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Cognitive outcome in acute simvastatin treatment for aneurysmal subarachnoid hemorrhage: A propensity matched analysis☆,☆☆

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ABSTRACT

Objectives: Experimental evidence has indicated the benefit of simvastatin in the treatment of subarachnoid hemorrhage (SAH). Recently, acute simvastatin treatment was not shown to be beneficial in neurological outcome using modified Rankin Scale. Cognitive function is another important dimension of outcome assessment and yet had not been investigated in statin studies for aneurysmal subarachnoid hemorrhage. We therefore explored whether acute simvastatin treatment would improve cognitive outcomes.
Methods: The study recruited SAH patients with acute simvastatin treatment enrolled in a randomized controlled double-blinded clinical trial (ClinicalTrials.gov Identifier: NCT01038193). A control cohort of SAH patients without simvastatin treatment was identified with propensity score matching of age and admission grade. Primary outcome measure was Montreal Cognitive Assessment (MoCA). Secondary outcome measures were delayed ischaemic deficit (DID), delayed cerebral infarction, modified Rankin Scale (mRS), and Mini-Mental State Examination (MMSE).
Results: Fifty-one SAH patients with acute simvastatin treatment and 51 SAH patients without simvastatin treatment were recruited for analysis. At 3 months, there were no differences in MoCA scores (MoCA: 21 +/− 6 vs. 21 +/− 5, $p = 0.772$). MoCA-assessed cognitive impairment (MoCA < 26) was not different (75% vs. 80%, OR 0.7, 95%CI 0.3 to 1.8, $p = 0.477$). There were also no differences in DID, delayed cerebral infarction, favorable mRS outcome, and MMSE scores, and MMSE-assessed cognitive impairment between both groups.
Conclusions: The current study does not support that acute simvastatin treatment improves cognitive outcome after aneurysmal subarachnoid hemorrhage.

1. Introduction

Although aneurysmal subarachnoid hemorrhage (SAH) accounts for only 3–5% of strokes, its profound consequences and unique window of intervention justify its classification as a separate entity [1]. Early aneurysm occlusion, expert endovascular neurosurgery and microsurgery, the use of oral nimodipine and neuro-intensive care are now the standards of care [2,3]. Nevertheless, SAH is still associated with mortality at one month for half of all patients, and the other half are left with disability [1].

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, that competitively blocked the rate-limiting enzyme of the mevalonate pathway for cholesterol biosynthesis and hence the formation of mevalonate [4,5]. Statins improve endothelial vasomotor function, increase nitric oxide bioavailability, possess antioxidant properties, counter thrombus formation, induce angiogenesis, endogenous cell proliferation and neurogenesis, increase synaptic protein synaptophysin, induce vascular stabilization and neuroblast migration, and suppressing cytokine responses during cerebral ischaemia [5–12]. Experimental evidence also indicates the benefit of simvastatin in the treatment of SAH [13–15]. However, the recently completed multi-center phase III trials assessing the effects of acute simvastatin treatment did not improve neurological outcome in terms of modified Rankin Scale (mRS) [16,17].

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Cognitive dysfunction after subarachnoid hemorrhage is increasingly recognized as a key outcome measure and could be a good surrogate outcome to brain injury [18–24]. In fact, in a recent consensus meeting, outcome measures focusing on cognitive or other neuropsychological outcomes were suggested to be applicable for use in SAH studies and should be explored [25]. Montreal Cognitive Assessment (MoCA) is a one-page cognitive screening test that is now usually administered within 10 min [26]. MoCA has been recently shown to be a valid and relevant cognitive screening assessment after SAH [18–23]. It is uncertain whether Simvastatin treatment can improve cognitive outcome after SAH. This gap in knowledge is very important, and should be addressed.

The objective of the study is to investigate whether simvastatin (started within forty-eight hours after SAH) daily over three weeks would improve cognitive outcome assessed by MoCA at three months.

2. Methods

The current study is a cohort study comparing patients with Simvastatin treatment in High Dose Simvastatin for Aneurysmal Subarachnoid Hemorrhage (HDS-SAH) Study (ClinicalTrials.gov Identifier: NCT01077206) [17,27], who also had MoCA, with matched patients without Simvastatin treatment in Cognitive Dysfunction after Aneurysmal Subarachnoid Hemorrhage (CD-SAH) Study (ClinicalTrial.gov Identifier: NCT01038193).

In the simvastatin arm, HDS-SAH patients were randomly assigned to receive either 80 mg (high dose) or 40 mg (lower dose) of simvastatin daily for 3 weeks [17,27]. A permuted-block randomisation was carried out using a computer system with an allocation list in random order generated by a statistician not associated with the project team to protect the blinding and integrity of the study. The study drug assignments were kept in sealed envelopes that were opened by site study investigators who were not involved in the clinical management of recruited patients. Both the assessors and the patients were blinded to the study drug allocation.

The studies conformed to the Declaration of Helsinki, and written informed consent was obtained from all participants or their next of kins. The patients were matched with age and admission WFNS grade using propensity scores IBM SPSS for Windows Version 22 with a match tolerance of 0.05.

3. Participants

Patients who were diagnosed with aneurysmal subarachnoid hemorrhage were screened and approached for recruitment into the above-mentioned studies. All participants or their legally acceptable representatives provided written informed consent. The study adhered to the international quality standards provided in the Good Clinical Practice guidelines. The inclusion criteria were as follows: aged 18 to 70 years; World Federation of Neurosurgical Societies (WFNS) grades 1 to 4; radiological diagnosis of subarachnoid hemorrhage; had an intracranial aneurysm that was considered the cause of subarachnoid hemorrhage; could be randomized within 96 h after the onset of subarachnoid hemorrhage; man or woman of non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any woman who was postmenopausal) or of childbearing potential but with a negative urine pregnancy test immediately before randomization. The exclusion criteria were as follows: unsalvageable patients likely on admission; pre-existing major hepatic, renal, neurological (other than unruptured intracranial aneurysms), pulmonary or cardiac disease; previous statin therapy; current course of Warfarin-type drugs; current course of amiodarone, verapamil or potent CYP3A4 inhibitors; suspected or known additional disease process that threatens life expectancy (e.g. malignancy); unlikely to return for 3-month follow-up assessment; known or strong suspicion of drug abuse or alcoholism.

4. Montreal Cognitive Assessment (MoCA)

The MoCA is a one-page 30-point test that is now usually administered within 10 min, and evaluates the following cognitive functions: visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, language, 5-min delayed verbal recall, and orientation [26]. The Hong Kong version has previously been validated in patients with SAH [18–23]. MoCA-assessed cognitive impairment was defined as a MoCA score less than 26 [26]. Sensitivity analysis using a MoCA score less than 22 (MoCA optimal cutoff score for cognitive domain deficit) was also included [19].

5. Mini-Mental State Examination (MMSE) Chinese Cantonese Version [28]

The MMSE comprises five sections (orientation, registration, attention and calculation, recall and language). The maximum total score is 30 and the test can usually be completed within 10 min. The Cantonese version was previously validated in a population of demented patients [28]. MMSE-assessed cognitive impairment was defined as a score of <27 [29].

Patient demographics, medical history, and relevant investigation results were collected. The severity of subarachnoid hemorrhage (SAH) was scored clinically using the WFNS grading scale and radiologically using the Fisher's scale. At three months after randomization, MoCA and MMSE scores were assessed by one of the two psychologist graduates trained by a research clinical psychologist. Modified Rankin Scale (mRS) scores were assessed by a nurse or clinician without knowledge of the treatment allocation [30].

Presence of delayed ischaemic deficits (DIDs): was defined as (i) clinical vasospasm as manifested by a fall of two or more points on the modified Glasgow Coma Scale, and/or new focal neurological deficit lasting more than 2 h, and/or CT perfusion evidence of cerebral ischaemia, and/or (ii) delayed cerebral infarction unrelated to surgery/intervention, rebleed, hydrocephalus, infection, electrolyte or metabolic disturbance [17]. Rebleed (as confirmed by computed tomography of the brain), hydrocephalus (as confirmed by computed tomography of the brain and requiring a ventriculo-peritoneal shunt), delayed cerebral infarction (as confirmed by interval computed tomography of brain), post-treatment (coiling or clipping) complications, adverse events, and overall mortality during treatment and follow-up were also documented.

We hypothesized that acute simvastatin treatment (started within forty-eight hours after SAH) 40–80 mg daily for three weeks would reduce MoCA-assessed cognitive impairment at 3 months after SAH. The primary outcome was MoCA-assessed cognitive impairment (<26) at 3 months, as defined above. Secondary outcome measures included DID, delayed cerebral infarction, MMSE, and mRS.

6. Statistical analysis

Data management and statistical analysis were done by the research team of the Division of Neurosurgery, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong. Data are being collected on handwritten forms and archived in a password-protected electronic database. Statistical analyses were carried out with IBM SPSS for Windows Version 22.

We performed analysis using two-sided probability, with $p < 0.05$ considered statistically significant. Proportions with MoCA-assessed cognitive impairment, MMSE-assessed cognitive impairment, DID, delayed cerebral infarction, mRS-defined favorable outcome were compared with chi-square statistics. Odds ratio (OR) values smaller than 1.0 indicated improvement in cognitive outcomes or reduction in DID or delayed cerebral infarction. OR values more than 1.0 indicated improvement in mRS-defined favorable outcome. MoCA and MMSE scores were compared with unpaired Student's t tests.