Magnesium for Treatment of Acute Lacunar Stroke Syndromes

Further Analysis of the IMAGES Trial

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Background and Purpose—A prespecified interaction analysis of the neutral Intravenous Magnesium Efficacy in Stroke (IMAGES) trial revealed significant benefit from magnesium (Mg) in patients with noncortical stroke. Post hoc analysis indicated that this effect was seen in lacunar clinical syndromes (LACS), interaction $P=0.005$. We have now examined whether this interaction could be explained by confounding baseline factors.

Methods—LACS was defined on the basis of neurological signs and did not include imaging. We investigated the interaction between baseline variables and Mg treatment on global outcome. We used logistic-regression models to test whether the Mg-LACS interaction remained significant after adjusting for stratification variables, sex, a novel stroke severity score, and baseline variables that had an interaction with treatment ($P<0.1$).

Results—The Mg (n=383) and placebo (n=382) groups of LACS patients were well matched on baseline factors. In addition to LACS, we found an interaction between beneficial Mg treatment effect and younger age ($P=0.003$), higher baseline diastolic blood pressure ($P=0.02$), higher mean blood pressure ($P=0.02$), and absence of ischemic heart disease ($P=0.07$). Even so, the adjusted Mg-LACS interaction remained significant (odds ratio [OR] 0.57; 95% CI, 0.39 to 0.83; $P=0.003$). In the LACS subgroup, Mg improved Barthel Index <95 (OR 0.73; 95% CI, 0.55 to 0.98), modified Rankin Scale >1 (OR 0.67; 95% CI, 0.50 to 0.91), and global outcome (OR 0.70; 95% CI, 0.53 to 0.92) but not Barthel Index <60 or mortality.

Conclusions—The positive treatment effect of Mg in LACS cannot be ascribed to general issues of severity, time to treatment, blood pressure, or other baseline factors; equally, this finding may be due to chance. A large trial of Mg treatment in LACS appears justified. **(*Stroke*. 2007;38:1269-1273.)**

Key Words: clinical trials ■ lacunar syndrome ■ magnesium

Most clinical trials for acute stroke either have grouped lacunar stroke syndromes alongside cortical syndromes or have even excluded them. The Intravenous Magnesium Efficacy in Stroke (IMAGES) randomized clinical trial[1] included all stroke syndromes but incorporated in the protocol a preplanned subgroup analysis of cortical versus noncortical stroke. The final results of IMAGES showed that randomized treatment with $MgSO_4$ did not reduce the global outcome rate (primary end point) compared with placebo.[1]

The planned interaction analysis revealed a significant benefit in the predefined subgroup of patients with noncortical stroke. This was an unexpected but biologically plausible beneficial effect of $MgSO_4$. Mg, in comparison with several other putative neuroprotectants, had previously been shown to confer white matter protection.[2] Post hoc analysis of IMAGES data indicated that the effect in subcortical stroke was greatest in patients with lacunar clinical syndrome (LACS) (odds ratio [OR] 0.70; 95% CI, 0.53 to 0.92) and confirmed a significant interaction between treatment and LACS ($P=0.005$).[1] IMAGES also reported a significant interaction between treatment effect and baseline mean arterial blood pressure (MABP) ($P=0.02$), with benefit in patients with a higher-than-median MABP in a post hoc analysis. Because Mg is known to lower BP, the effect of Mg on LACS may alternatively be mediated by reducing BP acutely.

In this further analysis, we aimed to confirm or refute the unexpected but biologically plausible findings of IMAGES. In particular, we investigated whether the interaction between Mg treatment and LACS is related to confounding factors that may have spuriously generated the apparent benefit in LACS patients. We examined the descriptive statistics, Mg treat-

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ment effect on outcome, and potential interactions within the subset of patients with LACS.

Subjects and Methods

IMAGES was an academically organized and sponsored, randomized, multicenter, international trial of acute stroke treatment with $MgSO_4$. It lasted >6 years from 1997 and was approved by research ethics committees of the participating institutions. From >100 centers, IMAGES randomized 2589 patients, and the efficacy dataset included 2386 patients. Treatment commenced within 12 hours of stroke onset and was continued for 24 hours. Global outcome was assessed at day 90±7 by a combination of the Barthel Index (BI)[3] and modified Rankin Score (mRS),[4] with favorable outcome defined as BI >90 or mRS <2.

Stroke was categorized into subtypes based on neurological signs collected at baseline. Investigators documented the presence of motor deficits for each of face, arm, and leg; dysphasia; hemianopia; brainstem signs; inattention/neglect; and hemisensory loss. The protocol did not require pretreatment confirmation of the clinical diagnosis by imaging, which was permitted up to day 7. Known hemorrhagic strokes were excluded only when imaging studies had shown this before randomization. The method used for LACS classification in the IMAGES trial was chosen to be simple but robust. All patients with both arm and leg weakness but without cortical features (sensory inattention or dysphasia), hemianopia, ataxia, or brainstem features were regarded as having had lacunar stroke. Patients with monoparesis were assumed to have a cortical syndrome.[1] This method allows inclusion of only 2 of the classic lacunar syndromes (pure motor stroke and sensorimotor stroke) and does not strictly correspond to the Oxfordshire Community Stroke Project[5] classification system.

Conventional neurological stroke severity scores were not assessed in IMAGES. An IMAGES stroke scale (ISS) was generated from the baseline neurological signs.[6] ISS ranges from 0 to 16; for the lacunar stroke syndrome subset, the median score was 5 (range 3 to 9, interquartile range 4 to 5).

Statistical Analysis

The interaction between baseline variables and Mg treatment on global outcome was tested after adjusting for stratification variables (age group, side of symptoms, time from onset to randomization, and stroke type) in the IMAGES efficacy dataset with use of a bivariate logistic-regression model. The efficacy of Mg on global outcome (adjusted for stratification variables) was separately assessed for each subgroup of baseline variables that had an interaction probability value <0.1. We tested whether the interaction between Mg treatment and LACS identified in post hoc analysis of the original IMAGES article[1] remained statistically significant after further adjustment for sex, ISS, and variables that had shown a significant interaction with treatment.

The remaining analysis was conducted solely on the LACS subgroup. Baseline factors were described for each treatment group to confirm that randomization had achieved good balance for case mix. BI and mRS outcomes at 3 months were tabulated by treatment group. In the LACS subset, after adjustment for stratification variables, we identified interactions between baseline variables and treatment on global outcome that were significant at $P<0.1$. LACS patients were stratified by variables that showed an interaction with treatment, and the treatment effects were presented within each stratum.

Results

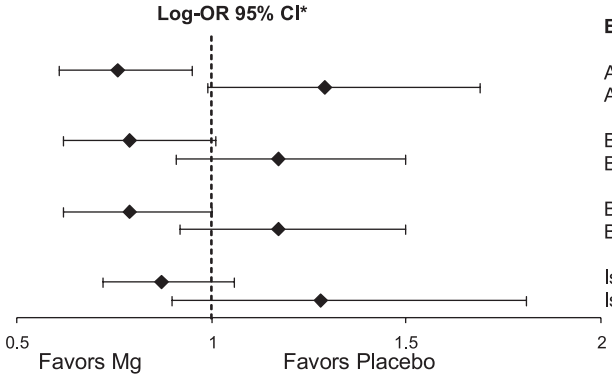
Efficacy Dataset (n=2386)

In addition to an interaction of Mg treatment with LACS in predicting global outcome, there was an interaction between Mg treatment and each of age, baseline diastolic BP (DBP), baseline MABP (all stratified by median; 71 years, 83 mm Hg, and 108 mm Hg, respectively), and history of ischemic heart disease (Figure 1). However, a statistically significant positive treatment effect was identified only in younger patients ($P=0.02$; Figure 1). Other baseline variables (sex, ISS score, baseline systolic BP, pulse pressure, predominant side of weakness, time from stroke to infusion, history of hypertension, previous stroke, previous transient ischemic attack, atrial fibrillation, valvular heart disease, diabetes mellitus, smoking in the past year, hyperlipidemia, and middle cerebral artery perforator infarction confirmed on brain imaging) failed to show any interaction with treatment.

After adjustment for the stratification variables, there was a significant interaction between Mg and LACS for all outcome measures apart from mortality (Table 1). After addition of sex, ISS score, and the variables that had an interaction with Mg treatment identified in Figure 1, the interaction between Mg and LACS remained significant (Table 1).

LACS Subgroup (n=765)

There were 765 (32.1%) patients with LACS in the efficacy dataset. The Mg group (n=383) included 31 (8.1%) patients with primary hemorrhage, and the placebo group (n=382) included 37 (9.7%) patients with primary hemorrhage. Primary hemorrhage included cases of primary intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage confirmed by imaging. The case mix was similar



Baseline variable subgroup	P-value	P-value of interaction with Mg
Age: ≤ median	0.0170	0.0034
Age: > median	0.0613	
Baseline DBP: > median	0.0552	0.0253
Baseline DBP: ≤ median	0.2079	
Baseline MAP: > median	0.0538	0.0240
Baseline MAP: ≤ median	0.2080	
Ischemic heart disease: No	0.1780	0.0691
Ischemic heart disease: Yes	0.1708	

Figure 1. Efficacy dataset: Mg efficacy on global outcome (adjusted for stratification variables) separately within each subgroup of baseline variables that have an interaction with Mg treatment ($P<0.1$). *ORs were adjusted for the stratification variables (age group, side of symptoms, and time from onset to treatment).

TABLE 1. Efficacy Dataset: Interaction Between Mg Treatment and LACS

	Model I* (n=2386)		Model II† (n=2276)	
Outcome Measure	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Global outcome	0.60 (0.42–0.85)	0.0046	0.57 (0.39–0.83)	0.0032
BI <95	0.61 (0.42–0.89)	0.0103	0.56 (0.38–0.84)	0.0048
BI <60	0.63 (0.41–0.99)	0.0441	0.61 (0.38–0.98)	0.0420
mRS >1	0.60 (0.41–0.88)	0.0098	0.58 (0.38–0.87)	0.0094
Mortality	0.85 (0.43–1.68)	0.6311	0.94 (0.46–1.92)	0.8609

*Adjusted for stratification variables only.

†Full model included age, baseline DBP, baseline MABP (all categorized by quartile), sex, ISS score, and history of ischemic heart disease, in addition to stratification variables.

between treatment groups (Table 2), although there was a tendency toward lower age and systolic BP and higher rates of diabetes in the Mg treatment group.

Figure 2 presents the distribution of outcome measures by treatment groups and adjusted ORs for dichotomous outcome measures. There was a beneficial treatment effect of Mg on BI <95, mRS >1, and global outcome. There was a nonsignificant tendency toward a beneficial effect of Mg on BI <60. There was no significant effect on mortality rate. When the full distribution of mRS at 3 months was analyzed with the Cochran-Mantel-Haenszel test ($P=0.0052$ univariate and $P=0.0223$ after correction for stratification variables and ISS), Mg still had a positive treatment effect. The adjusted proportional OR was 0.72 (95% CI, 0.56 to 0.93).

TABLE 2. LACS Subgroup: Demography and Baseline Characteristics by Treatment Group

Baseline Factors	Placebo (n=382)	Mg (n=383)
Age, y*	68.7 (12.6)	67.0 (12.7)
Baseline systolic BP, mm Hg*	164.3 (28.2)	160.3 (29.3)
Baseline DBP, mm Hg*	87.4 (17.3)	86.9 (17.7)
Baseline MABP, mm Hg*	113.0 (18.8)	111.4 (19.9)
Baseline pulse pressure, mm Hg*	76.9 (22.3)	73.5 (21.0)
Heart rate, bpm*	77.8 (16.1)	77.1 (14.1)
ISS†	5.0 (4.0, 5.0)	5.0 (4.0, 5.0)
Time from stroke to infusion, h†	7.7 (5.5, 10.0)	7.7 (5.6, 10.5)
Sex, women, n (%)	168 (44.0)	162 (42.3)
Principal lesion compatible with acute stroke? n (%)	193 (54.5)	189 (53.1)
If yes, is it in middle cerebral artery perforator territory? n (%)	95 (49.2)	91 (48.1)
Medical history, n (%)		
Hypertension	215 (56.3)	213 (55.6)
Previous stroke	66 (17.3)	60 (15.7)
Previous transient ischemic attack	56 (14.7)	50 (13.1)
Ischemic heart disease	79 (20.7)	79 (20.6)
Atrial fibrillation	36 (9.4)	48 (12.5)
Valvular heart disease	11 (2.9)	10 (2.6)
Diabetes mellitus	62 (16.2)	82 (21.4)
Smoker in past year	96 (25.1)	110 (28.7)
Hyperlipidemia	49 (12.8)	53 (13.8)

*Mean and (SD).

†Median and (interquartile range).

In the subset of patients with LACS, interactions were identified between Mg and both age ($P=0.09$) and baseline DBP ($P=0.03$) for prediction of global outcome. Median values for age (70 years) and DBP (86 mm Hg) were used for stratification. After adjustment for stratification variables, Mg was efficacious in patients of median age or younger (OR 0.57; 95% CI, 0.39 to 0.83) and in patients with a greater-than-median baseline DBP (OR 0.52; 95% CI, 0.35 to 0.76). When these 2 interactions were included in the logistic-regression models, Mg had a tendency to improve all outcome measures, but the effect was not statistically significant. The CIs for ORs were wide and substantially overlapped the CIs of Mg treatment effect adjusted for stratification variables only (Figure 2). There was no statistically significant difference between treatment groups in the rate of serious adverse events reported during the first 48 hours after trial entry (supplemental Table I, available online at http://stroke.ahajournals.org).

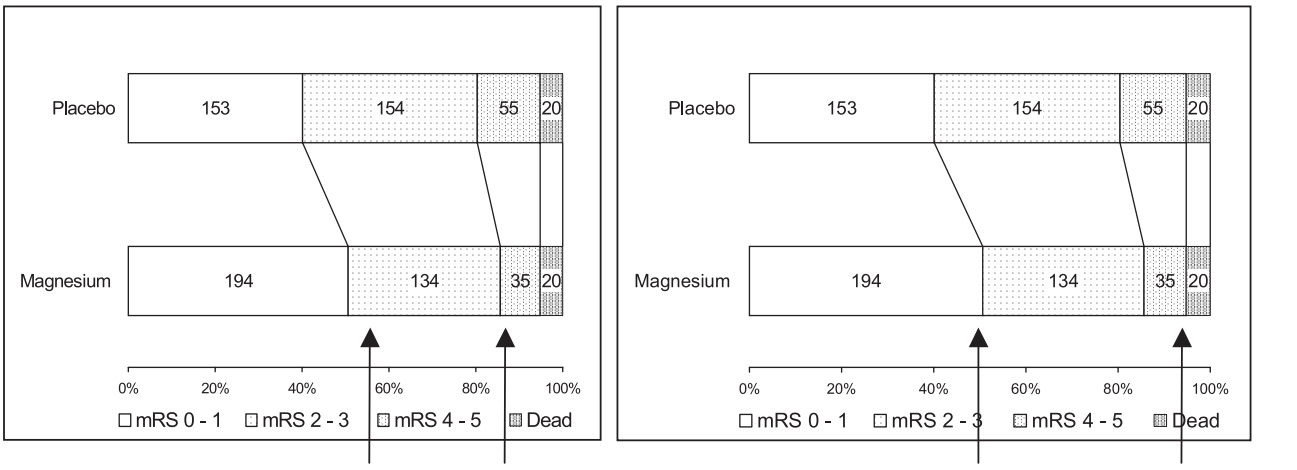
Discussion

The main finding of our analyses is that, even after adjustment for baseline factors such as sex, stroke severity, and variables that showed an independent interaction with Mg treatment or were used for stratification, Mg treatment improved the chances of a good functional outcome in patients with LACS. This indicates that the effect evident in the IMAGES subgroup analysis was not due to a confounding effect of other prerandomization factors and provides support for the possibility that Mg treatment improves outcome in LACS. Stroke patients who were younger, had a higher MABP or DBP, and did not have a history of ischemic heart disease especially benefited from Mg treatment.

The treatment groups in the LACS subset were well balanced. The treatment effect observed in LACS was consistent for both functional outcome measures, BI and mRS, but was absent for mortality; however, this is expected, because early mortality is rare in LACS patients, and neither the main IMAGES trial nor the subgroup had adequate power to detect an effect on mortality. Clearly, selection of an appropriate outcome measure for a lacunar stroke trial will be important and may not necessarily be the same as that used for an unselected population. It may be desirable to explore the potential of using novel patient-specific end points.[7]

After additional adjustment for Mg-age and Mg-DBP interactions, the effect of Mg had only a tendency toward benefit in the LACS subgroup, but the CIs were wide. In the larger dataset of all stroke patients, wherein statistical power was greater, the interaction between Mg and LACS remained significant, even after additional adjustment for interactions between Mg and age, DBP, MABP, and absence of a history of ischemic heart disease.

A benefit from Mg in acute white matter infarction is biologically plausible[2]; however, most animal-model studies support the effect of Mg on neuronal cell bodies. The tolerance of white matter to ischemia may be greater than for gray matter, so the time window for its protection may be



	BI < 95	BI < 60	Global outcome	mRS > 1	Mortality
OR* (95% CI)	0.73 (0.55-0.98)	0.74 (0.50-1.10)	0.70 (0.53-0.92)	0.67 (0.50-0.91)	1.05 (0.55-2.02)
P-value	0.039	0.131	0.012	0.009	0.884

Figure 2. LACS subgroup: treatment effect of Mg on outcome at 3 months. *Mg vs placebo, adjusted for stratification variables.

longer. Outcome assessment in animal models of stroke is predominantly based on histological lesion volume, which is largely determined by cortical infarction (and by extension, assumed to involve neuronal cell bodies). White matter constitutes a smaller proportion of the rodent brain, and quantitative measurement techniques for axonal injury are less clearly established, so evaluation of therapeutic effects on white matter has been difficult. Because most other possible neuroprotectant agents act at receptors or intracellular targets that are predominantly or exclusively present in neurons, cortical lesion volume is a relevant marker of effect, and exclusion of lacunar strokes from "proof-of-principle" clinical trials is a logical mechanism for enriching the trial population.[8] Although we should remain cautious until our findings can be confirmed independently in a prospective, randomized trial, this study suggests that lacunar stroke patients may represent a relevant and practical target population for agents with biological activity in white matter.

The pathophysiology of lacunar syndromes is poorly understood, but fluctuation in clinical status over time is a common observation that may be the basis for a beneficial effect being unrelated to the time from stroke to infusion. This again raises the possibility of a vasoactive mechanism in addition to, or instead of, a neuroprotectant one. Regardless of mechanism, the IMAGES data indicate no justification for exclusion of late-presenting patients from a future trial, at least up to 12 hours. Whether the treatment effect of Mg is mediated via lowering of BP or whether the BP effect is simply 1 of the manifestations of Mg treatment is unclear. The interaction between baseline BP and treatment was present in both the efficacy population and the LACS subset.

Although the ISS groupings showed a clear relation with outcome for the entire IMAGES population, the ISS has limited discriminatory power within the LACS subgroup: these patients mostly had ISS scores of 5 or below (upper quartile). Interaction between ISS and Mg treatment was identified neither in the efficacy dataset nor in the lacunar subset. Because of small numbers in the lacunar group and also the favorable prognosis of placebo-treated patients owing to a more benign natural history, our failure to demonstrate any interaction between Mg treatment and ISS may not be reliable. Our analysis is exploratory in nature and is not powered to provide definitive results.

Identification of the Lacunar Population

The term "lacune" refers to pathoanatomic findings at autopsy.[9] The computed tomography (CT)/magnetic resonance imaging equivalent of a lacune is a small, deeply placed infarct (SDI) and assumes that the imaged area of infarction is within a territory of a single, perforating artery and presents as small circular or oval changes approximately <1.5 cm in diameter.[9] Patients with lacunar stroke present mostly with 5 distinct stroke syndromes, collectively described as classic lacunar syndromes. Classic lacunar syndromes include (1) pure motor stroke, (2) sensorimotor stroke, (3) pure sensory stroke, (4) dysarthria–clumsy hand syndrome, and (5) ataxic hemiparesis. Lacunar stroke may thus be defined as a lacunar syndrome combined with an SDI on imaging or with imaging that is consistent with an SDI (ie, this may include a normal CT scan). The method used for LACS classification in the IMAGES trial included only pure motor stroke and sensorimotor stroke.[1] IMAGES required a single brain imaging study within 7 days of stroke.

In IMAGES, a LACS classification was reasonably specific for the middle cerebral artery perforator infarction in the efficacy population (70%) but had poor sensitivity (43%).[10] The imaging was consistent with LACS in 452 (59%) subjects: 186 middle cerebral artery perforator infarcts (where the principal lesion was consistent with an acute stroke), 38 atrophies only, and 228 normal scans. In sensitivity analysis, in those patients with a diagnosis that corresponded to the definition of classic lacunar infarcts, the results were entirely consistent with those in the main analysis. In particular, the OR estimate for global outcome was similar to

that in the main sample, and the CI entirely covered the range of CI in the original analysis (OR 0.75; 95% CI, 0.52 to 1.07, adjusted for stratification variables; and OR 0.90, 95% CI, 0.48 to 1.70 in the full model). Unsurprisingly, as the sample size was reduced substantially, the results were no longer significant.

Further selection of ischemic lacunar stroke patients from the LACS subgroup was done in sensitivity analysis only because the majority of scans were performed after randomization. This may have biased the assessment of treatment effect if Mg treatment caused the transformation of larger strokes to lacunar. Additionally, anatomically plausible infarcts on delayed CT scans may not be causal, because CT cannot discriminate reliably between acute and established lesions.

In the European Cooperative Acute Stroke Study I trial of tissue-type plasminogen activator treatment administered within 4.2 ± 1 hours of stroke onset, the predictive value, sensitivity, specificity, and accuracy of clinical presentation of lacunar stroke with pure motor stroke or sensorimotor stroke was poor when compared with the standard of CT assessment at 7 days.[11] Similarly, baseline CT appearances of leukoaraiosis and previous SDI had little value. Early CT signs were also insensitive variables. The absence of early CT signs combined with a pure motor stroke/sensorimotor stroke presentation corresponded to lacunar infarct in 26% of placebo and 33% of recombinant tissue-type plasminogen activator patients.[11] The study concluded that in the acute setting of thrombolysis treatment, lacunar infarcts were not recognizable on clinical and early CT grounds, either alone or in combination.[11]

Diffusion-weighted imaging is the most sensitive and specific imaging method for detection of subcortical ischemic lesions during the acute phase of stroke.[12] Diffusion-weighted imaging, in conjunction with the apparent diffusion coefficient map, can differentiate between acute and nonacute lesions. However, diffusion-weighted imaging was the routine acute imaging method at only very few centers worldwide during the IMAGES recruitment period.

Future clinical trials should encourage the use of baseline diffusion-weighted imaging to clarify the specific diagnostic modalities that may benefit Mg treatment. Until universal precise diagnosis is possible, a simple, reliable, clinical method of selection of LACS is justified because of data availability, clinical assessment before randomization, and the low accuracy of early CT assessment. Within this group, a benefit of Mg treatment on outcome remains a possibility.

In conclusion, this further analysis of the IMAGES data suggests that the positive interaction between Mg and LACS cannot be ascribed to confounding issues of severity, time to treatment, BP, or other baseline factors. A trial of Mg treatment in acute LACS is justified and necessary to confirm these results.

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Disclosures

None.

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