Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage
A Randomized Controlled Trial

Walter M. van den Bergh; on behalf of the MASH Study Group

Background and Purpose—Magnesium reverses cerebral vasospasm and reduces infarct volume after experimental subarachnoid hemorrhage (SAH) in rats. We aimed to assess whether magnesium reduces the frequency of delayed cerebral ischemia (DCI) in patients with aneurysmal SAH.

Methods—Patients were randomized within 4 days after SAH. Magnesium sulfate therapy consisted of a continuous intravenous dose of 64 mmol/L per day, to be started within 4 days after SAH and continued until 14 days after occlusion of the aneurysm. The primary outcome DCI (defined as the occurrence of a new hypodense lesion on computed tomography compatible with clinical features of DCI) was analyzed according to the “on-treatment” principle. For the secondary outcome measures “poor outcome” (Rankin ≥3) and “excellent outcome” (Rankin 0), we used the “intention-to-treat” principle.

Results—A total of 283 patients were randomized. Magnesium treatment reduced the risk of DCI by 34% (hazard ratio, 0.66; 95% CI, 0.38 to 1.14). After 3 months, the risk reduction for poor outcome was 23% (risk ratio, 0.77; 95% CI, 0.54 to 1.09). At that time, 18 patients in the treatment group and 6 in the placebo group had an excellent outcome (risk ratio, 3.4; 95% CI, 1.3 to 8.9).

Conclusions—This study suggests that magnesium reduces DCI and subsequent poor outcome, but the results are not yet definitive. A next step should be a phase III trial to confirm the beneficial effect of magnesium therapy, with poor outcome as primary outcome. (Stroke. 2005;36:1011-1015.)

Key Words: ischemia ■ magnesium ■ randomized controlled trials ■ subarachnoid hemorrhage

Because of its occurrence at young age and its often poor outcome, the loss of productive life years from subarachnoid hemorrhage (SAH) is as large as that from ischemic stroke, the most frequent cause of stroke.1 Death or dependence occurs in ≈70% of patients and is attributed to delayed cerebral ischemia (DCI) in approximately one third of all patients with poor outcome.2,3 DCI occurs most frequently between 4 and 10 days after the hemorrhage.4,5 Despite many years of research, the effectiveness of treatment to prevent or reverse it is modest.6 The current mainstay of treatment is nimodipine and maintaining normovolemia, but even with this strategy, DCI occurs in ≥27% of patients. Reducing the frequency and consequences of DCI will improve the outcome after SAH. The interval between the bleeding and the onset of DCI provides an opportunity for preventive treatment. This is a major advantage compared with cerebral ischemia from a thromboembolic event, in which neuroprotective agents can only be given after the onset of ischemia.

Hypomagnesemia occurs in >50% of patients with SAH and is related to the occurrence of DCI and poor outcome after 3 months.7 Magnesium was shown to have a neuroprotective effect in numerous stroke models, and it reversed cerebral vasospasm and reduced ischemic depolarization time and infarct volume after experimental SAH in rats.8–10 Putative mode of actions of magnesium include inhibition of the release of excitatory amino acids and blockade of the N-methyl-D-aspartate–glutamate receptor.11,12 Magnesium is also a noncompetitive antagonist of voltage-dependent calcium channels and has a dilatatory effect on cerebral arteries. Magnesium is readily available, inexpensive, and has a well-established clinical profile in obstetrical and cardiovascular practice.13,14 In the current study, we aimed to assess whether intravenous magnesium sulfate, started within 4 days after SAH onset, reduces the frequency of DCI in patients with aneurysmal SAH.

Methods
Between November 2000 and January 2004, we enrolled patients in the Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage (MASH) trial. This study was a randomized, double-blind, placebo-controlled multicenter trial with a factorial design: magnesium versus placebo and acetylsalicylic acid versus placebo. Only the results of the magnesium part of the trial are presented here. The
ethics committees of the participating hospitals approved the protocol of the trial.

Patients were included when they could be randomized within 4 days after aneurysmal SAH. The diagnosis of SAH was based on a positive computed tomography (CT) scan or xanthochromia of cerebrospinal fluid. Aneurysmal SAH was diagnosed if an aneurysm was present on conventional or CT/magnetic resonance angiography. If the CT scan showed a typical aneurysmal pattern of hemorrhage, the CT scan was negative, and xanthochromia of cerebrospinal fluid with an aneurysm by angiography confirmed the diagnosis of aneurysmal SAH. Exclusion criteria for the study were nonaneurysmal causes for SAH, renal failure (serum creatinin >150 μmol/L), age <18 years, no informed consent, or imminent death. The clinical condition at admission was assessed with the World Federation of Neurological Surgeons (WFNS) scale.15 A dichotomy was made between good neurological condition (WFNS score I, II, or III) and poor neurological condition (WFNS score IV or V) at admission.

We assessed the amount of cisternal and ventricular blood on the initial CT scan according to the method described by Hijdra et al.16 The sum scores of blood in the cisterns (range 0 to 30) and ventricles (range 0 to 12) were dichotomized at their median value. All patients were kept under close observation, with continuous monitoring of blood pressure, heart rate, ECG, and arterial oxygen saturation for at least 2 weeks after the onset of SAH. They were treated according to a standardized protocol that consisted of absolute bed rest until aneurysm treatment, administration of nimodipine, cessation of antihypertensive medication, and intravenous administration of fluid aiming for normovolemia. Recurrent bleeding was defined as a sudden clinical deterioration with evidence of fresh blood on a CT scan compared with a previous scan.

Interventions

Study medication was produced, randomized, and distributed by the University Medical Center Utrecht and stored at all participating centers. Magnesium sulfate therapy consisted of a continuous intravenous dose of 64 mmol/L per day, which started immediately after randomization and continued until 14 days after occlusion of the aneurysm, or for a maximum of 18 days after the onset of SAH when aneurysm treatment was performed >4 days after SAH onset. The placebo consisted of 50 mL of normal saline. The dose regime of 64 mmol/L per day was based on a dose finding study17 and aimed at maintaining serum magnesium levels within the range of 1.0 to 2.0 mmol/L during magnesium treatment. Monitoring of serum magnesium levels was not obligatory for the trial, but in 2 participating centers, magnesium measurements were part of clinical management. The principal investigators of the trial remained blinded for serum magnesium levels.

Outcomes

Because at this stage we aimed at preventing DCI rather than improving overall outcome, the predefined primary outcome measurement was the occurrence of DCI within 3 months after onset of SAH. Three months after the SAH, we assessed functional outcome with the modified Rankin Scale, a 6-point handicap scale that focuses on restrictions in lifestyle, by means of a telephone interview. The Rankin Scale, frequently used in stroke outcome research, is easy to administer and reliable in terms of interobserver agreement.18–20 Secondary predefined outcome measurements were: (1) occurrence of any new hypodensity on brain CT regardless of its cause; (2) death or disability (poor outcome), defined as a Rankin score of 4 or worse; and (3) nonexcellent outcome, defined as the proportion of patients with a Rankin score of 1 or worse. With a Rankin score of 0 (excellent outcome), the patient is considered having no symptoms, corresponding with a good quality of life.21 All CT scans made after SAH onset were analyzed for new hypodensities by 3 members of the steering committee always in the presence of the principal investigator (G.J.E.R.). All members of the steering committee who scored the CT scans were blinded for treatment allocation. Hypodensities on CT scan were classified according to the presumed origin as follows: (1) representing “spontaneous” cerebral ischemia; (2) caused by operation or endovascular treatment; (3) associated with the initial hemorrhage, usually an intracerebral hematoma; (4) caused by placement of a ventricular catheter; and (5) other. The primary outcome was defined as the occurrence of a new spontaneous hypodensity lesion as revealed by a CT scan compatible with clinical features of DCI (gradually developed focal deficits, decreased level of consciousness, or both). In case of uncertainty about the cause of postoperative hypodensities, the report of the operation was reviewed. After weighing all data, the committee came to a consensus. Patients with an uneventful clinical course in which no control CT scan was made were scored as having no new hypodensities.

Data Analysis

Trial design and conduct for the primary outcome DCI and for the secondary outcome “any hypodensity on CT” were according to the “on-treatment” principle. The secondary outcome measures “poor outcome” and “nonexcellent outcome” were analyzed according to the “intention-to-treat” principle.

To assess the effect of treatment on outcome at 3 months, we estimated risk ratios (RRs) with corresponding 95% CIs. For this clinical relevant outcome measurement, we used an intention-to-treat analysis.

Results

Infusion of the trial medication was begun in all 283 randomized patients, and no patients were lost to follow-up (Figure). No major side effects occurred (Figure legend). Patients were well matched for baseline data, including treatment of the aneurysm (Table 1).

In the explanatory, on-treatment analysis, magnesium treatment reduced the risk of the primary outcome measure DCI by 34% (hazard ratio, 0.66; 95% CI, 0.38 to 1.14), with a number needed to treat (NNT) of 14 (Table 2). There was no reduction of risk for the outcome event “any new hypodensities on CT, regardless of cause” (RR, 1.04; 95% CI, 0.79 to 1.37). In the intention-to-treat analysis, the risk reduction for poor outcome at 3 months was 23% (RR, 0.77; 95% CI, 0.54 to 1.09; NNT, 12). At that time, 18 patients in the treatment group had an excellent outcome (Rankin grade 0) compared with 6 patients in the placebo group. The relative risk for excellent outcome was 3.4 (95% CI, 1.3 to 8.9; NNT 11). In an intention-to-treat analysis of the primary outcome measure DCI, the hazard ratio was 0.61 (95% CI, 0.36 to 1.04).

Discussion

This study suggests that magnesium reduces DCI and subsequent poor outcome in patients with SAH, but the results are not yet definitive. The increase in excellent outcome in patients treated with magnesium was statistically significant,
Flow diagram of the progress through the phases of the trial.

We have no specified information on how many patients were assessed for eligibility or the reasons why they were excluded for randomization. Seventeen patients allocated to magnesium treatment discontinued intervention for the following reasons: no aneurysmal SAH (4); hypotension (1); phlebitis (2); bradycardia and atrium fibrillation (1); routine magnesium suppletion (1); hypermagnesemia (3); renal failure (1); death imminent (1); request of patient or family (1); and unreliable registration of treatment administration (2). Seventeen patients allocated to saline treatment discontinued intervention for the following reasons: no aneurysmal SAH (5); phlebitis (1); intracranial hematoma (1); trial medication lost (1); routine magnesium suppletion (1); request of patient or family (2); and unreliable registration of treatment administration (4).

but this predefined outcome measurement was not the primary aim of the analysis.

Although hypomagnesemia is associated with DCI and poor outcome,7 we aimed at reaching therapeutic serum magnesium levels instead of magnesium suppletion alone. Because magnesium intoxication, manifested by nausea, headache, and muscle weakness, can occur from levels of 2.0 mmol/L onward, our purpose was to maintain a serum magnesium level within the range of 1.0 to 2.0 mmol/L during magnesium treatment.

The result of our study is in line with the neuroprotective effect attributed to magnesium in several animal studies and small clinical trials.9,10,24,25 The only other randomized trial so far showed that “clinical vasospasm,” defined as a new focal neurological deficit that could not be accounted for by other cause, occurred in 6 of 20 patients receiving magnesium sulfate and in 5 of 16 patients receiving placebo (RR, 0.96; 95% CI, 0.36 to 2.6).26 Poor outcome occurred in 7 of 20 patients receiving magnesium sulfate and in 8 of 16 patients receiving placebo (RR, 0.70; 95% CI, 0.32 to 1.5).

In our study, we chose to analyze DCI and not vasospasm because vasospasm by itself does not always lead to DCI, quite apart from the practical problems of measuring arterial narrowing. However, prevention of DCI is only an indirect measure for a beneficial effect of magnesium treatment. A conclusive trial with functional recovery as primary outcome measure would have required a larger number of patients. We chose to start with an “explanatory” study with a proof-of-concept design.27 For the primary outcome measurement, regarding the explanatory research question, we used an on-treatment analysis. Because on-treatment analysis is improper for measuring the clinically more relevant effect on outcome, we used intention-to-treat analysis instead. Unfortunately, it turned out that we underpowered the study because we used the strict criteria for DCI as primary outcome measure rather than all hypodensities on CT scanning. This reduced the frequency of the primary outcome in the control group from the expected 50% (data pilot study)22 to 25%. Thanks to a relatively high inclusion rate, we could increase the number of patients within the 3-year randomization period from 200 to 283. The sizable proportion of patients with a poor clinical condition on admission (24%) indicates that this group of patients is well represented, allowing generalization of our study results to patients with SAH in general.

Our primary outcome measure did not include silent infarctions; however, these were contained in the secondary outcome measure “new hypodensities on CT.” We do not consider it likely that many patients who had an uneventful clinical course, and thereby no indication for a new CT scan, would have had a silent infarct at their scan, had it been made. Hence, we do not think that such additional scans, without a clinical indication, would have had a major influence on this secondary outcome. Moreover, we find the deterioration of the patient resulting in CT scanning an important aspect of the primary outcome measure because it already incorporates elements that are important for the patient, elements that will be taken into account to a greater extent in the primary outcome “poor outcome” of the phase III clinical trial that we have planned.

Given the supposed mode of action of magnesium treatment, one might expect a benefit of magnesium treatment in ischemic stroke. However, the recently published results of the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial showed that magnesium given within 12 hours of acute stroke did not reduce the risk of poor outcome.28 That magnesium treatment might nevertheless be beneficial in SAH is suggested by differences in pathophysiology and dose regime. In the IMAGES trial, treatment was started within 12 hours after stroke onset; however, the majority of patients received medication beyond 6 hours, with only 3% treated within 3 hours. In ischemic stroke, this could mean that most of the damage had already occurred. At the other end of the time frame, treatment was maintained for only 24 hours. However, the ischemic cascade continues for >24 hours.29 This leaves the possibility that secondary brain damage such as apoptosis was not counteracted. Because magnesium plays an important role in DNA stabilization, the potential beneficial effects of magnesium may not have been used in this manner. Although in our study population, the median start of treatment was 28 hours, it was continued for at least 2 weeks. Given the biphasic pattern of ischemia in SAH, it might be possible to prevent secondary brain ischemia. The results of our study suggest that prevention of ischemia with magnesium is more effective than treatment after onset of the ischemic event. Extended use of magnesium sulfate is needed to cover the period at risk for DCI.26

The risk reduction of magnesium is added to the risk reduction already achieved with the routinely administrated N-type calcium channel antagonist nimodipine. Nimodipine reduces the proportion of patients with poor outcome and ischemic neurological deficits after aneurysmal SAH.4 Because the actions of nimodipine and magnesium have an
overlap, the protective effect of magnesium by itself shown in this study may have been underestimated.

The results of this study suggest that magnesium reduces ischemic complications after SAH and thereby may reduce the risk of poor outcome after SAH, but as yet, the evidence for the introduction of magnesium treatment in clinical practice is inconclusive. A large phase III trial with “poor outcome” as the primary measure of outcome should provide final evidence for the effect of magnesium therapy in addition to the standard therapy. On the basis of the results of this study, 1101 patients are needed, which makes it feasible for an international trial to produce definitive results in just a few years. Given the fact that magnesium is safe and inexpensive, and has a small NNT in this phase II trial, even a small absolute benefit would lead to an enormous cost saving for health care services.

Appendix

Contributions of Authors and Study Group

Steering and Writing Committee
W.M. van den Bergh (study coordinator), A. Algra, F. van Kooten, C.M.F. Dirven, J. van Gijn, M. Vermeulen, and G.J.E. Rinkel (chair, principal investigator).

| TABLE 1. Baseline and Outcome Data According to Allocated Treatment |
|-----------------------------|------------------------------|-----------------------------|-----------------------------|
| Total n=283 | Intention to Treat | On Treatment n=249 |
| Mg | Placebo | Mg | Placebo |
| Total | 283 | 139 | 144 | 122 | 127 |

Baseline data

- No. randomized | 283 |
- Type of disease
  - Aneurysmal SAH (%) | 274 (97) |
  - Perimesencephalic SAH (%) | 4 (1) |
  - Other (%) | 5 (2) |
- Mean age | 54.6 |
- Women (%) | 184 (65) |

Clinical condition at admission

- WFNS I (%) | 133 (47) |
- WFNS II (%) | 68 (24) |
- WFNS III (%) | 13 (5) |
- WFNS IV (%) | 43 (15) |
- WFNS V (%) | 26 (9) |
- WFNS ≥4 (%) | 69 (24) |

- No. of patients with cisternal blood above median 23, (%) | 171 (60) |
- No. of patients with ventricular blood above median 2, (%) | 94 (33) |
- Intracranial hematoma amount (%) | 14 (5) |

Treatment aneurysm

- Surgery (%) | 155 (55) |
- Endovascular treatment (%) | 74 (26) |
- None | 54 (19) |
- Mean start study medication (h; median) (%) | 35 (28) |

Recurrent bleeding (%) | 41 (15) |

Outcome measurements

- New hypodensities on CT (%) | 128 (45) |
- DCI (%) | 57 (20) |
- Poor outcome, Rankin >3 (%) | 89 (31) |
- Excellent outcome, Rankin 0 (%) | 24 (8) |

| TABLE 2. Outcomes in the Trial According to Magnesium Treatment |
|-----------------------------|-----------------------------|
| RR (95% CI) | NNT |
| Primary outcome |
| DCI* | 0.66 (0.38–1.14)‡ | 14 (35 NNTH to 6 NNTB) |
| Secondary outcomes |
| New hypodensities on CT* | 1.04 (0.79–1.37) - |
| Poor outcome† | 0.77 (0.54–1.09) | 12 (37 NNTH to 5 NNTB) |
| Excellent outcome† | 3.4 (1.3–8.9) | 11 (7 NNTH to 43 NNTB) |

*On-treatment analysis; †intention-to-treat analysis; ‡hazard ratio.
Poor outcome is defined as a Rankin score of 4 or worse; excellent outcome is defined as a Rankin score of 0; this is a positive outcome, with an RR >1. NNTH indicates No. needed to benefit 1 patient; NNTH, No. needed to treat to harm 1 patient.

Downloaded from http://stroke.ahajournals.org/ by guest on September 22, 2017
Executive Committee
W.M. van den Bergh, A. Algra, M. van Buuren, and G.J.E. Rinkel.

Data Monitoring Committee

Participating Centers and Investigators (number enrolled patients per center)
University Medical Center Utrecht, Utrecht, The Netherlands (216): Departments of Neurosurgery (W.M. van den Bergh and J.W. Berkelbach van der Sprenkel), Neurology (W.M. van den Bergh, G.J.E. Rinkel, A. Algra, J. van Gijn, and M. van Buuren), Pharmacy (E.V. Uijtendaal), and Julius Center for General Practice and Patient-Oriented Research (A. Algra).
Erasmus Medical Center, Rotterdam, The Netherlands (40): Department of Neurology (S.L.M. Bakker and F. van Kooten).
VU University Medical Center, Amsterdam, The Netherlands (20): Department of Neurosurgery (C.M.F. Dirven).
Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (7): Departments of Neurosurgery (K.W. Albrecht) and Neurology (M. Vermeulen).

Development of Study Protocol

Inclusion of Patients

Outcome Assessment of Patients

Data Management
M.vB. and E.V.U.

Data Analysis
W.M.vdB. and A.A.

Independent Data Monitoring Committee

Executive Committee

Acknowledgments
We gratefully acknowledge the Netherlands Heart Foundation (grant 99.107) for financially supporting this study. Professor Rinkel is a clinical established investigator of the Netherlands Heart Foundation (grant D98.014). The funding source had no involvement in the study design, collection, analysis, and interpretation of data in writing of the report or in the decision to submit the article for publication.

References
Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial

Walter M. van den Bergh
on behalf of the MASH Study Group

Stroke. 2005;36:1011-1015; originally published online March 24, 2005;
doi: 10.1161/01.STR.0000160801.96998.57

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/5/1011