A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Simvastatin in Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Studies suggest statins ameliorate aneurysmal subarachnoid hemorrhage (SAH)-induced cerebral vasospasm and ischemic complications. We tested safety and feasibility of simvastatin 80 mg/d for vasospasm prevention in SAH patients.

Methods—Thirty-nine statin-naïve Fisher grade 3 SAH subjects were double-blind randomized to receive simvastatin 80 mg/d (n=19) or placebo (n=20), stratified by Hunt and Hess grade. Primary end points were death and drug morbidity.

Results—Mortality was 3/20 in the placebo and 0/19 in the simvastatin group. Study drug was withdrawn in 1 subject in each treatment group for reversible liver enzyme or creatine phosphokinase elevation. Angiographically-confirmed vasospasm occurred in 8/20 placebo and 5/19 simvastatin-treated subjects. Vasospasm-related ischemic infarcts developed in 5/20 placebo and 2/19 simvastatin-treated subjects.

Conclusion—Simvastatin for the prevention of delayed cerebral ischemia is safe and feasible after SAH. A larger study is needed to test its efficacy. (Stroke. 2008;39:2891-2893.)

Key Words: vasospasm ■ delayed cerebral ischemia ■ clinical trial

There are limited treatment options for aneurysmal subarachnoid hemorrhage (SAH)-induced vasospasm and subsequent ischemic complications. Statins have pleiotropic effects targeting many processes in the pathogenesis of vasospasm and reduce post-SAH vasospasm in animal models and pilot human studies. We conducted a prospective, randomized, double-blind study of the safety and feasibility of simvastatin treatment after SAH.

Methods
Thirty-nine adults (age ≥18) with Fisher grade 3 SAH were included. Subjects were eligible if their ruptured aneurysm(s) were secured and if study drug can be started within 96 hours of aneurysm rupture. Patients at high risk for early mortality (Hunt and Hess grade V, or intracranial pressure >30 cm H2O for >30 minutes) were excluded. Other exclusion criteria were abnormal baseline serum creatine phosphokinase (CPK), alanine aminotransferase (ALT), or aspartate aminotransferase (AST), prior statin use, and contraindication for statin use. The institutional review board approved this study (ClinicalTrials.gov Identifier: NCT00235963).

After informed consent from patient or health-care proxy, subjects were double-blind randomized to receive placebo or simvastatin 80 mg/d (until discharge from neurointensive care unit, or a maximum of 21 days), stratified by Hunt and Hess scores (I–II versus III–IV) to ensure an even distribution of this important outcome predictor. Plasma CPK, ALT and AST were monitored every 7 days. Study drug was stopped on unexplained 3-fold elevation of CPK or ALT/AST on 2 consecutive measurements 24 hours apart.

Primary end points of this study were death and incidence of drug morbidity defined as CK/AST/ALT elevation. Secondary outcomes included incidence of transcranial Doppler (TCD), angiographic or clinical vasospasm, vasospasm-related infarcts, clinical outcomes at discharge, and cardiac and infectious morbidities.

Angiographic vasospasm was defined as focal or generalized reduction of cerebral arterial caliber on conventional cerebral angiogram confirmed by a neuroradiologist and a neurocritical care physician. TCD vasospasm was defined as any peak systolic middle cerebral artery velocity (PSV_MCA) >200 cm/s and a Lindegaard ratio of >3. Clinically, delayed ischemic neurological deficit (DIND) was defined as any 2 or more point fall in modified Glasgow Coma Scale or unaccountable new focal neurological deficit lasting ≥2 hours. Vasospasm-related ischemic infarct was defined as the development of a new lesion consistent with infarction on CT or MRI in the vascular territory of angiographic or TCD vasospasm.

All patients received nimodipine and an anticonvulsant, were kept euthermic, euvoletic, and euglycemic, and had daily TCD monitoring per standardized protocols. Patients with abnormal TCD velocities or clinical vasospasm underwent CT or conventional cerebral angiography. Those with moderate or severe angiographic vasospasm received intraarterial (IA) nicardipine treatment. All patients with clinical, TCD, or angiographic vasospasm were treated with induced hypertension (systolic blood pressure >160 mm Hg) and hypervolemia (central venous pressure >8 cm H2O (HH)) until the resolution of vasospasm.

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2891
The basic characteristics of the study population are shown in Table 1. We performed intention-to-treat analyses using 2-sided probability values (SAS 9.1). Continuous variables were compared using Student t test (normally distributed variables) or Mann–Whitney U test (nonnormally distributed variables). Discrete variables were compared using χ² or Fisher’s exact test when appropriate.

### Results

Basic characteristics of 39 study subjects were comparable between groups (Table 1). Both groups received the first dose of study drug on average within 72 hours of SAH onset.

Table 2 summarizes the primary outcomes. There were 3 deaths in the placebo group and none in the simvastatin group. In 2 of the 3 deaths in the placebo group, there was evidence of clinical, TCD, and angiographic vasospasm, and the subjects died after withdrawal of care. The third subject who died had persistent poor neurological function without evidence of clinical, TCD, and angiographic vasospasm, and died after withdrawal of care per patient’s advance directive. Study drug was withdrawn in 1 subject in the placebo group for CK elevation. In both cases, the CK/ALT/AST elevations were asymptomatic and resolved spontaneously.

Exploratory efficacy data are shown in Table 3. We detected no between-group differences in incidence of angiographic or TCD vasospasm, DIND, vasospasm-related infarcts, or functional status at discharge. We measured the time to develop PSV<sub>MCA</sub> >200 cm/s or DIND, total dose of IA nicardipine used, and number of days on HH therapy as surrogates for vasospasm severity, and once again detected no between-group differences.

### Discussion

Results from this prospective, double-blind, placebo-controlled study suggest simvastatin 80 mg/d use is safe and feasible in Fisher grade 3 SAH patients. There was a trend for lower mortality in simvastatin-treated subjects, which must be confirmed in a larger study. Unlike prior pilot studies, however, our explorative analyses on vasospasm indices did not provide a clear support for benefit.

To date, 2 prospective randomized clinical trials have explored statin use in vasospasm prevention after SAH. Tseng et al<sup>4,5</sup> randomized 80 patients to receive placebo or pravastatin 40 mg/d within 96 hours after SAH, whereas Lynch et al<sup>3</sup> randomized 39 patients within 48 hours after SAH to receive placebo or simvastatin 80 mg/d. These studies and ours differed in the characteristics of study population as well as vasospasm definition. We excluded patients with prior statin use because statin pretreatment may prevent vasospasm,<sup>2</sup> whereas statin withdrawal may be harmful.<sup>6</sup> In the study by Lynch et al, inclusion of 2 patients in the statin group and 1 patient in the placebo group who were already on statin at the time of SAH may have contributed to the relatively favorable outcome in the statin group compared to placebo.

Previous trials have used different definitions of vasospasm. Lynch et al<sup>3</sup> defined TCD vasospasm as mean MCA flow velocity of >160 cm/s, whereas Tseng et al<sup>4,5</sup> used mean MCA flow velocity of >120 cm/s.<sup>5</sup> In this study, we examined vasospasm defined by clinical, TCD, and angiographic criteria. Contrary to the prior studies, we detected no significant difference in the incidence of vasospasm by all 3 definitions. Exploratory analyses showed a possible trend toward lower incidence of vasospasm-related infarcts in the
simvastatin-treated group, perhaps suggesting protection independent of vasospasm reduction. This is the third pilot trial reported to date, and both the positive and negative results of this as well as previous single-center trials must be interpreted with caution as the sample sizes were inevitably small. The findings from the current trial, although exploratory, support the safety of statin use in critically ill patients with SAH, and underscore the need for a larger trial powered to detect group differences in clinically meaningful endpoints.

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Disclosures
None.

References

Table 3. Exploratory Analyses of VSP Indices and Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=20)</th>
<th>Simvastatin (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional angiography</td>
<td>10 (50%)</td>
<td>7 (37%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Conventional angiographic VSP</td>
<td>8 (40%)</td>
<td>5 (26%)</td>
<td>0.50</td>
</tr>
<tr>
<td>CT angiography</td>
<td>11 (55%)</td>
<td>12 (63%)</td>
<td>0.89</td>
</tr>
<tr>
<td>CT angiographic VSP</td>
<td>8 (40%)</td>
<td>10 (53%)</td>
<td>0.43</td>
</tr>
<tr>
<td>TCD PSV_{MCA} &gt;200 cm/sec and Lindegaard ratio &gt;3*</td>
<td>10 (50%)</td>
<td>13 (68%)</td>
<td>0.24</td>
</tr>
<tr>
<td>No. of days PSV_{MCA} &gt;200 cm/sec (median, 25% to 75%)</td>
<td>1 [0–5]</td>
<td>4 [1.25–7.5]</td>
<td>0.11</td>
</tr>
<tr>
<td>Time to PSV_{MCA} &gt;200 cm/sec (days, ±SD)</td>
<td>4.8±1.4</td>
<td>5.9±2.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Maximum PSV_{MCA}, cm/sec±SD</td>
<td>227±84</td>
<td>253±49</td>
<td>0.3</td>
</tr>
<tr>
<td>No. of days of HH (median, 25% to 75%)</td>
<td>2 [0–7]</td>
<td>2 [0–7.75]</td>
<td>0.86</td>
</tr>
<tr>
<td>Endovascular intervention for VSP</td>
<td>6 (30%)</td>
<td>5 (26%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Total intra-arterial nicardipine, mg±SD</td>
<td>7±13</td>
<td>11±21</td>
<td>0.48</td>
</tr>
<tr>
<td>DIND</td>
<td>10 (50%)</td>
<td>7 (37%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Time to DIND, days, ±SD</td>
<td>5.4±1.9</td>
<td>6.2±2.6</td>
<td>0.41</td>
</tr>
<tr>
<td>VSP-related infarct on CT or MRI</td>
<td>5 (25%)</td>
<td>2 (11%)</td>
<td>0.41</td>
</tr>
<tr>
<td>No. of NICU days, ±SD</td>
<td>12±4</td>
<td>14±5</td>
<td>0.36</td>
</tr>
<tr>
<td>No. of hospital days, ±SD</td>
<td>18±9</td>
<td>20±12</td>
<td>0.74</td>
</tr>
<tr>
<td>Discharge home</td>
<td>7 (35%)</td>
<td>8 (42%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Discharge modified Rankin Scale ≤2</td>
<td>10 (50%)</td>
<td>7 (37%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*Lindegaard ratios were calculated only if PSV_{MCA} >200 cm/sec, using mean middle cerebral divided by internal carotid artery velocity.

VSP indicates vasospasm; PSV_{MCA} peak systolic middle cerebral artery TCD velocity; HH, hypertension, hypervolemia therapy; DIND, delayed ischemic neurological deficits; NICU, neurointensive care unit.

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