Clinicoradiological Profile and Serum Lipid Levels of Intracerebral Hemorrhage in Prior Statin Users

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Abstract

Objective We aimed to evaluate whether serum lipid levels can influence the clinicoradiological recovery of intracerebral hemorrhage (ICH) in prior statin users.

Patients and Methods Medical records were reviewed retrospectively in 381 ICH patients (253 men and 128 women). Cardiovascular disease (CVD) risk factors, blood pressure at admission and the first in-hospital day, admission and 30-day scores of National Institute Health Stroke Scale (NIHSS) and modified Rankin scale (mRS), hematoma volume (HV), serum lipid levels were compared between prior statin users and non-users.

Results Statins were pretreated in 56 patients (31 men and 25 women). Statin users were older age, and had higher frequencies of dyslipidemia, diabetes mellitus, atrial fibrillation, prior stroke history and large HV compared to non-users. Serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly decreased in the statin group compared to the non-statin group. There were no statistical differences in the other CVD risk factors, functional scores and other serum lipid levels between the two groups. HV was correlated inversely with serum levels of TC and LDL-C in both groups. Multiple logistic regression analysis showed that serum TC levels ≤ 150 mg/dL were associated with statin use [Odds ratio (OR)=5.5, 95% confidence interval (CI)=1.55-19.58], worsening of NIHSS score (OR=1.4, 95% CI=1.21-1.63) and HV (OR=1.1, 95% CI=1.07-1.13) in ICH patients. A significant association was found between worsening of NIHSS score (OR=2.0, 95% CI=1.32-3.12) and worsening of mRS score (OR=3.3, 95% CI=1.33-8.00), HV (OR=1.3, 95% CI=1.01-1.76), and serum TC levels ≤ 150 mg/dL in statin users.

Conclusion Prior statin users with serum TC levels ≤ 150 mg/dL had worsening of outcome and HV. Excessive lowering of serum TC levels due to statin pretreatment may cause unfavorable clinicoradiological recovery of ICH. Physicians should monitor serum lipid levels carefully in statin users.

Key words: statin, intracerebral hemorrhage, serum total cholesterol levels, cardiovascular disease risk factor, functional outcome, hematoma volume

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Introduction

Statin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, has multifunctional effects in addition to lowering cholesterol synthesis (1). Statin treatment attenuates a variety of experimental animal diseases, including ischemic stroke (2), intracerebral hemorrhage (ICH) (3, 4), head trauma (5), subarachnoid hemorrhage (6, 7) and motor neuron degeneration (8). Clinical studies have also suggested

that statins are associated with better outcomes after ischemic stroke (9) and subarachnoid hemorrhage (10). ICH is a lethal form of stroke with mortality rates approaching 50% (11). Many previous studies have reported that serum lipid profile influenced the functional outcome or mortality in ICH patients (12-18). Cholesterol-lowering treatment with statins may increase the incidence of ICH or a risk of recurrent ICH because statins are known to inhibit platelet aggregation and thrombogenesis (19, 20). A high-dose administration of atorvastatin increased the incidence of hemorrhagic

stroke in patients who had prior history of stroke or transient ischemic attack during the previous 1-6 months (21). Recently, prior treatment of statins has been advantageous for clinical recovery and neuroradiological aspects in ICH patients (22-25). Other studies exhibited no protective effects of statins in ICH patients (26, 27). Little is known how serum lipid levels influence the clinicoradiological prognosis of ICH in prior statin users. Here we evaluated the serological lipid profile and clinicoradiological variables between pre-ICH statin users and non-users.

Patients and Methods

Study participants

ICH was diagnosed by computed tomography (CT) [Aquilion™ 16, Toshiba, Otawara, Japan] within 12 hours after clinical onset. A total of 381 consecutive patients with a diagnosis of non-traumatic ICH were admitted to our department between 2006 and 2009. The medical records and brain CT findings were reviewed retrospectively. We excluded the following ICH patients; hemorrhagic transformations of ischemic strokes and hemorrhage from trauma, tumors or arteriovenous malformations. Detailed medical history and condition at pre-ICH, including use of statins, antiplatelets and anticoagulants, were obtained by direct interview to each patient or family member, and medical information by previous physicians. The present study was approved by the ethical committee of Toho University Omori Medical Center.

Clinical variables and serum lipid levels

Cardiovascular (CVD) risk factors were analyzed on the following 8 items: obesity (body mass index ≥ 25.0 kg/m²); current smoker; heavy alcohol intake (≥ 34 g/day of ethanol); hypertension [systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg] or currently under treatment; diabetes mellitus (DM) [fasting blood sugar ≥ 126 mg/dL or hemoglobin A_{1c} ≥ 6.5 %] or currently under treatment; dyslipidemia [serum low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL or high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL] or currently under treatment; atrial fibrillation (AF); and prior history of stroke. SBP was reviewed at admission and the first in-hospital day. Neurological deficits were graded with National Institute Health Stroke Scale (NIHSS) and modified Rankin scale (mRS). Both scores were examined at admission and 30 days after ICH onset. Alternation score of NIHSS and mRS were calculated as point at admission minus point at post-stroke 30 days, respectively. Worsening score of NIHSS or mRS was defined as that alternation score less than -1 point. Serum samples of total cholesterol (TC), LDL-C, HDL-C and triglyceride (TG) were obtained at admission. TC and TG levels were measured by enzymatic methods with an RX-30 device (Nihon Denshi, Tokyo, Japan). HDL-C levels were measured by phosphotungstic acid magnesium methods

with an MTP-32 (Corona Electric, Ibaraki, Japan). LDL-C was calculated with the Friedewald formula as follows: LDL-C (mg/dL) = TC (mg/dL) - HDL-C (mg/dL) - 0.2 × TG (mg/dL) (28).

Neuroradiological variables

Brain CT was performed according to a standardized protocol that a slice thickness was 4 mm for the posterior fossa and 8 mm for the supratentorial regions. ICH volume was calculated by the ABC/2 technique that A is the greatest hemorrhage diameter, B is the diameter 90° degrees to A, and C is the number of CT slices with hemorrhage multiplied by the slice thickness (29). Intraventricular hematoma (IVH) on the admission CT was assessed. Hematoma location was categorized into 5 regions: the cerebral subcortex; the basal ganglia; the thalamus; the brainstem; and the cerebellum. Brain CT cans were reviewed by an experienced neurologist and a trained neuroradiologist who were blinded to the treatment status at the time of CT assessment.

Statistical analysis

Comparison of clinicoradiological variables and serum lipid levels between the statin group and the non-statin group used unpaired Student's t-test or χ^2 test. Binary correlation between serum lipid levels and clinicoradiological variables was analyzed by Spearman's rho correlation. Multiple logistic regression analysis was performed to identify an independent risk factor for worsening score of NIHSS and mRS, and hematoma volume (HV). Data were analyzed by PASW Statistics 18.0 (IBM, Chicago, USA).

Results

Univariate analysis of clinical variables and serum lipid profile

Clinical variables and serum lipid levels are shown in Table 1 and Table 2, respectively. Mean age (SD) was 67.6 (12.5) years [64.7 (12.2) in men and 73.4 (11.2) in women]. Fifty-six patients (31 men and 25 women) were pretreated with statins. The frequency of prior statin use was 15.0% in ICH patients (14.0% in men and 24.3% in women). The various types of statins were as follows: atorvastatin in 17 patients, pravastatin in 12, pitavastatin in 12, rosuvastatin in 11 and simvastatin in 4. Statins were administered at Japanese standard doses. Mean duration of statin use (SD) was 2.3 (1.2) years. Neurosurgical procedures were performed in 19 patients (2 statin users and 17 non-users). As compared to statin non-users, univariate analysis showed significantly higher frequencies of dyslipidemia, DM, AF and prior stroke history in statin users. The age of statin users was significantly older than in non-users. Serum levels of TC and LDL-C were significantly decreased in statin users compared to non-users. Gender, other CVD risk factors, serum TG and HDL-C levels, admission and the first in-hospital day SBP, NIHSS score, mRS score, and frequency of anti-

Table 1. CVD Risk Profiles and Functional Score of NIHSS and mRS in Statin Users and Non-users

	Statin group (n=56)	Non-statin group (n=325)
Men/women	31/25	222/103
Age years	73.0 (10.8)***	66.7 (12.6)
Hypertension	48 (86%)	286 (88 %)
Obesity	14 (25%)	72 (22%)
Heavy drinker	11 (20%)	65 (20%)
Current smoker	16 (29%)	87 (27%)
Dyslipidemia	56 (100 %)***	50 (15%)
Diabetes mellitus	20 (36%)*	46 (14%)
Atrial fibrillation	9 (16%)* 23 (7%)	
Prior history of stroke	13 (23%)**	14 (4%)
Anticoagulant medication	4 (7.1%)	24 (5.8%)
PT-INR (anticoagulant users)	1.4 (2.0)	1.5 (2.3)
Admission SBP	150.2 (17.7)	146.8 (16.1)
The 1st day SBP	131.2 (13.0)	128.3 (15.4)
Admission NIHSS score	17.4 (8.9)	18.2 (9.5)
30-day NIHSS score	16.5 (7.7)	16.2 (9.6)
Changes of NIHSS score	0.9 (4.8)	1.6 (5.5)
Admission mRS score	3.5 (1.0)	3.6 (1.5)
30-day mRS score	3.2 (1.5)	3.2 (1.9)
Changes of mRS score	0.2 (0.9)	0.4 (1.1)

CVD: cardiovascular disease; mRS: modified Rankin Scale; NIHSS: National Institute Stroke Scale; PT-INR: prothrombin time- international normalized ratio; SBP: systolic blood pressure

Data of age, PT-INR NIHSS score, mRS score, and changes of NIHSS score and mRS score were expressed in mean (SD).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by χ^2 test; between the statin group and the non-statin group.

Table 2. Serum Lipid Levels in Statin Users and Non-users

	Statin group (n=56)	Non-statin group (n=325)
TC	167.0 (45.4)**	191.6 (44.6)
LDL-C	93.4 (37.4)*	110.4 (37.5)
HDL-C	54.5 (17.1)	59.9 (21.3)
TG	116.0 (48.4)	133.4 (118.4)

HDL-C: high-density cholesterol; LDL-C: low-density cholesterol; TC: total cholesterol; TG: triglyceride

Data were expressed in mean (SD) mg/dL.

* $p < 0.01$, ** $p < 0.001$ by unpaired Student's t-test; between the statin group and the non-statin group.

coagulant medication did not differ statistically between the statin group and the non-statin group.

Neuroradiological variables in statin users and non-users

Neuroradiological profile is summarized in Table 3. ICH location and IVH rate did not differ statistically between the statin and the non-statin group. HV was increased significantly in statin users compared to statin non-users.

Binary correlation between serum lipid levels, functional outcome and HV

Alternation of NIHSS score was linked to serum TC levels (Spearman's $\rho=0.64$, $p<0.001$) and serum LDL-C levels (Spearman's $\rho=0.58$, $p<0.001$). That of mRS score was inversely correlated with serum TC levels (Spearman's $\rho=-0.38$, $p<0.001$) and serum LDL-C levels (Spearman's $\rho=-0.39$, $p<0.001$). HV was inversely correlated with serum TC and LDL-C levels in statin users and non-users (Fig. 1 and Fig. 2). No significant relationship existed between alternation of NIHSS score and mRS score, HV, and serum levels

Table 3. Neuroradiological Profile of ICH in Statin Users and Non-users

	Statin group (n=56)	Non-statin group (n=325)
Hematoma location		
Cerebral subcortex	13 (23%)	65 (20%)
Basal ganglia	7 (13%)	53 (16%)
Thalamus	20 (36%)	124 (38%)
Brainstem	4 (7%)	18 (6%)
Cerebellum	12 (21%)	65 (20%)
IVH	12 (21%)	65 (20%)
Hematoma volume		
Mean (SD) cm ³	40.2 (36.4)*	16.9 (27.8)

ICH: intracranial hematoma; IVH: intraventricular hematoma

*p < 0.001 by unpaired Student's t-test; between the statin group and the non-statin group.

Figure 1. A. Binary correlation between serum TC levels and hematoma volume in the statin group (Spearman's rho = -0.85, p<0.001). B. Binary correlation between serum TC levels and hematoma volume in the non-statin group (Spearman's rho = -0.44, p<0.001). Hematoma volume was correlated inversely with serum TC levels in both statin users and non-users. **Figure 2.** A. Binary correlation between serum LDL-C levels and hematoma volume in the statin group (Spearman's rho = -0.67, p<0.001). B. Binary correlation between serum LDL-C levels and hematoma volume in the non-statin group (Spearman's rho = -0.46, p<0.001). Hematoma volume was correlated inversely with serum LDL-C levels in both statin users and non-users.

of HDL-C and TG.

Multiple logistic regression analysis of serum lipid levels

Odds ratio (OR) was adjusted by clinical variables, including age, dyslipidemia, DM, AF, prior history of stroke,

SBP at admission and the first in-hospital day, and anticoagulant medication. A significant association was found between HV, worsening of NIHSS score and mRS score, statin use and serum TC levels ≤150 mg/dL in ICH patients (Table 4). In the statin group, serum TC levels ≤150 mg/dL were significantly linked to HV and worsening of NIHSS

Table 4. Multiple Logistic Regression Analysis in ICH Patients

	OR	95% CI	p value
Age	1.007	0.971 - 1.007	0.7045
Male gender	2.586	0.774 - 8.646	0.1228
Worsening of NIHSS score	1.404	1.214 - 1.626	< 0.0001
Worsening of mRS score	1.754	1.060 - 2.907	0.0286
Hematoma volume	1.105	1.073 - 1.138	< 0.0001
Statin use	5.512	1.551 - 19.588	0.0083
Admission SBP	0.989	0.959 - 1.019	0.4715
The 1st day SBP	1.021	0.993 - 1.050	0.1416
Anticoagulant medication	1.295	0.177 - 9.456	0.7985

Dependent variable: serum TC levels ≤ 150 mg/dL.

CI: confidence interval; ICH: intracerebral hemorrhage; NIHSS: National Institute Stroke Scale; OR: odds ratio; SBP: systolic blood pressure; TC: total cholesterol

Table 5. Multiple Logistic Regression Analysis in Statin Users

	OR	95% CI	p value
Age	1.072	0.970 - 1.184	0.1712
Male gender	3.128	0.370 - 26.443	0.2949
Worsening of NIHSS score	2.028	1.321 - 3.115	0.0012
Worsening of mRS score	3.257	1.326 - 8.000	0.0100
Hematoma volume	1.334	1.013 - 1.756	0.0400
Admission SBP	0.996	0.954 - 1.040	0.8592
The 1st day SBP	1.046	0.995 - 1.099	0.0759
Anticoagulant medication	2.479	0.281 - 21.836	0.4133

Dependent variable: serum TC levels ≤ 150 mg/dL.

CI: confidence interval; mRS: modified Rankin Scale; OR: odds ratio; SBP: systolic blood pressure; TC: total cholesterol

score and mRS score (Table 5). Age, dyslipidemia, DM, AF and prior history of stroke were not significantly associated with HV and worsening of functional scores. There were no statistical differences between serum HDL-C and TG levels, and clinicoradiological variables.

Discussion

The present study revealed that prior statin use had no benefits for clinicoradiological recovery in ICH patients. As compared to statin non-users, the clinical profile of statin users suggested older age and higher rates of dyslipidemia, DM, AF and prior stroke history. Serum TC and LDL-C levels were decreased significantly in statin users compared to non-users. With respect to the relationship between serum lipid levels and clinicoradiological variables, serum levels of TC and LDL-C were associated with alternation of NIHSS score and mRS score. Inverse correlation was found between serum levels of TC and LDL-C, and HV. Multiple logistic regression analysis showed that serum TC levels ≤ 150 mg/dL were associated with statin use, HV and worsening score of NIHSS score and mRS.

Low serum cholesterol levels were reported to increase a risk factor of developing ICH or mortality (12-18). Hypercholesterolemia was associated with a lower risk of

ICH (18). Theoretically, the question arises that lipid-lowering effects of statins improve or worsen functional outcome of ICH patients. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, hemorrhagic stroke occurred more frequently in patients treated with atorvastatin (80 mg/day) compared to placebo (21). The post hoc analysis of the SPARCL study suggested no significant association between hemorrhagic stroke risk and serum LDL-C levels (30). Previous studies also pointed out that the standard doses of statins did not increase the incidence of ICH (18, 31). Post-ICH statin treatment did not elevate the risk of recurrent ICH (26). Three recent studies from Israel, Spain and North America have supported the favorable effects on clinicoradiological recovery of ICH in prior statin users (22-25). ICH patients pretreated with statins had less disability at admission and good outcome at discharge (22). Surrounding edema of hematoma and the 30-day mortality were decreased in prior statin users with ICH (23, 24). Another Spanish study reported a significant association between pre-ICH statin use and good outcome at 3 months. Serum TC and TG levels did not differ statistically between statin users and non-users (25). In contrast, the present study revealed that serum TC levels were significantly decreased in statin users compared to non-users. Interestingly, both studies disclosed the result that lower serum

TC levels were correlated with poor outcome. In contrast to the protective effects of statins, two studies described no benefits of prior statin use on functional outcome, 90-day mortality and HV in ICH patients (26, 27). In addition to a previous study of Spain (25), an Israel study mentioned that serum LDL-C levels were measured in 18 of 101 ICH patients pretreated with statins. Those levels did not differ statistically between survivors and non-survivors (27). The previous studies of prior statin users did not analyze the relationship between serum lipid levels and clinoradiological severity of ICH (22-27). A recent study using decision analysis model has addressed an increased risk of ICH recurrence by statin use (32). In the present study, statin users with serum TC levels ≤ 150 mg/dL had worsening of functional score and an increase of HV. At least, the marked reduction of serum TC levels due to statin treatment was thought to play a partial role in the clinoradiological severity of ICH.

A limitation of our case-control study is relatively the small number of prior statin users with ICH. Since serum TC and LDL-C levels were significantly lower in statin users than in non-users, it was not sufficient to analyze how statins can alter clinoradiological recovery of ICH in prior statin users without hypocholesterolemia. Finally, further large prospective studies are needed to elucidate the incidence and the clinoradiological outcome of ICH in statin users.

Conclusion

The present study indicated that serum TC and LDL-C levels were associated with functional scores and HV. Serum TC levels ≤ 150 mg/dL were an independent factor of unfavorable outcome and HV in pre-ICH statin users. Thus, physicians need to monitor serum lipid levels carefully in statin users.

The authors state that they have no Conflict of Interest (COI).

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