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Does Cognitive Dysfunction after Carotid Endarterectomy Vary by Statin Type or Dose?

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Abstract Our previous work demonstrates that asymptomatic carotid endarterectomy (CEA) patients demonstrate less perioperative neurologic injury, defined as stroke and early cognitive dysfunction (eCD) observed within 24hr of CEA, when taking statins pre-operatively. This study examines whether the incidence of eCD observed 24hr after asymptomatic CEA varies as a function of statin type or dose. Patients with asymptomatic carotid stenosis scheduled for CEA consented to participate in an observational IRB-approved study (N=324). Patients were evaluated with an extensive battery of neuropsychometric tests pre-operatively and 24hr post-operatively. Of the 324 consented patients, 200 were taking statins. Patients taking pravastatin and fluvastatin exhibited no eCD, while patients taking lovastatin (17.7%) and rosuvastatin (16.7%) exhibited incidences of eCD similar to those not taking statins (20.2%). Patients taking simvastatin exhibited a significantly lower incidence of eCD than those taking atorvastatin (3.0% vs. 16.0%, P=0.005). Patients taking a maximal dose of any statin exhibited a significantly lower incidence of eCD than patients taking sub-maximal doses (2.7% vs. 15.9%, P=0.002). These observations suggest that the incidence of eCD may in fact vary as a function of statin type and that maximal doses may be the optimal dose for patients undergoing CEA. This variation may be due to the physico-chemical properties of statins such as lipophilicity, molecular size, and blood brain barrier penetrability. These findings should be used to inspire randomized prospective work to determine the safety, feasibility, and outcomes of optimizing statin use prior to CEA.

Keywords Carotid Endarterectomy, Cognitive Dysfunction, Statins

1. Introduction

Carotid endarterectomy (CEA) is a common revascularization procedure performed to reduce the risk of future stroke in patients with asymptomatic high-grade carotid artery stenosis[1,2]. There is some risk of perioperative neurologic injury associated with asymptomatic CEA, defined by both clinical stroke and early cognitive dysfunction (eCD). As perioperative stroke is exceedingly rare, investigators are using subtler, more common forms of neurologic injury like eCD to study and improve the neurologic morbidity and safety of carotid revascularization[3-6]. The incidence of eCD exhibited 24hr after CEA is approximately 25%[7-9]. The neurologic outcome of eCD has been associated with markers of neuronal injury[10] and other groups have associated it with decreased quality of life[11] thus validating its clinical significance.

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It is commonly thought that statin type has little impact on the efficacy of statins in lowering low-density lipoprotein, but we consider that different statins may not be equally effective in modulating systemic and neuro-inflammation. One study examined the effect of different statins on the regression of coronary atherosclerosis and found that there were no differences in lipid profiles from baseline to 6 months based on statin type, but did find that rosuvastatin was more effective in treating atherosclerosis than atorvastatin[14,15]. Additionally, researchers have reported that certain statins may be more effective in reducing inflammation in stroke-prone rats [15,16]

Studies have suggested that statin therapy initiated on admission for symptomatic CEA is protective against ischemic stroke and mortality[12].We have previously demonstrated that patients taking statins prior to asymptomatic CEA exhibit significantly less perioperative stroke and significantly less eCD than patients not taking statins prior to asymptomatic CEA[13]. No studies have evaluated whether there are differences among the statin types or doses in the context of eCD in asymptomatic CEA patients. Therefore, we propose to evaluate our patient cohort for differences among the statin types and doses.

In this retrospective observational follow up study, we

aim to determine whether the incidence of eCD observed 24hr after asymptomatic CEA varies by statin type and dose. We hypothesize that the incidence of eCD will vary by statin type and dose as statins have a variety of pleiotropic effects and different physico-chemical properties that may be influential in the context of eCD in asymptomatic CEA patients.

2. Methods

2.1. Patients

Three hundred twenty-four (324) asymptomatic CEA patients with high-grade carotid artery stenosis were enrolled with written informed consent in this IRB-approved observational study from 1995 to 2012 (www.ClinicalTrials.gov NCT00597883). All patients were previously reported in a previous observational study evaluating the incidence of perioperative stroke and eCD in symptomatic patients taking and not taking statins prior to CEA[13].

Eligible patients were those schedule for elective CEA, asymptomatic status defined as negative for history of previous stroke or transient ischemic attack, English-speaking, no axis-I psychiatric disorders, and ability to complete the neuropsychometric testing pre-operatively and post-operatively.

2.2. Cognitive Measures

All patients were evaluated with an extensive battery of neuropsychometric tests pre-operatively and again 24hr post-operatively. The neuropsychometric tests evaluate four cognitive domains – verbal memory (Controlled Oral Word Association Test, Hopkins Verbal Learning Test, and/or Buschke Selective Reminding Test), visuo-spatial organization (Rey-Osterrieth Complex Figure Copy and Recall), motor function (Grooved Pegboard and/or Finger Tapping Test), and executive action (Halstead-Reitan Trials A and B).

The criteria for eCD are based on difference scores calculated for each test by subtracting the pre-operative test performance from the post-operative test performance at 24hr. Z-scores were generated based on a surgical reference group's performance to account for practice effect of repeated neuropsychometric testing, trauma of surgery, residual of a general anesthetic, and the overnight hospital stay experience. Patients were designated to have eCD by one of two criteria to account for both focal and global/hemispheric deficits: (1) ≥2SD worse performance in two or more cognitive domains or (2) ≥1.5SD worse performance in all four cognitive domains. Further details regarding the surgical reference group as well as each test's specific scoring rubric are available in previous studies [7-9,13,17].

2.3. Statistics

Statistical analysis was performed using R environment for statistical computing (R Development Core Team, Vienna, Austria, 2008). Descriptive analyses were performed for all statin types. Comparative analyses were limited to simvastatin/atorvastatin and maximal dose/sub-maximal dose as group sizes were not adequate to conduct multiple comparisons. For comparative analyses, Student's t-test, Fisher's exact test, Pearson's $\chi 2$ test, and simple logistic regression were used where appropriate. $P \leq 0.05$ was considered significant.

3. Results

3.1. Statin Types

Two hundred (200) patients were taking statins prior to CEA (61.7%). Of the 200 patients taking statins, 94 were taking atorvastatin (47.0%), 66 simvastatin (33.0%), 17 lovastatin (8.5%), 12 rosuvastatin (6.0%), 9 pravastatin (4.5%), and 2 fluvastatin (1.0%).

Patient characteristics of each statin type group are presented in Tables 1 and 2. Although no statistical comparisons were conducted on the less commonly used statins presented in Table 1, the statin type groups appear to be fairly comparable to each other. Pravastatin and fluvastatin exhibited no eCD, while lovastatin (17.7%) and rosuvastatin (16.7%) exhibited eCD similarly to no statins (20.2%).

Simvastatin and atorvastatin were the most commonly used statins in our cohort. Patient characteristics of those taking simvastatin and atorvastatin are presented in Table 2. The only significant differences between simvastatin and atorvastatin were patients taking simvastatin had significantly higher levels of HDL (58.7±17.6mg/dL vs. 41.7±14.0mg/dL, $P<0.001$) and significantly lower levels of LDL (78.6±36.3mg/dL vs. 108.6±67.0mg/dL, $P=0.001$) than those taking atorvastatin. Patients taking simvastatin exhibited significantly less eCD than those taking atorvastatin (3.0% vs. 16.0%, $P=0.005$).

Table 1. Patient Characteristics: Lovastatin, Rosuvastatin, Pravastatin, Fluvastatin, No Statin*

	Lovastatin N=17	Rosuvastatin N=12	Pravastatin N=9	Fluvastatin N=2	No Statin N=124
Age >75	35.3%	33.3%	22.2%	50.0%	33.1%
Sex, male	70.6%	41.7%	44.4%	50.0%	61.3%
BMI	27.3±4.7	31.0±7.6	28.4±6.6	30.2±5.1	26.3±3.8
Education	14.0±2.5	13.2±4.3	16.2±3.6	11.5±0.7	14.7±3.1
DM	23.5%	8.3%	22.2%	100%	16.1%
HTN	82.4%	66.7%	44.4%	50.0%	45.2%
Smoking	64.7%	83.3%	44.4%	100%	65.3%
PVD	41.2%	41.7%	22.2%	50.0%	25.0%
LDL	95.9±27.5	75.0±21.4	83.2±31.3	158.2±52.0	119.9±45.5
Triglycerides	152.7±59.3	143.3±74.8	165.3±64.3	156.5±47.4	139.4±62.3
Cholesterol	174.9±32.1	149.5±36.6	156.3±35.3	228.0±79.2	190.6±50.6
HDL	48.4±20.6	45.8±20.1	40.1±14.3	38.5±17.7	42.8±16.6
eCD	17.7%	16.7%	0%	0%	20.2%

*Mean ± standard deviation or percentage (%); BMI – body mass index in units of kg/m^2; DM – diabetes mellitus; HTN – hypertension; PVD – peripheral vascular disease; LDL – low-density lipoprotein; HDL – high-density lipoprotein; eCD – early cognitive dysfunction exhibited 24hr after CEA

Table 2. Patient Characteristics: Simvastatin & Atorvastatin*

	Atorvastatin N=94	Simvastatin N=66	P†
Age >75	27.7%	19.7%	0.24
Sex, male	67.0%	78.8%	0.10
BMI	27.2±4.7	27.1±4.4	0.83
Education	15.2±3.6	14.4±3.6	0.15
DM	23.4%	15.2%	0.19
HTN	50.0%	60.6%	0.18
Smoking	72.3%	81.8%	0.16
PVD	36.4%	27.7%	0.24
LDL	108.6±67.0	78.6±36.3	0.001
Triglycerides	135.5±64.5	127.6±57.4	0.44
Cholesterol	177.2±64.8	162.8±41.5	0.12
HDL	41.7±14.0	58.7±17.6	<0.001
eCD	16.0%	3.0%	0.005

*Mean ± standard deviation or percentage (%); BMI – body mass index in units of kg/m^2; DM – diabetes mellitus; HTN – hypertension; PVD – peripheral vascular disease; LDL – low-density lipoprotein; HDL – high-density lipoprotein; eCD – early cognitive dysfunction exhibited 24hr after CEA

†Comparative analyses were conducted with Student's t-test, Fisher's exact test, Pearson's $\chi 2$ test, and simple logistic regression where appropriate

3.2. Statin Doses

The number of patients taking each dose of each statin type is presented in Table 3. The most commonly used statin type and dose were atorvastatin 40mg (18.0%), simvastatin 40mg (16.5%), and atorvastatin 20mg (16.0%). No statistical comparisons among each statin type and dose could be made as each group was fairly small. Therefore, patients were designated as part of one of two groups for dose analysis: all patients taking the maximally tolerated doses of their respective statin (N=74) and patients taking any sub-maximal dose of their respective statin (N=126). Maximally tolerated doses for each statin type are defined as follows: atorvastatin 80mg, simvastatin 40mg or 80mg, lovastatin 20mg, rosuvastatin 20mg, pravastatin 40mg, and fluvastatin 20mg (Table 3). Simvastatin 80mg was discontinued by the FDA in 2011 shortly before the conclusion of this study; therefore, we considered both the previously defined maximal dose of 80mg and the currently defined maximal dose of 40mg as maximal doses of simvastatin.

Patients taking a maximal dose of any statin exhibited a significantly lower incidence of eCD than patients taking sub-maximal doses (2.7% vs. 15.9%, P=0.002).

Table 3. Statin Type and Dose*

	Atorvastatin N=94	Simvastatin N=66	Lovastatin N=17	Rosuvastatin N=12	Pravastatin N=9	Fluvastatin N=2
5mg	-	-	2/9 (22.2%)	1/4 (25.0%)	-	-
10mg	2/15 (13.3%)	0/3 (0%)	1/5 (20%)	0/1 (0%)	0/3 (0%)	-
20mg	7/32 (21.9%)	1/13 (7.7%)	0/3 (0%)	1/7 (14/3%)	0/5 (0%)	0/2 (0%)
40mg	6/36 (16.7%)	1/33 (3.0%)	-	-	0/1 (0%)	-
80mg	0/11 (0%)	0/17 (0%)	-	-	-	-

*Number of patients with eCD out of the number of patients taking the respective dose of the type of statin (percentage with eCD in the respective statin type and dose group). Shaded cells are those of maximal doses for each statin type

4. Discussion

Our previous work demonstrates that patients taking statins prior to asymptomatic CEA exhibit a lower incidence of perioperative stroke and eCD than those patients not taking statins. No previous work has examined whether the incidence of eCD varies by statin type or dose in an asymptomatic CEA population. Due to the pleiotropic effects and different physico-chemical properties of each statin type, we sought to investigate whether the incidence of eCD varies by statin type and dose.

Patients taking simvastatin demonstrate a significantly lower incidence of eCD than patients taking atorvastatin. Patients taking pravastatin and fluvastatin demonstrated no eCD while patients taking lovastatin and rosuvastatin demonstrated incidences of eCD comparable to patients taking no statins. Maximally tolerated doses of statins appear to be the doses at which the incidence of eCD is the lowest regardless of statin type.

Statins have a variety of pleiotropic effects aside from lowering low-density lipoproteins[18-21]. Additionally, each statin has its own physico-chemical properties that may be influential in the context of eCD in asymptomatic CEA patients. For example, lipophilicity and molecular size plays a significant role in the ability of a statin to cross the blood brain barrier and act locally on brain tissue[18,22,23]. Simvastatin is a very lipophilic molecule that is also relatively small in size as it is based on a monacolin J-molecule. Atorvastatin is also a lipophilic statin, but significantly less lipophilic than simvastatin, and significantly larger in molecular size [18]. Work done in mice brains, as well as in human cerebrospinal fluid, have documented that simvastatin is able to enter the brain more readily than other statins [18,22,24]. Additionally, it is reasonable to consider that statins that are not as lipophilic or as small as simvastatin may also penetrate the blood brain barrier, but may require higher doses in order to do so effectively. Maximal doses of any statin type appear to have a lower incidence of eCD compared to sub-maximal doses. This finding may suggest that an alternative statin treatment for patients that cannot tolerate the side effects of lipophilic statins could be a maximal dose of a less lipophilic statin. However, this suggestion needs to be confirmed and explored further.

We speculate that the lipophilicity and small molecular size of simvastatin may allow it to penetrate the blood brain barrier and exert its pleiotropic effects directly on the brain more effectively than atorvastatin and the other less lipophilic statins like rosuvastatin and lovastatin. Neuroprotective properties of statins have been recently explored[19,25] and the subject of many clinical trials in a variety of neurologic contexts like Alzheimer's disease [26,27], stroke[28,29], and subarachnoid haemorrhage[30]. Statins may exert anti-inflammatory effects and regulate nitric oxide production[19] in the brain tissue and therefore attenuate the insult of ischemic-reperfusion injury of asymptomatic CEA. Currently unpublished data from our group suggests patients with baseline elevated inflammation as well as reduced blood flow through the middle cerebral artery during cross-clamp are at significantly higher risk of eCD implicating inflammation and/or ischemic-reperfusion injury are involved in the mechanism of eCD.

An anomaly in our data is that none of the 9 patients taking pravastatin exhibited eCD. This is troubling as pravastatin is one of the least lipophilic statins of the group and, according to the blood brain barrier penetration hypothesis, pravastatin should be less efficient in crossing into the brain. This anomaly may be partially explained by the fact that patients taking pravastatin are younger, have more years of education, have less hypertension, fewer smokers, and less peripheral vascular disease than the other statin groups. These characteristic factors may play a role in this observation. However, more work is necessary to draw conclusions about pravastatin.

We do recognize that our study has limitations. This study is retrospective and was conducted at a single centre in New York City. The group sizes are not comparable among all the statin types and doses and the groups were not randomized limiting our statistical power and utility. However, we do present our comparative and descriptive analyses to inspire future prospective work. Information regarding duration of statin use, reason of statin prescription, and adherence to

statin regimen were not available.

5. Conclusions

These observations suggest that the incidence of eCD may in fact vary as a function of statin type and that maximal doses may be the optimal dose for patients undergoing asymptomatic CEA. This variation may be due to the physico-chemical properties of statins such as lipophilicity, molecular size, and blood brain barrier penetrability. These findings should be used to inspire randomized prospective work to determine the safety, feasibility, and outcomes of optimizing statin use prior to asymptomatic CEA.

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