

Magnesium Sulfate Administration in Subarachnoid Hemorrhage

Jose I. Suarez · The Participants in the International Multidisciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

Published online: 12 July 2011
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Abstract Magnesium offers theoretic vascular and neuroprotective benefits for patients with subarachnoid hemorrhage. An electronic literature search was conducted to identify original research studies describing intravenous magnesium treatment in patients with SAH published in English between January 1990 and October 2010. Seventeen articles were identified and reviewed, including one phase III randomized-controlled clinical trial and six phase II randomized-controlled trials. Study quality was low for most of the included studies, with the phase III trial considered to be of moderate quality. Due to inconsistently reported benefits and the occurrence of side effects, phase II data suggested that intravenous magnesium for SAH provided either no overall net benefit or uncertain trade-offs. Benefit was likewise not supported in the single phase III clinical trial.

Keywords Delayed cerebral ischemia · Infusion · Intravenous · Neuroprotection · Vasospasm

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Introduction

Magnesium is a noncompetitive calcium antagonist with several important vascular and potentially neuroprotective effects [1, 2]. For instance, magnesium can lead to vasodilatation by blocking the voltage-dependent calcium channel and decreasing glutamate release and the entry of calcium into the cell [3, 4]. In addition, magnesium also attenuates the effect of various potent vasoconstrictors, such as endothelin 1, and blocks the formation of reactive oxygen species [5].

These potentially helpful effects of magnesium on vasodilation and consequent neuroprotection has led some investigators to study the ability of magnesium to prevent of cerebral vasospasm and delayed cerebral ischemia after subarachnoid hemorrhage (SAH). This manuscript was designed to examine the current level of evidence for a role of magnesium in SAH management.

Methods

A Pubmed and EMBASE (Ovid) literature search was conducted for studies investigating the treatment of SAH with intravenous magnesium, using the key word “magnesium” plus at least one of the following additional terms: “subarachnoid hemorrhage,” “neuroprotection,” “clinical trials,” “cerebral vasospasm,” “delayed ischemic deficit,” and “clinical outcome.” Papers could be included if they reported on original studies with human subjects and were published in English between January 1990 and October 2010. Selected articles were those that directly addressed intravenous magnesium treatment in patients with SAH. Quality of data for each included study was determined using the GRADE approach [6].

Summary of Literature

Seventeen papers were included in this review: one phase III randomized-controlled clinical trial [7], six phase II randomized-controlled trials [8–13], one phase I trial [14], four prospective case series [15–18], two case–control studies [19, 20], two retrospective case series [21, 22], and one case report [23]. Study details and quality are described in Table 1.

The quality of most of the studies was low or very low, with the lowest quality given to case–control, case series, and case reports. Although still generally representing fairly low quality, more complete data were provided through phase II and III studies.

Phase I–II Studies

All phase II studies enrolled adult patients who were treated within the first 72 h of symptom onset. There were important differences in methodology among the studies and several limitations. Dosages of magnesium infusions varied among studies and only one paper presented a rational explanation for choosing the rate and quantity of magnesium infused. The latter was based in the only phase I study investigating the safest of 3 different dosage regimens [19]. However, the authors failed to mention how they reached the sample size chosen for their dose-escalation study. Despite this caveat, a review of available phase II data suggests that an infusion of 64 mmol/day of magnesium sulfate is safe in patients with SAH.

Another difficulty with the interpretation of phase II clinical trials is that the primary and secondary outcome measures employed also differed among studies. Reported outcome used a range of potential endpoints, including good or poor outcome defined by the Glasgow outcome scale (GOS), frequency of symptomatic vasospasm or delayed cerebral ischemia (DCI), and the occurrence of adverse events. Differences in the outcome measures make direct comparisons between studies difficult.

Additional limitations included varied aneurysm treatment and relatively small sample sizes. Most patients entered into these trials were treated with surgical clipping for their ruptured cerebral aneurysms; however, other treatments were also used. Sample sizes ranged from 40 to 283 patients. Only one of these studies mentioned power or sample size calculations.

The largest phase II study was powered based on the assumption that intravenous magnesium would reduce the risk of hypodense lesions on computed tomography (CT) by 40% ($1-\beta = 80\%$ with $\alpha = 5\%$) [10]. Patients received active treatment with magnesium sulfate as a continuous infusion at 64 mmol/l per day until 14 days after aneurysm treatment or up to a maximum of 18 days ($n = 139$), or

saline placebo ($n = 144$). There was no reduction of risk for the outcome of any new hypodensity on CT (the primary endpoint), regardless of cause (RR 1.04; 95% CI 0.79–1.37). DCI (not defined in the article) was reduced by 34% (HR 0.66; 95% CI 0.38–1.14) in the magnesium-treated group, with a number needed-to-treat to benefit one patient of 14. A total of 18 magnesium-treated patients and 6 placebo patients experienced an excellent outcome (RR 3.4; 95% CI 1.3–8.9). Because this was a prospective, randomized, controlled study, the initial grading was high. However, quality was downgraded to low since this was a phase II study and was not powered to detect differences in a meaningfully important clinical outcome.

Most of phase II studies included in this review reported no difference in adverse events between magnesium and placebo. However, the study by Muroi et al. [12] reported hypotension in 3 patients with placebo versus 15 with magnesium infusion (11% vs. 48%, $P = 0.04$) and hypocalcemia in no placebo patients versus 8 with magnesium (0% vs. 26%, $P = 0.005$). Furthermore, magnesium infusion had to be stopped in 16 patients (52%) due to side effects. Based on these results, phase II data suggest either no net benefit or uncertain trade-offs with intravenous magnesium for SAH.

Phase III Studies

The only phase III study published at the time of this review studied 327 adult patients with SAH who received study medication within 48 h of symptom onset [7]. Outcomes were clearly defined. The primary outcome was achieving a favorable outcome using the extended GOS (GOSE 5–8) at 6 months. Secondary outcome measures included clinical vasospasm within 2 weeks, modified Rankin scale score 0–2 at 6 months, Barthel Index ≥ 85 at 6 months, and quality of life SF-36 at 6 months. Achieving a favorable GOSE at 6 months was similar with intravenous magnesium and placebo (64% vs. 63%; OR 1.0, 95% CI 0.7–1.6). There were likewise no differences in all secondary outcomes. Predefined subgroups based on age, admission world federation of neurosurgical societies (WFNS) grading, preexisting hypertension, intracerebral hemorrhage, intraventricular hemorrhage, location of aneurysm, or size of aneurysm did not affect outcomes. Hypotension (SBP < 90 mmHg requiring vasopressors) occurred in 15% treated with magnesium versus 13% with placebo ($P = 0.590$). Mortality rate was similar between treatments (10% with magnesium vs. 12% in placebo). There were no between-treatment differences in incidences of heart failure, renal failure, pneumonia, sepsis, pulmonary emboli, myocardial infarction, or gastrointestinal bleeding.

The initial grading of this trial was high, based on the phase III clinical trial design. However, grading was

Table 1 Summary of studies reviewed

Citation	Type of study	N	Main findings	Aneurysm treatment	Limitations	Final grade	Quality of evidence	Balance of risk versus harm
Wong, et al. [7]	RCT phase III	327	GOSE at 6 months was similar: 64% magnesium versus 63% placebo (OR 1.0; 95% CI 0.7–1.6). No difference in all secondary outcomes	141 clipping (43%), 157 coiling (48%), 28 no treatment (8%)	Lack of on-site trial monitoring; lack of daily blood pressure data; hypotension threshold definition too low	Low	Moderate	No net benefit
Westermaier et al. [8]	RCT phase II	107	Delayed ischemic infarction: 22% with magnesium versus 51% placebo ($P = 0.0020$; OR 0.28; 95% CI 0.12–0.64). No difference in DIND, GOS at 6 months, or mortality	47 clipping (44%), 53 coiling (49%), 7 conservative (6%)	Single center; not powered to detect difference in long-term clinical outcome; adverse events not clearly defined	Low	Low	Uncertain trade-offs
Wong et al. [9]	RCT phase II	60	Favorable outcome in 66% with magnesium group versus 54% placebo (OR 1.43; 95% CI 0.68–3.06). No difference in BI and NIHSS	40 clipping (67%), 17 coiling (28%), 3 no treatment (5%)	Single center; not powered to detect differences in long-term clinical outcome; no power calculation or sample size mentioned; adverse events not clearly defined	Low	Low	Uncertain trade-offs
van den Bergh et al. [10]	RCT phase II	283	Patients in magnesium group had DCI reduced by 34% (HR 0.66; 95% CI 0.38–1.14) with NNT of 14	155 clipping (55%), 74 coiling (26%), 54 (19%) none	Not powered to detect differences in long-term clinical outcome	Low	Low	Uncertain trade-offs
Schmid-Elsasser et al. [11]	RCT phase II	104	Infarction attributable to VSP in 19% ($N = 10$) with magnesium and 22% ($N = 11$) with nimodipine. There was no difference in clinical outcomes	78 clipping (75%), 22 coiling (21%), 4 conservative	Not powered to detect differences in long-term clinical outcome; sample size calculations not mentioned	Low	Low	Uncertain trade-offs
Muroi et al. [12]	RCT phase II	58	TCD-detected VSP in 39% ($N = 12$) with magnesium and 37% ($N = 10$) placebo ($P = 0.085$). Good recovery at 3 months: 48% ($N = 15$) with magnesium and 22% ($N = 6$) placebo ($P = 0.083$). Treatment was stopped in 52% of patients because of side effects	56 clipping (97%), 2 coiling (3%)	No mention of sample size calculation; no mention as to who interpreted head CT scans	Low	Low	No net benefit
Veyna et al. [13]	RCT phase II	40	Good outcome (GOS 4–5) in 65% with magnesium and 50% placebo ($P = 0.36$). Symptomatic VSP in 30% with magnesium and 31% placebo ($P > 0.84$)	Clipping or coiling, with no breakdown mentioned	No mention of sample size calculation; no definitions of adverse events; unclear as to whether outcomes were obtained by blinded assessor	Low	Low	No net benefit

Table 1 continued

Citation	Type of study	N	Main findings	Aneurysm treatment	Limitations	Final grade	Quality of evidence	Balance risk versus harm
van den Bergh et al. [14]	phase I dose-finding	14	Serum magnesium levels were 1.03 ± 0.14 mmol/l with 16 mmol bolus plus 16 mmol/day infusion, 1.1 ± 0.15 with 30 mmol/day infusion, and 1.38 ± 0.18 with 64 mmol/day infusion. All patients in group 16 mmol bolus plus infusion group experienced facial flushing during bolus injection. No other side effects	10 clipping (71%), 3 coiling (21%), 1 no treatment	No mention of how decision to next dose was reached or how treatments were allocated; no mention of sample size calculations	Very low	Very low	Uncertain trade-offs
Stippler et al. [15]	Retrospective case-control	76	Symptomatic VSP in 18% ($N = 7$) with magnesium and 42% ($N = 16$) in controls ($P = 0.025$; OR 1.99; 95% CI 0.99–3.7). No difference in the other clinical outcome measures	33 clipping (43%), 43 coiling (57%)	No mention of power or sample size calculation; no mention of medication-associated adverse effects; no mention of rationale for dose chosen	Very low	Very low	Uncertain trade-offs
Boet and Mee [16]	Prospective case series	10	TCD VSP in 5 patients, symptomatic VSP in 3. Two patients had GOS of 3 and the others 5	9 clipping, 1 coiling	No controls; small sample size	Very low	Very low	Uncertain trade-offs
Brewer, et al. [17]	Prospective cross-over	14	No difference in TCD MCBFVs after treatment. Symptomatic VSP in 4 patients	10 clipping, 2 coiling, 1 angio negative, 2 failed	Cross-over design; no mention of sample size calculation	Very low	Very low	No net benefit
Mori et al. [18]	Prospective case series	10	Nine patients experienced increased vessel diameter from 7 to 40%. MCBFVS improved in 6 patients. Five patients had “good recovery” at 6 months (not well defined), 1 moderate disability, 1 severe disability (developed meningitis), and 3 were vegetative	10 clipping	Small sample size; no controls; high complication rates	Very low	Very low	No net benefit
Friedlich et al. [19]	Retrospective case series	85	24 patients in the “no magnesium” group (52%) experienced clinical VSP compared to 6 in the “magnesium” group (15%)	Patients receiving magnesium: 15 clipping (38%), 24 coiling (62%). Patients without magnesium: all 46 clipping (100%)	Small sample size; retrospective	Very low	Very low	Uncertain trade-offs
Kerz et al. [20]	Retrospective case-control	93	DCI in five patients (18%) receiving statin and magnesium, five (24%) receiving statin, and eight (16%) without either treatment. No difference in mortality. Hypotension in 22% of patients	45 clipping, 32 coiling, 14 no treatment	Small sample size; retrospective; no power analysis	Very low	Very low	Uncertain trade-offs

Table 1 continued

Citation	Type of study	N	Main findings	Aneurysm treatment	Limitations	Final grade	Quality of evidence	Balance of risk versus harm
Yahia et al. [21]	Prospective case series	19	Clinical VSP in 2 (11%) patients. No adverse cardiovascular events reported. No deaths. Most patients had "good outcomes": GOS 5 in ten patients and GOS 4 in eight patients	Not mentioned	Small sample size; no controls	Very low	Very low	Uncertain trade-offs
Shah et al. [22]	Retrospective case series	14	No infarctions in 12 patients (86%). No difference in angiograms or clinical outcomes between this cohort and historic controls	Not mentioned	Small sample size; no controls	Very low	Very low	Uncertain trade-offs
Barile et al. [23]	Case report	1	12.2% decrease in MCBFV for 4 h. Patient developed cerebral ischemia in left MCA (affected vessel)	No treatment	Single case report	Very low	Very low	Uncertain trade-offs

BI Barthel index, *CI* confidence interval, *CT* computed tomography, *DCI* delayed cerebral ischemia, *DIND* delayed ischemic neurologic deficit, *GOS* Glasgow outcome scale, *GOSE* extended Glasgow outcome scale, *MCA* middle cerebral artery, *MCBFV* mean cerebral blood flow velocity, *N* number of subjects, *NIHSS* national institute of health stroke scale, *NNT* number needed to treat, *OR* odds ratio, *RCT* randomized controlled trial, *RR* relative risk, *TCD* transcranial Doppler ultrasound, *VSP* vasospasm

reduced to moderate quality of evidence due to: lack of on-site trial monitoring, absence of daily blood pressure data, and the use of a hypotension threshold definition considered to be lower than what is typically used in clinical practice.

Conclusion

Limited low to moderate quality data on intravenous magnesium treatment during SAH are available through clinical trials, with very low quality data from case series and a case report. While maintaining magnesium within normal limits in patients with SAH is reasonable, the current evidence does not support routine use of continuous intravenous infusions of magnesium sulfate in patients with SAH. Furthermore, significant side effects associated with intravenous magnesium may offset any potential benefit.

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