36).

Findings 1204 patients were enrolled, one of whom had his treatment allocation lost. 606 patients were assigned to the magnesium group (two lost to follow-up), 597 to the placebo (one lost to follow-up). 158 patients (26·2%) had poor outcome in the magnesium group compared with 151 (25·3%) in the placebo group (risk ratio [RR] 1·03, 95% CI 0·85–1·25). Our updated meta-analysis of seven randomised trials involving 2047 patients shows that magnesium is not superior to placebo for reduction of poor outcome after aneurysmal subarachnoid haemorrhage (RR 0·96, 95% CI 0·84–1·10).

Interpretation Intravenous magnesium sulphate does not improve clinical outcome after aneurysmal subarachnoid haemorrhage, therefore routine administration of magnesium cannot be recommended.

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Introduction

Prognosis after aneurysmal subarachnoid haemorrhage is poor; case fatality after 1 month is 27–44% and—although case fatality seems to have decreased over the past 10 years—20% of survivors cannot live independently.^{1,2}

Delayed cerebral ischaemia occurs usually between 4 to 10 days after aneurysmal subarachnoid haemorrhage, and is an important cause of poor outcome.^{3,4} Because of the interval between the onset of haemorrhage and the onset of cerebral ischaemia, outcome might be improved with treatments to prevent ischaemia.³ Oral nimodipine helps prevent delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage, but despite its use delayed cerebral ischaemia affects about 25% of patients receiving nimodipine.^{3,5}

Magnesium is neuroprotective and has a well-documented clinical profile.⁶ It is beneficial for treatment of eclampsia, which shares pathophysiological mechanisms with delayed cerebral ischaemia.^{7,8} Mechanisms of neuroprotection by magnesium include

inhibition of excitatory glutamate release, and blockage of the NMDA-glutamate receptor and voltage-dependent calcium channels.^{6,9} In our randomised phase 2 trial, which included 283 patients in The Netherlands, delayed cerebral ischaemia occurred in 22 of 139 (16%) patients who received intravenous magnesium 64 mmol/day plus usual care with oral nimodipine compared with 35 of 144 (24%) patients who received placebo plus nimodipine. 38 of 139 (27%) patients who received magnesium had poor outcome versus 51 of 144 (35%) in the placebo group (risk ratio [RR] 0·77, 95% CI 0·54–1·09).¹⁰ A Cochrane review⁵ of treatment with calcium antagonists after aneurysmal subarachnoid haemorrhage included three trials (379 patients) of magnesium in addition to nimodipine, and confirmed that intravenous magnesium plus nimodipine is superior to placebo for the prevention of delayed cerebral ischaemia (RR 0·66, 95% CI 0·45–0·96) and poor outcome (0·75, 0·57–1·00).

In this study, we test the effect of intravenous magnesium sulphate on outcome after aneurysmal subarachnoid haemorrhage.

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Methods

Study design and patients

We did this phase 3 randomised, placebo-controlled trial at six Dutch, one Scottish, and one Chilean centre. The trial protocol has been published.¹¹

Patients were eligible for inclusion if they were admitted to the neurological or neurosurgical units of one of the participating hospitals within 4 days of haemorrhage. Investigators based the diagnosis of aneurysmal subarachnoid haemorrhage on the presence of extravasated blood in the basal cisterns by brain CT, or—if CT was negative—by xanthochromia of cerebrospinal fluid. For patients with a normal CT scan and xanthochromia of cerebrospinal fluid, proof of an aneurysm was a prerequisite for inclusion. We included patients with a perimesencephalic pattern of haemorrhage on CT only if they had an aneurysm of the posterior circulation. Exclusion criteria were age younger than 18 years, renal failure (defined as serum creatinine concentration of more than 150 µmol/L), bodyweight less than 50 kg, or imminent death. The study complies with the Declaration of Helsinki and good clinical practice guidelines. We obtained ethics committee approval from every centre. All patients provided written and oral informed consent.

Randomisation and masking

The randomisation code was produced by the University Medical Center Utrecht (The Netherlands) pharmacy. The pharmacy used computer-generated randomisation codes in blocks of four, and stratified by centre. The pharmacy produced identical, sequentially numbered, randomly assigned boxes of study medication, containing either magnesium sulphate or placebo. Local investigators assigned the participant to the box with the lowest study number. The randomisation key was kept by the pharmacy of the University Medical Center Utrecht. Patients, treating physicians, and investigators assessing outcomes and analysing data were masked to the allocation.

Procedures

At admission to hospital, investigators recorded sex, age, and World Federation of Neurological Surgeons subarachnoid haemorrhage grade¹² for each patient. A score of 1–3 was deemed a good clinical condition, and a score of 4–5 was deemed a poor clinical condition.

Study medication consisted of vials containing 64 mmol magnesium sulphate or placebo (saline), produced by the pharmacy of the University Medical Center Utrecht and distributed to the participating centres (except for the centre in Chile, which produced its own study medication). An intravenous magnesium dosing regimen of 64 mmol per day after aneurysmal subarachnoid haemorrhage is safe and maintains serum magnesium concentrations at between 1.0 and 2.0 mmol/L.¹³ Furthermore, symptomatic hypermagnesaemia does not occur in patients with normal renal

function.¹⁴ Therefore, participants received a fixed daily dose of 64 mmol magnesium sulphate reconstituted in 0.9% saline, or placebo, as soon as possible after providing consent. Investigators administered study medication continuously via intravenous infusion and continued for 20 days after haemorrhage onset, or until hospital discharge or death if it occurred sooner. Investigators checked renal function at least once every 2 days to prevent symptomatic hypermagnesaemia. Monitoring of magnesium concentration was not mandatory. We discouraged, but permitted, investigators to treat hypomagnesaemia at admission with intravenous magnesium sulphate. Investigators treated patients according to local protocols, which included oral nimodipine 360 mg/day, bed rest until aneurysm occlusion, and early aneurysm occlusion, and aimed at achievement of normovolaemia.

The primary outcome was dependence¹⁵ (defined as a modified Rankin Scale score of 4 or 5) or death, 3 months after haemorrhage. The research nurse and study coordinator collected outcome data centrally, and assessed the Rankin score by semi-structured telephone interview in the patient's own language. The interview

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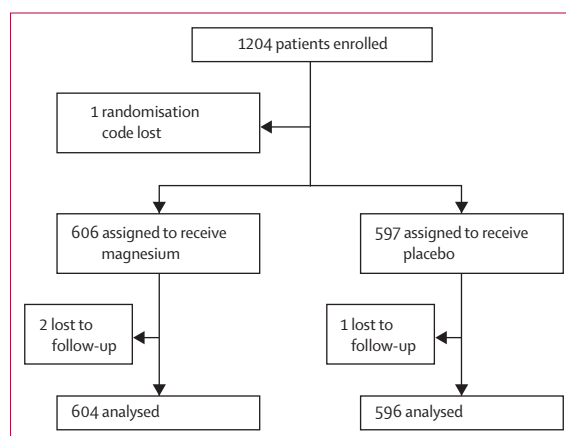


Figure 1: Trial profile

	Magnesium group (n=606)	Placebo group (n=597)
Mean age (SD; years)	57 (13)	57 (12)
Female (%)	422 (70%)	416 (70%)
World Federation of Neurological Surgeons subarachnoid haemorrhage grade >4	144 (24%)	130 (22%)
Aneurysm treatment		
Coiling	344 (57%)	324 (54%)
Clipping	197 (33%)	195 (33%)
None	65 (11%)	76 (13%)
Unknown	0 (0%)	2 (<1%)
Median time to received study medication from symptom onset (IQR; h)	33 (21–60)	41 (23–59)

Table: Baseline characteristics

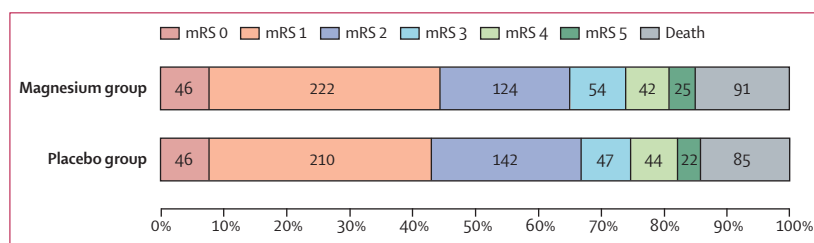


Figure 2: Distributions of mRS score in the magnesium and placebo groups

Data are number of patients with each mRS score. Tested with Mann-Whitney U test; $p=0.95$. mRS=modified Rankin Scale score.

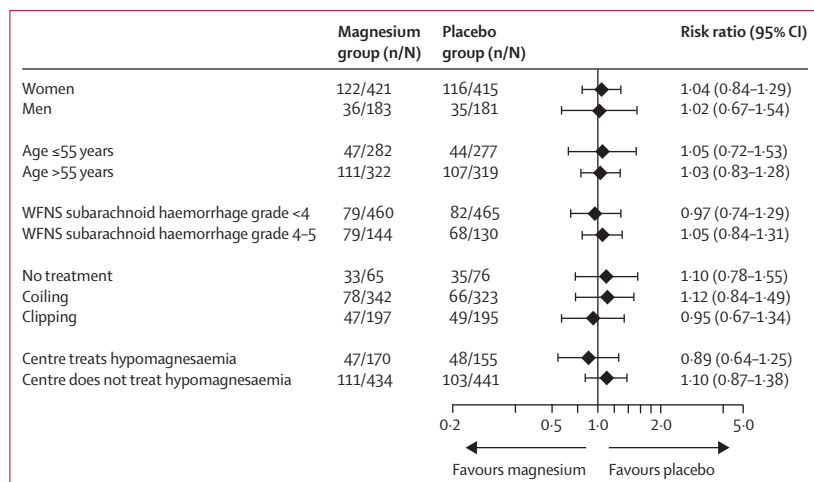


Figure 3: Subgroup analyses for primary outcome

WFNS score was unknown for one patient. Treatment type was unknown for two patients. RR=risk ratio. WFNS=World Federation of Neurological Surgeons.¹²

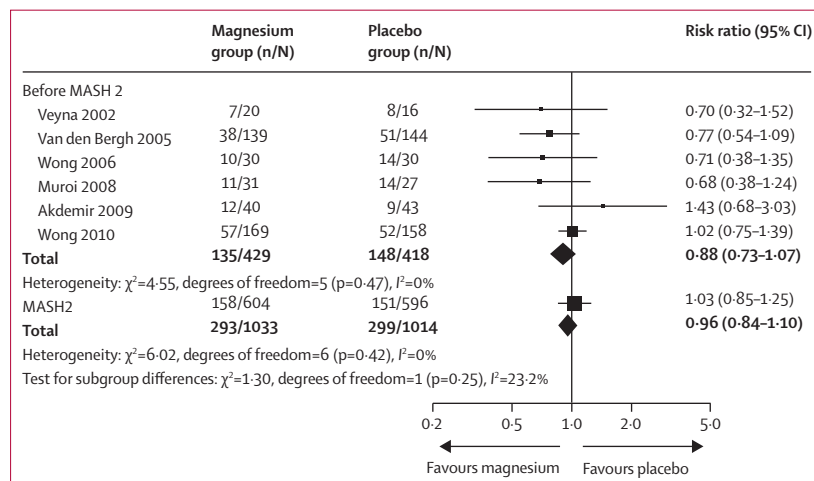


Figure 4: Meta-analysis of effect of magnesium therapy after subarachnoid haemorrhage on poor outcome

was translated into Dutch and Spanish with the standard procedure^{16,17} for forward-backward translation. Secondary outcome measures were no symptoms (modified Rankin Scale score of 0) 3 months after haemorrhage and the difference between the distribution of all scores on the modified Rankin Scale.

Statistical analysis

In our pilot study, 35% of patients in the untreated group had a poor outcome compared with 27% in the intervention group (RR 0.77).¹⁰ On the basis of these data we estimated that 1082 patients would be needed to confirm this effect with an α of 5% and 80% power. To allow for reliable detection of a slightly smaller effect (risk ratio 0.78) we decided to enrol 1200 patients. A research nurse entered all baseline and outcome data in the study database. The study coordinator analysed the data. The data were checked and results discussed by the executive committee. The data monitoring committee did two interim analyses during the study, after 350 and 750 patients had completed 3-month follow-up, with reference to a pre-defined stopping rule, and recommended continuation of the trial on both occasions. We analysed the results according to intention to treat by comparing poor outcome at 3 months in each group with a risk ratio and 95% CI. We did planned sensitivity analyses by assigning patients lost to follow-up to either a good outcome or a poor outcome irrespective of treatment group, and assigning patients with unknown randomisation codes to either the magnesium group or the placebo group. Planned subgroup analyses were done according to age, sex, clinical condition at admission, method of treatment of aneurysm, and whether the centre treated hypomagnesaemia with intravenous magnesium supplementation. We compared the distributions of the modified Rankin Scale scores with the non-parametric Mann-Whitney U test. We updated our previous Cochrane meta-analysis⁵ with results of MASH 2 and eligible randomised trials that had been published since the start of MASH 2 and the last update of the Cochrane review.¹⁸⁻²⁰ We used Cochrane Review Manager (version 5.1) software for the meta-analysis and SPSS (version 15.0) for all other analyses.

This study is registered with controlled-trials.com (ISRCTN 68742385) and the EU Clinical Trials Register (EudraCT 2006-003523-36).

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 1204 participants between April, 2004, and September, 2011. Of these, 1124 were enrolled in The Netherlands, 59 in Scotland, and 21 in Chile. The randomisation code of one patient was missing because the medication packaging containing the study number was lost, leaving 606 participants allocated to the magnesium group and 597 to the placebo group (figure 1). Age, sex, clinical condition at admission, or method of aneurysm treatment did not differ substantially between the two

groups at baseline (table). Outcome data were unavailable for one patient in the placebo group and two in the magnesium group (99·8% of patients completed follow-up). One was homeless with no available address or phone number, the second had been included while on holiday in The Netherlands, and the third could not be reached.

Magnesium had no effect on the primary outcome; 158 (26·2%) of 604 patients in the magnesium group and 151 (25·3%) of 596 in the placebo group had a poor outcome (RR 1·03, 95% CI 0·85–1·25). The proportion of patients with no symptoms did not differ between the magnesium (46 of 604 patients; 7·6%) and placebo (46 of 596; 7·7%) groups (RR 0·99, 95% CI 0·67–1·46). Furthermore, the distribution of modified Rankin Scale scores between the magnesium and the placebo groups was not significantly different ($p=0·95$; figure 2).

Subgroup analyses for poor outcome showed much the same estimates of effect for women and men, old and young patients, good or poor clinical condition at admission, different methods of aneurysm treatment, and between centres that give magnesium for hypomagnesaemia (figure 3).

According to the protocol, investigators reported only unexpected serious adverse events. Study treatment was stopped for one patient because of asymptomatic hypocalcaemia, for two patients because of asymptomatic hypermagnesaemia, and for one patient because of suspected symptomatic hypermagnesaemia, all of which occurred in the magnesium group. The latter patient also had renal insufficiency but study treatment was not stopped for this reason. This patient violated the protocol, which stipulated stopping treatment when serum creatinine concentration was higher than 150 $\mu\text{mol/L}$.

We updated our previous meta-analysis.⁵ Without the inclusion of MASH 2 data, poor outcome did not differ between magnesium and placebo groups (RR 0·88, 95% CI 0·73–1·07), which is consistent with the results from another meta-analysis.²¹ Our final meta-analysis of 2047 patients, including the MASH 2 results, showed no difference between groups (RR 0·96, 0·84–1·10; figure 4).

Discussion

Results from MASH 2 alone, and in combination with the other trial data (panel), show that intravenous magnesium does not affect outcome after aneurysmal subarachnoid haemorrhage. Subgroup analyses did not identify a subgroup of patients who might benefit from magnesium treatment.

Various explanations exist for magnesium not improving outcome after aneurysmal subarachnoid haemorrhage. First, the putative pathophysiological mechanisms leading to delayed cerebral ischaemia and poor outcome after aneurysmal subarachnoid haemorrhage, which are targeted by magnesium treatment,^{6,9} might not be as important as other mechanisms that are not known to be affected by magnesium (eg, immediate ischaemia at the time of haemorrhage²²). Second,

Panel: Research in context

Systematic review

We updated our previous Cochrane review⁵ with articles indexed by Medline before Jan 31, 2012. We also searched the Cochrane Stroke Group Trials Register (up to April 2006) and Embase (up to March 2006) for randomised controlled trials comparing magnesium sulphate versus control in addition to nimodipine. We then searched the reference lists of identified articles and contacted stroke investigators for details of other published and unpublished studies. Two reviewers (SDMD and AA, WMvdB, or GJER) independently extracted the data and assessed trial quality based on masking, outcome, type of analysis, and loss to follow-up. We excluded studies without control groups and those that were open-label. We contacted investigators to obtain missing information. The results of our meta-analysis showed no difference between groups.

Interpretation

Randomised trials have suggested that magnesium is beneficial, but this finding was not reproduced in MASH 2.⁵ Previous studies were much smaller than MASH 2, and were not adequately powered, so the results might have been due to chance and might have been subject to publication bias. A randomised controlled trial of magnesium for aneurysmal subarachnoid haemorrhage—published when our study was still ongoing—was also neutral, but did not have enough power to definitely rule out an effect.²⁰ The MASH 2 trial is the first adequately powered randomised controlled trial that shows no beneficial effect of magnesium on outcome after aneurysmal subarachnoid haemorrhage, which is confirmed by our meta-analysis (figure 4).^{18–20}

magnesium is not known to affect other complications of aneurysmal subarachnoid haemorrhage that affect outcome, including hydrocephalus, rebleeding, electrolyte disturbances, hyperglycaemia, and cardiac and pulmonary dysfunction.²³ Third, intravenously administered magnesium does not seem to cross the blood–brain barrier well. Doubling serum magnesium leads to only an 11–21% increase in magnesium concentration in cerebrospinal fluid.²⁴ However, higher serum magnesium concentrations might cause systemic complications. Higher concentrations of magnesium in the subarachnoid space can be achieved by intracisternal infusion instead of intravenous infusions. This route of administration leads to intracranial vasodilatation but requires invasive techniques with cisternal and lumbar drains, which have higher risks of complication.²⁵ Finally, vasodilation of cerebral arteries by magnesium does not necessarily prevent delayed cerebral ischaemia and improve outcome, since vasoconstriction is not the only cause of delayed cerebral ischaemia.²⁶

Our trial has several strengths. The trial included many patients, was masked, and more than 99% of patients were followed up for assessment of a clinically relevant

outcome. The treatment that the participants received is probably representative of care for aneurysmal subarachnoid haemorrhage in middle-income to high-income countries. A substantial number of patients with poor clinical condition at admission were included, which also adds to the generalisability of our results. We have shown that a telephone interview is a reliable way of measuring the modified Rankin score in patients with aneurysmal subarachnoid haemorrhage.²⁷

A limitation of our study is that we collected key baseline and outcome data, but did not call patients back for study visits for detailed assessment of quality of life. Because our study was pragmatically designed to assess whether magnesium improved clinical outcome after aneurysmal subarachnoid haemorrhage, we chose poor outcome as our primary outcome measure. Delayed cerebral ischaemia is only a surrogate or explanatory outcome measure, and so we did not include delayed cerebral ischaemia as a secondary outcome. For the same reason, we did not include other baseline measurements such as amount of blood in CT scan or systemic illness, nor did we do close on-site monitoring.

Furthermore, we do not have complete information about adherence to study medication. We did not require magnesium concentration to be routinely checked, in view of the results of our dose-finding and safety studies.^{13,14} We cannot exclude the possibility of unmasking of investigators by checking patients' serum magnesium concentrations, although such unmasking will not have affected the primary or secondary outcome data, which were collected centrally by masked personnel. An effect of magnesium treatment on cognitive symptoms—which are common after aneurysmal subarachnoid haemorrhage²⁸—might have been missed by the modified Rankin Scale. We measured clinical outcome 3 months after haemorrhage, which is a usual period for outcome assessment in stroke studies, and although a benefit might be detected later, we consider it unlikely in view of the probable mechanism of action of magnesium in the acute period after aneurysmal subarachnoid haemorrhage.

Magnesium has been studied in patients with ischaemic stroke and intracerebral haemorrhage in the IMAGES trial,²⁹ which included almost 2600 patients, but did not show a beneficial effect on outcome. In the IMAGES trial, median time from symptom onset to treatment was 7 h (only 3% of patients were treated within 3 h), which might be too long after ischaemic damage for a neuroprotective effect. In our study, median time to treatment was 33 h in the magnesium group, which is similar to the median time in MASH 1 (28 h).¹⁰ In the same way, time to treatment with magnesium in MASH 2 might not have been short enough to ameliorate acute ischaemic injury and prevent delayed cerebral ischaemia because the initiation of the cascade leading to secondary injury might be irreversible.

The MASH 2 trial has implications for clinical practice. Administration of magnesium after aneurysmal

subarachnoid haemorrhage is standard practice in many centres. On the basis of the results of MASH 2—a trial of treatment of aneurysmal subarachnoid haemorrhage with sufficient power to detect a clinically significant improvement in outcome—and in combination with data from other trials, we do not recommend routine use of intravenous magnesium 64 mmol/day for the improvement of outcome after aneurysmal subarachnoid haemorrhage.

Contributors

SMDM coordinated the study, analysed and interpreted data and wrote the first draft of the report. WMvdB, GJER, and AA obtained funding, conceived, designed, and supervised the study, and contributed to subsequent versions of the report. RA-SS obtained funding for the study in Scotland. AA also analysed and interpreted data. WPV, FvK, HAJMK, JB, RJvO, RA-SS, and PML were local study investigators, organised the study, included patients, and helped revise the report. All authors approved the final report.

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Conflicts of interest

We have no conflicts of interest.

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