ABSTRACT

Statins could have physiologic properties that may benefit patients that have been diagnosed with various acute neurological diseases. This review aims to summarize the literature pertaining to stain use in acute neurological disease such as subarachnoid hemorrhage, intracerebral hemorrhage (ICH), cerebral ischemia (CI), traumatic brain injury, status epilepticus and meningitis. The authors reviewed published abstracts and manuscripts pertaining to experimental and clinical trials relevant to statins in acute neurological disease. Although acute statin therapy in the setting of subarachnoid hemorrhage might reduce delayed cerebral ischemia and mortality, it should not be considered standard care at this time. Acute statins therapy has not demonstrated any benefit yet following an ICH or CI. Acute statin withdrawal may worsen outcome in acute CI. Observational and case-control studies suggest that pretreatment with statin at time of onset may be associated with better outcomes. Even though preclinical studies have shown statins to have beneficial effects, there has been no clinical evidence. In conclusion, current published studies have not shown that acute statin therapy has any beneficial effects in acute neurologic diseases and therefore further large randomized clinical trials are needed.

Key words: Statin; dyslipidemia; stroke prevention; subarachnoid hemorrhage; intracerebral hemorrhage; cerebral infarction

INTRODUCTION

The drug class of potent inhibitors of cholesterol biosynthesis called the 3-hydroxy-methyglutaryl coenzyme A reductase inhibitors, are also commonly referred to as statins. They are classified as a therapeutic class of lipid lowering agents and are established in the primary and secondary prevention of vascular diseases. Recent experimental and clinical evidence suggests that statins have cholesterol...
independent beneficial pleiotropic effects, including immunomodulation, neuroprotection and cellular senescence. These properties could be beneficial in various acute neurologic diseases.

Statins were initially developed for secondary prevention of cardiovascular disease via secondary to dyslipidemia. Initial studies in neurological disease focused on patients with stroke or at high risk of stroke. Long-term statin therapy was associated with meaningful reductions in stroke, myocardial infarction and vascular death in both primary and secondary stroke prevention. Promising data has been published from studies of acute myocardial infarction and case controlled studies of statin use prior to stroke led to an interest in determining the role of statins in the acute setting, such as reducing early recurrence of ischemic event or beneficial for long-term functional outcome.

The aim of this review is to summarize the literature regarding the use of statins in common acute neurological diseases; subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH) and acute cerebral infarction (ACI). This is a summary of the published clinical studies for statin with SAH, ICH and ACI.

### Table 1: Summary the published clinical studies for statin with subarachnoid hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Size (S:P)</th>
<th>Statin therapy</th>
<th>Initiation</th>
<th>Duration</th>
<th>Vasospasm</th>
<th>DCI</th>
<th>Poor outcome</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials</td>
<td></td>
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<td></td>
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<tr>
<td>Tseng et al.[15]</td>
<td>80 (40:40)</td>
<td>Pra 40 mg qd</td>
<td>72 h</td>
<td>14 days or discharged</td>
<td>43% vs. 63% (P = 0.006)</td>
<td>5% vs. 30% (P &lt; 0.001)</td>
<td>43% vs. 53% (P = 0.7)</td>
<td>5% vs. 20% (P = 0.04)</td>
</tr>
<tr>
<td>Lynch et al.[16]</td>
<td>39 (19:20)</td>
<td>Sim 80 mg qd</td>
<td>48 h</td>
<td>14 days</td>
<td>26% vs. 60% (P = 0.03)</td>
<td>26% vs. 60% (P = 0.03)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Chou et al.[17]</td>
<td>29 (19:20)</td>
<td>Sim 80 mg qd</td>
<td>96 h</td>
<td>21 days or ICU discharged</td>
<td>68% vs. 50% (P = 0.24)</td>
<td>37% vs. 50% (P = 0.41)</td>
<td>63% vs. 50% (P = 0.41)</td>
<td>0% vs. 15% (P = 0.23)</td>
</tr>
</tbody>
</table>

Observational cohort study

<table>
<thead>
<tr>
<th>Study</th>
<th>Size (S:P)</th>
<th>Statin therapy</th>
<th>Initiation</th>
<th>Duration</th>
<th>Vasospasm</th>
<th>DCI</th>
<th>Poor outcome</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al.[21]</td>
<td>150 (71:79)</td>
<td>Sim 80 mg qd (93%)</td>
<td>Previously used</td>
<td>14 days</td>
<td>42% vs. 41% (P = 0.91)</td>
<td>28% vs. 23% (P = 0.46)</td>
<td>28% in both group</td>
<td>N/A</td>
</tr>
<tr>
<td>McGirt et al.[22]</td>
<td>340 (170:170)</td>
<td>Sim 80 mg qd</td>
<td>N/A</td>
<td>14 days</td>
<td>25.3% vs. 30.5% (P = 0.277)</td>
<td>N/A</td>
<td>21.7% vs. 18.2% (P = 0.416)</td>
<td>18% vs. 15% (P = 0.488)</td>
</tr>
<tr>
<td>Kern et al.[23]</td>
<td>135 (72:58)</td>
<td>Pra 40 mg qd</td>
<td>N/A</td>
<td>14 days</td>
<td>52% vs. 50% (P = 0.17)</td>
<td>N/A</td>
<td>34.7% vs. 31.0% (P = 0.95)</td>
<td>14% vs. 27% (P = 0.4)</td>
</tr>
<tr>
<td>Kern et al.[23]</td>
<td>100 (49:51)</td>
<td>Sim 20, 40 mg qd</td>
<td>N/A</td>
<td>14 days</td>
<td>N/A</td>
<td>20% vs. 16% (P = 0.74)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

S:P: statin:placebo; Pra: pravastatin; Sim: simvastatin; qd: once a day; TCD: transcranial Doppler; DCI: delayed cerebral ischemia; N/A: not available; ICU: intensive care unit; H: hours.

Figure 1: Flow chart of the literature selection for (a) subarachnoid hemorrhage, (b) intracerebral hemorrhage and (c) acute cerebral infarction. RCTs: randomized controlled trials.
hemorrhage (ICH), cerebral infarction, traumatic brain injury (TBI), status epilepticus and meningitis. Studies were identified by performing a PubMed search using following key words: “statin” and each disease which was discussed in this review. Study selection was performed by two reviewers independently and the third reviewer would step in if there were any disagreement. The studies only published in English were selected. Discussion between reviewers was made to get a final consensus. The results were described in Figure 1. The main focus was the evidence for timing of statin initiation as well as specific agent and doses in the patient presenting to the emergency department and acute care unit.

**SAH**

Symptomatic cerebral vasospasm and delayed cerebral ischemia (DCI) is a major source of disability, unfavorable outcome and cause of death after aneurysmal SAH. Although the exact mechanism of SAH associated vasospasm and DCI are not well known, experimental studies suggest multifactorial pathogenesis involving inflammation, No depletion, endothelial injury, free radical and microvascular by autoregulation.[9-11] The pleiotropic effects of statin may be beneficial in attenuation of SAH associated vasospasm and DCI via inhibit the underlying mechanism of vasospasm and DCI. The results from 3 different animal models (mice, rabbits and dogs), have supported this hypothesis.[12-14]

Clinical evidence suggesting benefits in by reducing DCI and possibly vasospasm and early in-hospital mortality that has come from 6 randomized controlled trials (RCTs)[15-20] [two of which have only published as abstracts[19,20], four observational cohort studies[21-24] [Table 1] and two case-control studies.[25,26]

All 6 RCT were phase II, single-center trials and none of which enrolled more than 100 patients.[15-20] One RCT[17] focused on patents with Fisher grade 3 and the other RCTs[15,16,18-20] included all grades. The statins used in these trials were either pravastain 40 mg[15,19] or simvastatin 80 mg[16-18,20] administrated within 96 h (range from 24-96 h) following aneurysmal SAH. Three RCTs administered statin for 2 weeks,[15,16,18] two used statin for 3 weeks,[17,20] and the other prescribed statins when patients were admitted to the intensive care unit.[19] Because the definition of vasospasm varied between trials, the effects of statins on vasospasm were inconsistent. Vasospasm-related DCIs was based on both neurological deterioration and neuroimaging findings in all trials. Statin therapy reduced the incidence of DCI in three trials,[15,16,18] but showed a non-significant trend to reduce the DCI in two trials[17,20] and was neutral in one trial.[19] None of these trials showed significant benefits of early statin therapy on functional outcomes by modified Rankin Scale or Glasgow Outcome Score.[15,17-20] Mortality was reduced by statin therapy in three RCTs,[15,17,20] but not in others.[18,19]

A meta-analysis with high quality four RCTs[15-18] showed that use of statin after SAH significantly reduced both DCI [odd ratios (OR) 0.41, 95% confidence interval (CI) 0.20-0.82, \( P < 0.001 \)] and mortality (OR 0.29, 95% CI 0.09-0.93, \( P = 0.04 \)).[27] When data from non-published
RCTs19,20 was included in the analysis, statin therapy significantly reduced DCI (fixed model, OR 0.38, 95% CI 0.23-0.65, P < 0.001) and was associated with a trend toward reduced mortality (fixed model, OR 0.51, 95% CI 0.25-1.02, P = 0.06).22

Four single centers reported observation from cohorts that ranged from 49 to 170 patients of statin therapy following aneurysmal SAH.21-24 These observational studies were considered to low quality because of relatively small sample sizes, heterogeneity in baseline, clinical management and definition of clinical outcome. A meta-analysis was performed using these 4-observation cohort studies, one case control study25 and 6 RCTs which included 1,542 patients, whom 385 received statin.27 Statin use after aneurysmal SAH was not significant associated with reduced DCI (OR 0.96, 95% CI 0.71-1.31, P = 0.80) or mortality (OR 1.16, 95% CI 0.78-1.73, P = 0.47). A more recent case-control study with atorvastatin suggested that the atorvastatin may have an anti-ischemic effect on imaging, but no clinical benefit after aneurysmal SAH.28

Consistent across all studied, there were no significant adverse effects associated with statin use after aneurysmal SAH. Asymptomatic elevation of liver enzyme within unexpected range was reported in 3 RCTs15,17,18 with only 1 patient having to discontinue statin because of myalgia.18

**ICH**

Although case-control studies of statin use before ICH has demonstrated an association with favorable outcomes and reduced mortality after ICH,29 there are no clinical studies of early initiation after ICH onset. Preclinical studies have shown beneficial effects on functional outcome in several animal models of ICH.30-31 Pleiotropic effects of statin such as neuroprotection and stimulation of neurogenesis and synaptogenesis might be contributed to this benefit.32 A multicenter observational cohort study in Israel, including 89 patients with statin from a total of 312 ICH patients, showed that the prior use of statins was associated with good neurologic outcome at discharge of the patients (OR 2.97, 95% CI 1.25-7.35, P = 0.004) and reduced mortality (OR 0.47, 95% CI 0.25-0.74, P = 0.004) without an effect on hematoma expansion. A meta-analysis was performed of 6 trials that used statins before ICH and the data showed a increased association with favorable outcomes (OR 1.19, 95% CI 1.38-2.65, P < 0.0001) and reduced mortality (OR 0.55, 95% CI 0.32-0.70, P = 0.005) without an effect on hematoma expansion.
Although there have been concerns of statins increasing the risk of ICH, recent evidence suggest that the statins did not increase the risk of ICH. The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study found increased risk of subsequent ICH (unadjusted hazard ratio 1.68, 95% CI 1.09-2.59) among subjects with prior stroke randomized to high-dose atorvastatin. Mild antithrombotic properties and lipid lowering effect of statins might be explained mechanism of association between statins and risk of ICH. However, recent meta-analysis have been reported that low cholesterol concentrations with intensive statin therapy did not correlate with risk for ICH. A recent large systematic review and meta-analysis of 23 randomized trials that provided a cumulative total of 526,518 patients years of follow-up with median 3.9 years found no evidence that statins were associated with developing ICH (risk ratio 1.10, 95% CI 0.86-1.44). A second meta-analysis using 12 cohort studies that provide a total of 219,458 patient-years of follow-up or 6 case-control studies also did not show any risk of ICH with statin (each risk ratio 0.94, 95% CI 0.81-1.10 and risk ratio 0.60, 95% CI 0.41-0.88).

ACUTE CEREBRAL INFARCTION

There are numerous published work that demonstrates the beneficial effects of statins in animal models of ischemic stroke. These experimental models have evaluated effects of statin treatment prior to and after initiation of cerebral infarction. Statins have been shown to improve endothelial function and increase cerebral perfusion in the ischemic penumbra by improving no production immediately after treatment initiation. The anti-oxidative and anti-inflammatory properties of statins can affect secondary brain injury in the setting of ischemia. A meta-analysis of 1,882 animals in 41 studies with ischemic occlusive stroke models showed that use of statin reduced infarction volume by 25% (95% CI 21-30%, P < 0.001) and improved neurologic outcome by 20.36% (95% CI 14-26%, P < 0.001). Furthermore pretreatment with statin (median 14 days, range 5-14) was more effective than initiation after ischemia (median 4 h, range 1-12) in infarct size reduction (33.57%, 95% CI 28.47-38.53% vs. 16.02%, 95% CI 11.63-20.42%; χ² = 408, P < 0.001) and improve neurologic outcome (26.52%, 95% CI 15.05-37.99% vs. 14.37%, 95% CI 7.26-21.48%; χ² = 17, P < 0.001).

Most studies have shown that the use of statins at the time of ischemic stroke may confer a beneficial effect. A population-based prospective study of 953 patients did not demonstrate early improvement in functional outcome after a first ischemic stroke event (OR 0.76, 95% CI 0.53-1.09, P = 0.134). A small observational study noted more favorable outcomes in a 3-month period in which the patients were given statins for 3 months prior to the stroke statin group. Pretreatment with statin was associated with decreased in-hospital mortality and reduced stroke severity. The largest observational study evaluated 12,689 cases with acute ischemic stroke and found that statin use before and during hospitalization was strongly associated with improved survival (hazard ratio 0.59, 95% CI 0.53-0.65, P < 0.001).

The question of in-hospital cessation of statin therapy is an important as stroke patients may be dysphagic and NPO after admission. This important question was addressed in the same large observational cohort of 12,689 cases and statin discontinuation in the acute phase of stroke, even for a brief period, was associated with a substantially greater risk of death (hazard ratio 2.5, 95% CI 2.1-2.9; P < 0.001). A small single-center randomized blinded study of statin withdrawal vs. continuation confirmed the need to continue treatment in this population. The acute statin withdrawal was associated with increase in early neurologic deterioration (OR 8.67, 3.05-24.63) and death/dependency (OR 4.66, 1.46-14.91).

There is currently not enough evidence to confirm the beneficial effect of statin treatment in acute phase of ischemic stroke. A recent pilot clinical trial called “MISTICS” randomized 60 patients within 3 to 12 h after acute ischemic stroke to simvastatin or placebo for 90 days. This study showed that simvastatin therapy improved functional outcome (46.4% vs. 17.9%, P = 0.02). However, there were safety concerns as statin therapy was associated with increased incidence of infection (OR 2.4, 95% CI 1.06-5.4) and a trend to increase mortality (25.0% vs. 10.7%, P = 0.16). Other randomized trials of statin therapy in acute stroke were limited by insufficient recruitment and insufficient data for analysis.

One potential strategy for translating the efficacy of statins in preclinical models may be to use very high doses or intravenous routes for statin initiation. The neuroprotection with Statin Therapy for Acute Recovery Trial (MISTICS) randomized 33 patients with acute ischemic stroke < 24 h of onset wastesting a short-term high-dose lovastatin at 1, 3, 6, 8, and 10 mg/kg per day for 3 days. Patients were followed for 30 days and clinical and laboratory outcome measured in this Phase IB trial and the maximum tolerated dose was estimated to be 8 mg/kg per day.

Despite the lack of evidence for treating acute stroke with statin, there is no doubt that in-hospital initiation should occur when statin therapy is indicated. The SPARCL study clearly defined the role of statins in secondary stroke prevention, yet did not address the best...
time to initiate therapy. Studies comparing in-hospital initiation with outpatient initiation of preventative therapies have consistently shown better compliance over the long-term. For stroke patients, participation in a hospital-based prevention initiative with in-hospital initiation of antithrombotic, statin and antihypertensive was associated with very high rates of compliance at 3 months. In-hospital initiation of statins is associated with high rates of continuation and achievement of National Cholesterol Education Program guideline goals. In one study 92 statin-naïve patients with an indication for treatment, hospital initiation of statin therapy yielded a 93% rate of adherence, lowered mean low-density lipoprotein cholesterol levels from 120 to 78 mg/dL and increased the proportion of patients with low-density lipoprotein cholesterol levels lower than 100 mg from 36% to 88% at 3 months.

**TBI AND SCI**

Statins have demonstrated benefit in animal models of TBI and spinal cord injury (SCI). Statins treatment prior to experimental TBI was associated with reduced the cortical contusion volume and cerebral edema. Statin therapy after TBI in rat decreased post-traumatic apoptosis in hippocampus and peri-contusional cortex and increased neuronal proliferation leading to improvement of cognitive abilities. The experimental studies in preclinical SCI models also suggest that statin treatment could significantly improve functional outcome via anti-inflammatory and anti-apoptotic effects.

Clinical evidence for the effect of statins moderate to severe neurotrauma needs further extensive studying. Only one small prospective, randomized, double blind trail of statin treatment initiation within 24 h of moderate TBI was found. The study included only 8 patients with statin and the 13 controls. The statin administration was associated with a reduced duration of amnesia (hazard ratio 53.76, 95% CI 1.58-1,824.64), but no difference in disability at 3 months.

**STATUS EPILEPTICUS AND EPILEPSY**

Animal models suggest that statin administration might be a therapeutic strategy for epilepsy through neuroprotection in status epilepticus (SE) and prevention of epileptogenesis progression. Lovastatin administration after pilocapine-induced SE suppressed mRNA expression of hippocampal cytokines (such as interleukin-1b, interleukin-6, tumor necrosis factor a, and kinin B1 receptor) and reduced SE-induced hypothermia. Lovastatin also decreased cell loss in hippocampal CA1, CA3 and hilus of dentate gyrus after pilocapine-induced SE that is a critical step of epileptogenesis. In the chronic temporal lobe epilepsy (TLE) model, 2 weeks administration of simvastatin after kainic acid-induced SE lead to not only attenuated microscopic morphological changes, but also reduced seizure activity in the brain at 4 to 6-month after SE. On the other hand, 2 weeks treatment of atorvastatin did not affect the duration of SE or development of epilepsy in electrically induced rat TLE model.

There is no evidence that the neuroprotective properties of statin will have a clinical benefit in acute epileptic syndromes.

**CENTRAL NERVOUS SYSTEM INFECTION**

Simvastatin can attenuate leukocyte invasion into the central nervous system (CNS) and systemic complication of pneumococcal meningitis in an experimental model of bacterial meningitis rodents. Simvastatin treatment significantly reduced cerebrospinal fluid leukocyte counts with dose-dependent manner, but did not altered cerebellar bacterial titers. The marked hypothermia was dose-dependently reversed by statin treatment. This neuroprotective effects can be explained by anti-inflammatory pleiotropic property of the statin. Statin treatment did not result in an improvement of the clinical score or a reduction of increased intracranial pressure and blood-barrier breakdown. Clinical studies of the effects of statin treatment in acute CNS infection are lacking.

**CONCLUSION**

Some preclinical and clinical evidence has shown that statin therapy following SAH could be safe and beneficial in terms of reducing DCI and possibly cerebral vasospasm and early in-hospital mortality. However, methodology of clinical studies was varied and beneficial effects were inconsistent, statin therapy following SAH should not be considered standard care at this time. Statin use before ICH or before and during acute ischemic stroke is safe and can reduce in-hospital mortality and improve functional outcome, whereas statin withdrawal in the hospital after acute ischemic stroke, even for a brief period, can cause early neurologic deterioration and death. Despite the lack of clinical evidence for statin initiation after ICH or acute ischemic stroke, we can achieve better long-term compliance with in-hospital initiation when statin therapy is indicated. Even though benefit in preclinical studies, there is no clinical evidence that the pleiotropic properties of statins will have a clinical benefit in neurotrauma, epilepsy and CNS infection.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES


