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.

Key Words: clinical trials ▪ lacunar syndrome ▪ magnesium
miento 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 MgSO4. 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 by a combination of the Barthel Index (BI) and modified Rankin Score (mRS), 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. 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 classification system.

Conventional neurological stroke severity scores were not assessed in IMAGES. An IMAGES stroke scale (ISS) was generated from the baseline neurological signs. 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, and time from onset to treatment). 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), and the treatment effects were presented within each 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<0.01. LACS patients were stratified by variables that showed an interaction with treatment, and the treatment effects were presented within each stratum.

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...
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).

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 1, 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; 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

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**Table 1. Efficacy Dataset: Interaction Between Mg Treatment and LACS**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Model I* (n = 2386)</th>
<th>Model II† (n = 2276)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>P Value</strong></td>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td>Global outcome</td>
<td>0.60 (0.42–0.85)</td>
<td>0.0046</td>
</tr>
<tr>
<td>BI &lt;95</td>
<td>0.61 (0.42–0.89)</td>
<td>0.0103</td>
</tr>
<tr>
<td>BI &lt;60</td>
<td>0.63 (0.41–0.99)</td>
<td>0.0441</td>
</tr>
<tr>
<td>mRS &gt;1</td>
<td>0.60 (0.41–0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.85 (0.43–1.68)</td>
<td>0.6311</td>
</tr>
</tbody>
</table>

*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.

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

<table>
<thead>
<tr>
<th>Baseline Factors</th>
<th>Placebo (n = 382)</th>
<th>Mg (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>66.7 (12.6)</td>
<td>67.0 (12.7)</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg*</td>
<td>164.3 (28.2)</td>
<td>160.3 (29.3)</td>
</tr>
<tr>
<td>Baseline DBP, mm Hg*</td>
<td>87.4 (17.3)</td>
<td>86.9 (17.7)</td>
</tr>
<tr>
<td>Baseline MABP, mm Hg*</td>
<td>113.0 (18.5)</td>
<td>111.4 (19.9)</td>
</tr>
<tr>
<td>Baseline pulse pressure, mm Hg*</td>
<td>76.9 (22.3)</td>
<td>73.5 (21.0)</td>
</tr>
<tr>
<td>Heart rate, bpm*</td>
<td>77.8 (16.1)</td>
<td>77.1 (14.1)</td>
</tr>
<tr>
<td>ISS†</td>
<td>5.0 (4.0, 5.0)</td>
<td>5.0 (4.0, 5.0)</td>
</tr>
<tr>
<td>Time from stroke to infusion, h†</td>
<td>7.7 (5.5, 10.0)</td>
<td>7.7 (5.6, 10.5)</td>
</tr>
<tr>
<td>Sex, women, n (%)</td>
<td>168 (44.0)</td>
<td>162 (42.3)</td>
</tr>
<tr>
<td>Principal lesion compatible with acute stroke? n (%)</td>
<td>193 (54.5)</td>
<td>189 (53.1)</td>
</tr>
<tr>
<td>If yes, is it in middle cerebral artery perforator territory? n (%)</td>
<td>95 (49.2)</td>
<td>91 (48.1)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>215 (56.3)</td>
<td>213 (55.6)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>66 (17.3)</td>
<td>60 (15.7)</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td>56 (14.7)</td>
<td>50 (13.1)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>79 (20.7)</td>
<td>79 (20.6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>36 (9.4)</td>
<td>48 (12.5)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>11 (2.9)</td>
<td>10 (2.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (16.2)</td>
<td>82 (21.4)</td>
</tr>
<tr>
<td>Smoker in past year</td>
<td>96 (25.1)</td>
<td>110 (28.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>49 (12.8)</td>
<td>53 (13.8)</td>
</tr>
</tbody>
</table>

*Mean and (SD).
†Median and (interquartile range).
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. 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. 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. 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. 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. 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%). 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

![Figure 2. LACS subgroup: treatment effect of Mg on outcome at 3 months. *Mg vs placebo, adjusted for stratification variables.](http://stroke.ahajournals.org/Downloadedfrom)
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 signs was reduced substantially, the results were no longer significant. 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.

Acknowledgements

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Disclosures
None.

References
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