Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage (IMASH)

A Randomized, Double-Blinded, Placebo-Controlled, Multicenter Phase III Trial

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Background and Purpose—Pilot clinical trials using magnesium sulfate in patients with acute aneurysmal subarachnoid hemorrhage have reported trends toward improvement in clinical outcomes. This Phase III study aimed to compare intravenous magnesium sulfate infusion with saline placebo among such patients.

Methods—We recruited patients with aneurysmal subarachnoid hemorrhage within 48 hours of onset from 10 participating centers. The patients were randomly assigned to magnesium sulfate infusion titrated to a serum magnesium concentration twice the baseline concentration or saline placebo for 10 to 14 days. Patients and assessors were blinded to treatment allocation. The study is registered at www.strokecenter.org/trials (as Intravenous Magnesium Sulphate for Aneurysmal Subarachnoid Hemorrhage [IMASH]) and www.ClinicalTrials.gov (NCT00124150).

Results—Of the 327 patients recruited, 169 were randomized to receive treatment with intravenous magnesium sulfate and 158 to receive saline (placebo). The proportions of patients with a favorable outcome at 6 months (Extended Glasgow Outcome Scale 5 to 8) were similar, 64% in the magnesium sulfate group and 63% in the saline group (OR, 1.0; 95% CI, 0.7 to 1.6). Secondary outcome analyses (modified Rankin Scale, Barthel Index, Short Form 36, and clinical vasospasm) also showed no significant differences between the 2 groups. Predefined subgroups included age, admission World Federation of Neurological Surgeons grade, pre-existing hypertension, intracerebral hematoma, intraventricular hemorrhage, location of aneurysm, size of aneurysm, and mode of aneurysm treatment. In none of the subgroups did the magnesium sulfate group show a better outcome at 6 months.

Conclusions—The results do not support a clinical benefit of intravenous magnesium sulfate infusion over placebo infusion in patients with acute aneurysmal subarachnoid hemorrhage. **(*Stroke*. 2010;41:921-926.)**

Key Words: aneurysm ■ intracranial aneurysm ■ magnesium ■ subarachnoid hemorrhage

Although spontaneous subarachnoid hemorrhage accounts for only 3% to 5% of all strokes and 4.4% of deaths from stroke, the relative youth of the affected individuals means that this event is responsible for approximately 25% of all years of life lost as a result of stroke.[1–3] Complications such as early brain injuries and delayed ischemic neurological deficits remain a major cause of morbidity and mortality in this group of patients.

Pilot clinical trials using magnesium sulfate in patients with acute aneurysmal subarachnoid hemorrhage have reported trends toward reduction in delayed cerebral ischemia and improvement in clinical outcomes.[4–11] As a result, some referral centers have started the practice of routine magnesium sulfate infusion in patients with aneurysmal subarachnoid hemorrhage. Given the results of these pilot clinical trials, a Phase III clinical trial for magnesium sulfate infusion after aneurysmal subarachnoid hemorrhage was needed to establish or confirm its potential benefit. The study objective was thus to test the hypothesis that intravenous magnesium sulfate infusion for 10 to 14 days, in addition to oral nimodipine, improves the neurological outcome in terms of the Extended Glasgow Outcome Scale[12,13] at 6 months in patients with acute aneurysmal subarachnoid hemorrhage.

Methods

This study was an academically funded, investigator-initiated, multicenter, randomized controlled trial with blinded outcome assessment conducted at multiple sites in Hong Kong, China, Southeast

Received October 22, 2009; final revision received January 13, 2010; accepted January 19, 2010.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.109.571125**

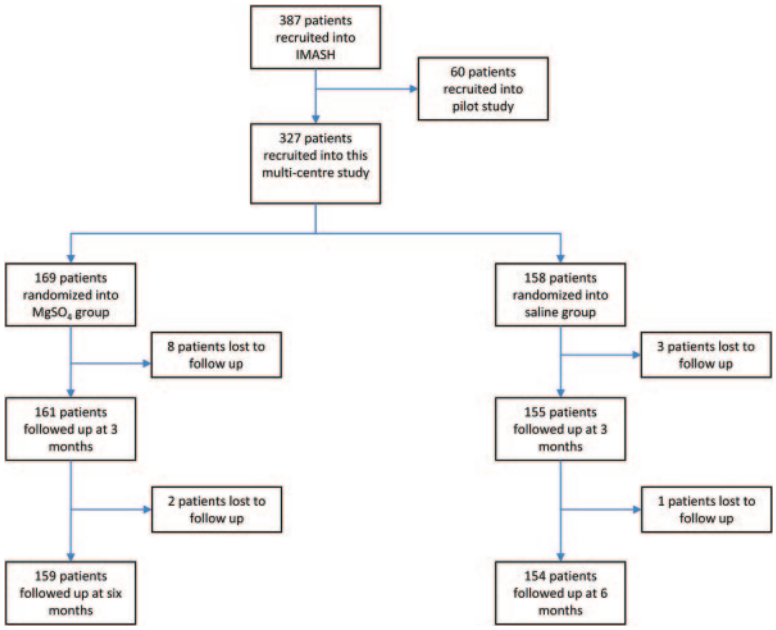

Figure 1. Trial patient profile.

Asia, and Australia between June 1, 2002, and December 31, 2008. The study protocol (www.surgery.cuhk.edu.hk/imash-trial) received ethics committee approval from all of the participating centers. All participants or their legally acceptable representatives provided written informed consent.

Participants

Patients with aneurysmal subarachnoid hemorrhage were randomly assigned to receive either an intravenous magnesium sulfate infusion or a normal saline infusion (placebo). The inclusion criteria were as follows: aged ≥18 years; radiological diagnosis of subarachnoid hemorrhage; had an intracranial aneurysm that was considered the cause of subarachnoid hemorrhage; could be randomized within 48 hours after the onset of subarachnoid hemorrhage; and woman of nonchildbearing potential (ie, physiologically incapable of becoming pregnant, including any woman who was postmenopausal) or of childbearing potential but with a negative urine pregnancy test immediately before randomization. The exclusion criteria were as follows: death within 48 hours after admission was anticipated; major hepatic, pulmonary, or cardiac disease; recent myocardial infarct (<6 months from ictus); significant renal impairment (plasma creatinine concentration >200 μmol/L); clinical indication or contraindication to magnesium infusion; pre-existing neurological disability from stroke, dementia, or other neurological diseases; or concurrent participation in another clinical trial.

After confirmation of intracranial aneurysm by CT or catheter angiography, patients were randomly allocated to receive either a magnesium sulfate ($MgSO_4$) or saline infusion. Participating centers then arranged a research staff or investigator, not involved in the clinical care or outcome assessment of patients, to arrange for the study drug infusion and discuss with the coordinating center regarding any queries such as withholding or titrating study drugs. The regimen for $MgSO_4$ infusion was based on the pilot study from one of the investigators.[4] For patients receiving the active treatment, 20 mmol $MgSO_4$ was administered over 30 minutes followed by a continuous infusion of 80 mmol $MgSO_4$ per day for up to 14 days after hemorrhage. The plasma total magnesium concentration was measured daily. The laboratory results were reviewed by a research nurse or equivalent. Infusion was adjusted so that the plasma magnesium concentration was raised to approximately twice the baseline value and <2.5 mmol/L. The patients in the control group received an equivalent volume of normal saline and changes in infusion rates were also occasionally recommended to keep patients blinded.

Study Methodology

All patients were treated in referring neurosurgical centers for aneurysmal subarachnoid hemorrhage. Patients were given 60 mg oral nimodipine 4-hourly for 14 days if blood pressure remained stable. Patient demographics, medical history, and baseline and daily serum magnesium levels were collected. The severity of subarachnoid hemorrhage (SAH) was scored clinically using the World Federation of Neurological Surgeons grading scale[14] and radiologically using the Fisher scale.[15] At 3 months after randomization, the Extended Glasgow Outcome Scale (GOSE),[12,13] modified Rankin Scale (mRS),[16] and Barthel Index[17] scores were assessed by a nurse or clinician without knowledge of the treatment allocation. At 6 months after randomization, the GOSE, mRS, Barthel Index, and Short Form-36[18] scores were assessed by a nurse or clinician without knowledge of the treatment allocation. Adverse events and overall mortality during treatment and follow-up were documented. Radiological data were assessed and reported by the respective study site neuroradiologists. As a safety measure, all serious adverse events that were not part of the natural history of the condition (fatal, life-threatening, requiring or prolonging hospitalization, or others) were reported to and assessed by the Data Monitoring and Safety Committee.

We hypothesized that intravenous magnesium sulfate infusion would improve the 6-month clinical outcome of patients with acute aneurysmal SAH. The primary outcome was the favorable outcome (GOSE score 5 to 8) at 6 months. Secondary outcomes included: clinical vasospasm during the initial 2 weeks, mRS (excellent outcome as 0 to 1 and good outcome as 0 to 2) at 6 months, Barthel Index (at least 85) at 6 months, and Short Form-36 at 6 months. Clinical vasospasm was defined clinically as new focal neurological deficits (motor or speech deficits) that developed after SAH or a decrease in the Glasgow Coma Scale of ≥2 points for >6 hours or new cerebral infarction not related to posttreatment (coiling or clipping) complications, rebleed, progressive hydrocephalus, electrolyte or metabolic disturbance, or infection. The diagnosis was based on clinical, radiological, and laboratory assessments by independent neurosurgeons.

A computer-generated randomization list was generated by the central randomization office of the Division of Neurosurgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong. Sites in Hong Kong and Australia obtained randomization through the Internet; other sites in China and Southeast Asia obtained randomization through sealed envelopes in order. Group assignments and subsequent handling of infusion were done by a dedicated site

research nurse or equivalent. Patients, assessors, and healthcare staff were blinded to group identity.

Statistical Analysis

For sample size estimation, we calculated the sample size from Veyna's study, which was the only randomized pilot study available at the time of the study design.[10,19] In Veyna's study, 65% of the $MgSO_4$ group and 50% of the placebo group had a favorable neurological outcome (GOSE 5 to 8). We elected to use the same primary outcome, and based on these figures, the required sample size for a 2-tailed test with a 5% significance level and 80% power was 348 patients.

Analyses were done on an intention-to-treat basis. When 6-month efficacy outcomes could not be obtained due to withdrawal or loss to follow-up, the last available outcome was used in its place (last observation carried forward method).

All prespecified subgroup analyses were compared with the primary outcome. The prespecified subgroups were: age (<65, at least 65), pre-existing hypertension (presence, absence), admission World Federation of Neurological Surgeons grade (1 to 2, 3 to 5), intracerebral hematoma (presence, absence), intraventricular hemorrhage (presence, absence), location of aneurysm (anterior circulation versus posterior circulation), size of aneurysm (<12 mm, at least 12 mm), and mode of aneurysm treatment (clipping, coiling).

The trial data were collected on printed forms and entered into a computer using ACCESS 2003 software (Microsoft Inc, Redmond, Wash) Statistical analyses were generated using SPSS for Windows Version 15.0 (SPSS Inc, Chicago, Ill). This study was reported in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement.[20] For outcome measures other than clinical vasospasm, OR values >1.0 or positive value of mean differences indicated an advantage of intravenous magnesium sulfate infusion over the placebo. For clinical vasospasm, OR values <1.0 indicated an advantage of intravenous magnesium sulfate infusion over the placebo. Other statistical tests included χ^2 test, Mann-Whitney U test, and proportional odds analysis as appropriate. Statistically significant difference was defined as a $P<0.05$.

Results

We enrolled 387 patients in 10 participating hospitals from June 2002 to December 2008 with 6-month data completed in June 2009. Barriers to recruitment included late presentation, refusal, or next of kin or investigator unavailable for consent. The pilot study included the first 60 patients from the Prince of Wales Hospital.[20] In the present study, we report the results of the 327 patients subsequently recruited from the 10 participating hospitals. The trial patient profile is presented in Figure 1 and the baseline characteristics of the patients are shown in the Table. There were no significant imbalances between the 2 groups.

In the primary outcome analysis, the proportions of patients with a 6-month favorable outcome (GOSE 5 to 8) were similar, 64% (108 of 169) in the $MgSO_4$ group and 63% (100 of 158) in the saline group (OR, 1.0; 95% CI, 0.7 to 1.6). Data for GOSE and mRS are shown in Figure 2. There were no significant differences in distributions and in proportional odds analyses.

In the secondary outcome analyses, there were no significant differences between the 2 groups. The proportions of patients with clinical vasospasm were similar, 25% (42 of 169) in the $MgSO_4$ group and 18% (29 of 158) in the saline group (OR, 1.5; 95% CI, 0.9 to 2.5). The proportions of patients with a good outcome at 6 months (mRS 0 to 2) were similar, 57% (97 of 169) in the $MgSO_4$ group and 58% (91 of 158) in the saline group (OR, 1.0; 95% CI, 0.6 to 1.5). The proportions of patients with an excellent outcome (mRS 0 to 1) at 6 months were similar, 46% (77 of 169) in the $MgSO_4$ group and 45% (71 of 158) in the saline group (OR, 1.0; 95% CI, 0.7 to 1.6). The proportions of patients able to carry out independently basic activities of daily living (Barthel Index at least 85) at 6 months were similar, 57% (97 of 169) in the $MgSO_4$ group and 61% (96 of 158) in the saline group (OR, 0.9; 95% CI, 0.6 to 1.4). Completion of Short Form-36 questionnaires was feasible in 189 (58%) communicable survivors at 6 months, 99 patients of the $MgSO_4$ group and 90 patients of the saline group. Their Short Form-36 physical scores were similar (mean±SD), 67.3±26.1 in the $MgSO_4$ group and 65.5±25.3 in the saline group (mean difference was 3.8 and 95% CI was −5.6 to 9.2). Their Short Form-36 mental scores were also similar, 65.4±22.0 in the $MgSO_4$ group and 64.5±24.1 in the saline group (mean difference was 3.4 and 95% CI was −5.7 to 7.6).

Time from ictus to the start of study drug infusion (mean±SD) was 31.7±15.5 hours. Average serum magne-

Table. Baseline Characteristics of Patients (N=327) in the Magnesium Sulphate Infusion Group and the Placebo (Saline) Group*

	MgSO4 Group (n=169)	Saline Group (n=158)
Age, years		
Mean (SD)	57.0 (12.5)	57.0 (12.5)
Median (range)	55 (19–90)	57 (31–89)
Sex		
Male	61 (36)	58 (37)
Female	108 (64)	100 (63)
Admission WFNS		
5	20 (12)	17 (11)
4	42 (25)	39 (25)
3	17 (10)	14 (9)
2	40 (24)	43 (27)
1	50 (30)	45 (29)
Fisher CT grade		
1	1 (1)	1 (1)
2	8 (5)	16 (10)
3	141 (83)	121 (77)
4	19 (11)	20 (13)
Aneurysm location		
ICA	59 (35)	57 (36)
ACA	53 (31)	43 (27)
MCA	31 (20)	33 (21)
PC	16 (10)	15 (10)
Aneurysm treatment		
Coiling	85 (50)	72 (46)
Clipping	72 (43)	69 (44)
No treatment	11 (7)	17 (11)

*Data are numbers (%) unless otherwise indicated.

WFNS indicates World Federation of Neurological Surgeons; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PC, posterior circulation.

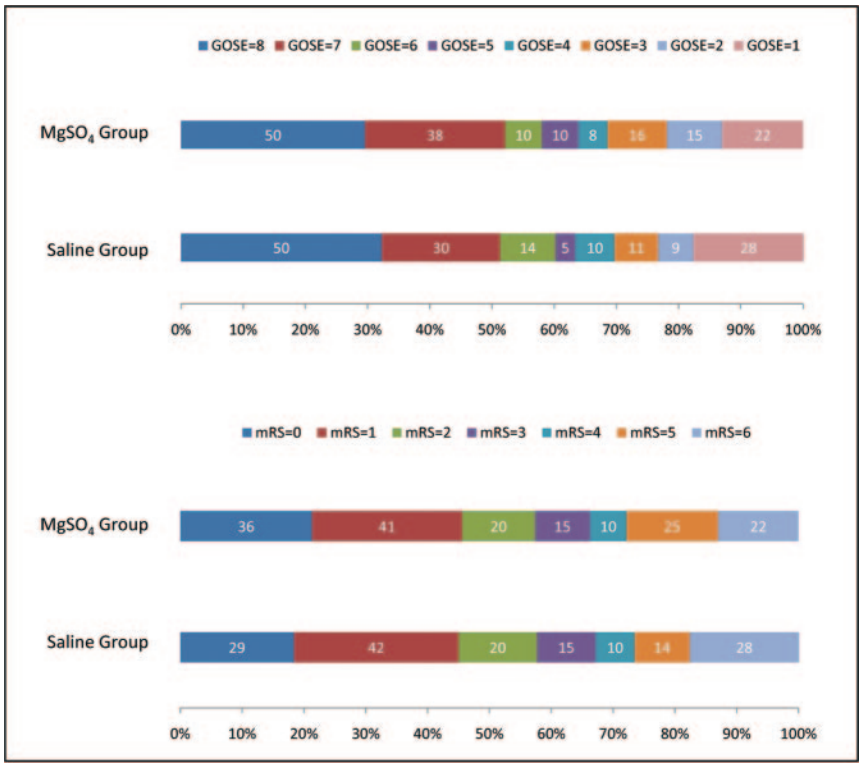

Figure 2. GOSE and mRS distributions.

sium concentrations were significantly higher in the $MgSO_4$ group than in the saline group (1.67±0.27 mmol/L versus 0.91±0.16 mmol/L, respectively; $P<0.001$). Two hundred ninety-five patients (91%) completed at least 10 days of study drug infusion. Study drug infusion was stopped for 3 patients (1%) because of severe limb weakness (1, $MgSO_4$ group), refractory hypernatremia (1, saline group), or severe hypocalcemia (1, $MgSO_4$ group). Other patients had their study drug infusion for <10 days because of early discharge (2, saline group), death (15; 7 in the $MgSO_4$ group, 8 in the saline group), or refusal to continue intravenous infusion (11; 7 in $MgSO_4$ group, 4 in saline group). There was no difference in the admission mean blood pressure (121±23 mm Hg in $MgSO_4$ group, 118±24 mm Hg in saline group). Hypotension (persistent systolic blood pressure <90 mm Hg requiring inotropes and not related to septic shock) occurred in 15% (26 of 169) of the $MgSO_4$ group and 13% (21 of 158) of the saline group ($P=0.590$). There was no difference in the incidence of cardiac failure, acute renal failure, pneumonia, sepsis, pulmonary embolism, myocardial infarction, or gastrointestinal bleeding between the 2 groups. No mortality related to study drug infusion was reported. Inpatient mortalities were similar, 10% (17 of 169) in the $MgSO_4$ group and 12% (19 of 158) in the saline group (OR, 0.8; 95% CI, 0.4 to 1.6).

Transcranial Doppler measurement was feasible through temporal windows and recorded for 210 patients (54%). Daily maximum middle cerebral artery velocities were collected throughout the study drug infusion period. The mean values were similar between the $MgSO_4$ and saline infusion groups (82±31 cm/s versus 87±61 cm/s, respectively; $P=0.487$).

The results of the subgroup analyses are shown in Figure 3. In none of the subgroups did the $MgSO_4$ group show a better outcome at 6 months (GOSE 5 to 8).

Discussion

One possible explanation of the lack of action could be the low cerebrospinal fluid penetration of peripherally infused magnesium sulfate. Using our current regimen, we increased cerebrospinal fluid magnesium concentration by 11% to 21% and increased brain-free intracellular magnesium by 13% with no improvement in cerebral perfusion.[21–23] The lack of vasodilatory effects was also demonstrated by the lack of difference in transcranial Doppler mean middle cerebral artery velocities in the current study. We did not include angiography vasospasm as a study parameter because at the time of the protocol design, CT angiogram was not validated for vasospasm assessment and routine digital subtraction angiographic incurred additional risk. Although it remains possible that higher target magnesium concentrations such as 2.5 mmol/L can result in improvement in outcome, the highest concentrations achieved are limited by toxicity. Direct intracisternal infusion overcomes the problem of peripheral toxicity and may achieve a cerebrospinal fluid magnesium level sufficient to reverse cerebral vasospasm and augment its neuroprotective effects.[24] Another possible explanation of the lack of action could be the inability to provide neuroprotection for early brain injury with the current time window of administration. Whether earlier administration within the first 2 hours, like in the ongoing FAST_MAG Trial (Field Administration of Stroke Therapy—Magnesium Phase 3 Clinical Trial http://www.fastmag.info/index.htm), remains unanswered.

Another concern is the primary outcome and the sample size estimation based on the selection of primary outcome.[25] A post hoc power analysis with 63% favorable outcome in the control group yielded 0.85 for 15% improvement and 0.49 for

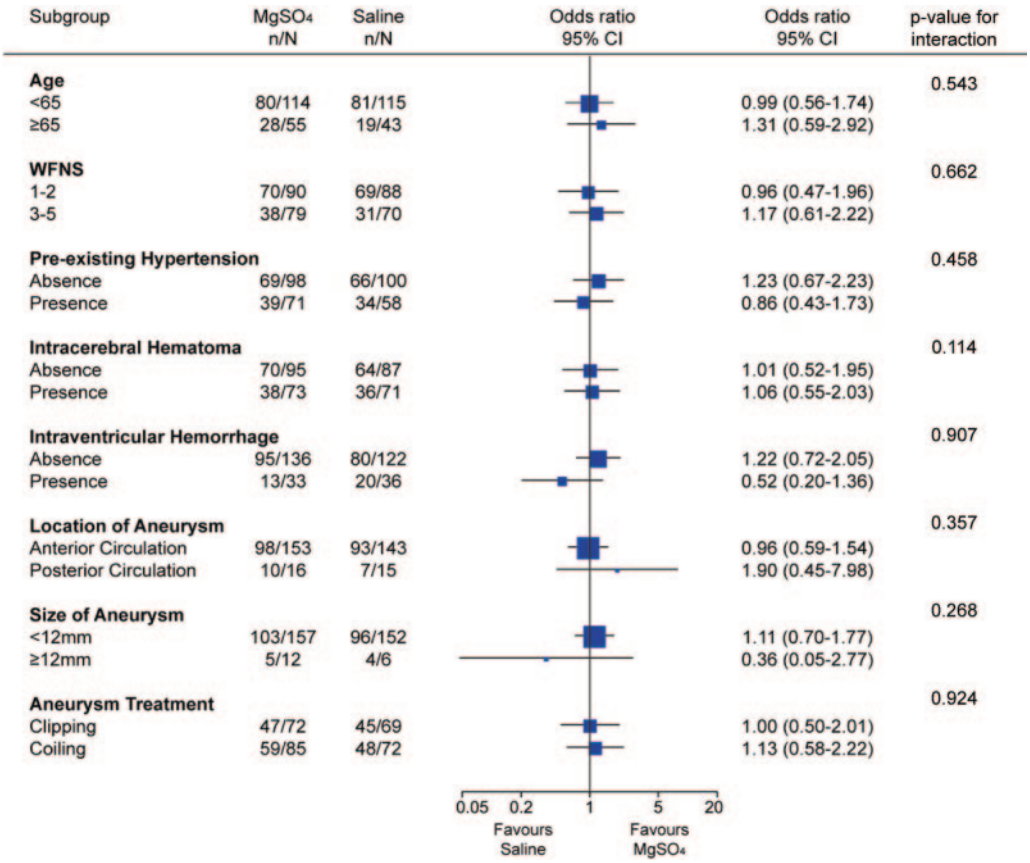

Figure 3. Prespecified subgroup analysis. n indicates number of favorable outcomes (GOSE 5 to 8); N, number randomized in the group; WFNS, World Federation of Neurological Surgeons grade.

10% improvement. Although there may be doubt about underpowering of the study based on a 50% unfavorable outcome and 15% improvement in outcome from Veyna's series[10] and we did consider revising the sample size based on a lower rate of unfavorable outcome and lesser degree of improvement in outcome,[11] the lack of any trends on the different clinical outcome measures and subgroup analysis supports the validity of our negative result.

In future research, composite cognitive function should be considered as an outcome measure.[26] Abnormalities in cognitive function are common after surgery for aneurysmal SAH, even among patients with a good functional outcome, and can occur in up to 44% of survivors.[27–29]

This academically funded study was done without any industry support using generic medications and weakness would include lack of on-site trial monitoring due to restraints in funding. We have not incorporated daily blood pressure data in the trial design. Magnesium sulfate infusion was known to lower blood pressure,[30] and whether this would translate into adverse effect in clinical outcome remained to be investigated. The use of the last observation carried forward method could have introduced bias regarding the possible benefits or hazards. However, the effect would be small in our analysis because of the small number (4%) of missing data. Moreover, the recruited population was representative of patients with acute aneurysmal SAH managed in daily practice. In conclusion, our results do not support a significant clinical benefit of intravenous magnesium sulfate infusion over placebo infusion in patients with acute aneurysmal SAH.

Source of Funding

This study was supported by the Research Grants Council of Hong Kong (CUHK Ref. No. CUHK4183/02 M).

Disclosures

None.

Appendix: IMASH Investigators and Participating Hospitals

Steering Committee (CUHK, Hong Kong, China): W.S. Poon, G.K.C. Wong, R. Boet, J.M.K. Lam, X.L. Zhu, M.T.V. Chan, and T. Gin; Data Monitoring and Safety Committee: John Pickard (Cambridge, UK) and Benny C.Y. Zee (Hong Kong, China); Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong, China (189 patients): G.K.C. Wong, R. Boet, W.S. Poon; Pamela Youde Nethersole Eastern Hospital, Hong Kong China (34 patients): C.K. Wong and M.W.Y. Lee; Hospital University Sains Malaysia, Kubang Kerian, Malaysia (32 patients): J.M. Abdullah and R. Ghani; Austin Health, Melbourne, Australia (17 patients): D. Cowie and S. Poustie; Second Affiliated Hospital of Guangzhou Medical College, Guangzhou, China (15 patients): M.C. Li; Alfred Hospital, Melbourne, Australia (14 patients): P.S. Myles and S. Wallace; Tuen Mun Hospital, Hong Kong, China (12 patients): D.T.S. Fong and S.C. Yuen; First Affiliated Hospital of Sun Yat Sen University, Guangzhou, China (10 patients): Z.S. Huang and Y.M. Sun; Beijing Tiantan Hospital, Capital Medical University, Beijing, China (2 patients): J.Z. Zhao; Kwong Wah Hospital, Hong Kong, China (2 patients): J.C.K. Kwok and K.Y. Chan.

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Stroke. 2010;41:921-926; originally published online April 8, 2010;
doi: 10.1161/STROKEAHA.109.571125
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628