The Effect of Statin Therapy in Stroke Outcome: A Double Blind Clinical Trial

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Brief Communication

ABSTRACT

Background: Through a clinical trial we evaluated statin therapy benefits over stroke outcome.

Methods: All patients with moderate stroke in Middle Cerebral Artery (MCA) were registered during February 2006 to February 2008, in Al Zahra Hospital, Isfahan, Iran. Among 55 patients who were enrolled in the present study, 25 subjects received 20 mg lovastatin daily, for 90 days after stroke attack (group 1) and 30 patients received no treatment (group 2). Patients were assessed at admission, 7 and 90 days after stroke. National Institutes of Health Stroke Scale (NIHSS) score was recorded in the day 1 and 7 in the hospital with a questionnaire and BARTHEL index was estimated 90 days after stroke incidence by a telephone survey or in an outpatient visit. Data were analyzed by means of χ^2, '*t*' test and Independent '*t*' test.

Results: NIHSS score measured in first day immediately after stroke attack and following 7 days, did not differ significantly in two groups. Moreover, BARTHEL index recorded within 90 days was not also different comparing group 1 and 2. After 90 days, no mortality was recorded in group 2, while one patient expired in group treating with statins (*P*-value>0.05).

Discussion: We did not find statins administration to play any role in stroke recovery and consequent long-term prognosis. More researches with larger samples are needed to establish the possible favorable outcome of statins when administered in cerebrovascular diseases.

Keywords: Ischemic stroke, lovastatin, stroke prognosis, statins

INTRODUCTION

3-Hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors (statins) have an important role in coronary heart disease (CHD) therapy, through reducing cholesterol levels.[1-6] Clinical trials performed to study effects of statins in CHD, also reported a decline in risk of stroke development. This lead to assumption, that statins could be an efficient drug for stroke prevention.[7] Although, Dyslipidemia is known as

a certain risk factor for coronary arterial disease (CAD), its role over stroke has been not convincible for a long time. Further than lowering of cholesterol levels, recent studies showed statins to play additional roles. It is noted that statins in addition to its antiatherosclerotic and antithrombotic properties, also hold anti-inflammatory and neuroprotective effects which have been introduced as cholesterol-independent actions or pleiotropic effects.[8] Experiences of animal models with brain ischemia performed for evaluating the neuroprotective effects of statins, concluded that utilizing statins will diminish the size of brain damage.[9-11] In clinical surveys also there are recent studies showing that statins may improve stroke prognosis which is suggested to be due to its neuroprotective effects.[9,11,12[Probable explanation for favorable result of poststroke statin therapy is believed to be due to their capability in inducing angiogenesis, neurogenesis, and synaptogenesis.[13,14] To evaluate statins therapy benefits over stroke outcome, we assessed whether if statin administration improves ischemic stroke prognosis comparing with controls.

METHODS

Through a clinical trial performed in Al Zahra Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan. Iran, all patients with moderate stroke in middle cerebral artery (MCA) during February 2006 to February 2008 were registered. We included all subjects older than 45, presenting with evidence of acute stroke approved by a neurologist by the means of CT or MRI and clinical findings. According to guidelines of the American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute, we excluded patients with primary intracranial hemorrhage, epileptic seizure early after stroke attack, history of craniotomy or brain tumor, dissection of vertebrobasilar or carotid artery, treating with intravenous tissue plasminogen activator [tPA], patients having contraindication for receiving statins or ones with recognized allergic reaction, serum creatine phosphokinase levels more than 190 U/I, myositis, or rhabdomyolysis. In addition, ischemic stroke was characterized as a rapid growing loss of brain functions because of a failure in the brain blood supply, continuing at least 24 hours.[15,16] We also excluded the patients with previous heart disease and with recent stoke.

The study was ethically approved by the Reseaech Council. Informed written consent was obtained from all participants. Patients enrolled in our study were divided into two groups, through a double blind randomized assortment, which was accomplished by random number tables. One received 20 mg lovastatin, daily, for 90 days and other were regarded as controls, treated with no statins. All patients were assessed at admission, 7 and 90 days after stroke. National Institutes of Health Stroke Scale National Institutes of Health Stroke Scale (NIHSS) score was recorded in the day 1 and 7 in the hospital by a neurologist through a questionnaire.[17] BARTHEL index[18] was estimated 90 days after stroke incidence by a telephone survey or in an outpatient visit. Moreover, within the questionnaire we recorded the history of Diabetes Mellitus, hypertension, hyperlipidemia and smoking.

Hypertension (HTN) was recorded if the patient had a history of HTN with systolic blood pressure more than 140 mmHg or diastolic blood pressure greater than 90 mmHg, at the time of diagnosis.[19] History of diabetes mellitus was regarded as positive when there was a evidence of persistent fasting hyperglycemia (blood glucose>110 mg/dl).[20] Positive history of hyperlipidemia was documented when the patient consumed lipid-lowering drugs or a persistent increase of total cholesterol (>200 mg/dl) was recorded in the past.[21] These parameters are considered as major risk factors for stroke development, therefore were compared between two groups. We also asked about drug history and if the patient has received statins prior to stroke incidence.

Statistical analysis

Data were analyzed with SPSS (version 15) and χ^2 and '*t*' test were employed for comparing NIHSS score and BARTHEL index within two groups. Independent '*t*' test was also utilized to evaluate the difference among two groups in the first and 90 days after stroke, regarding BARTHEL index.

RESULTS

Among, 55 patients (29 male and 26 female)

who were enrolled in the present study, 25 subjects received lovastatin (group 1) and 30 patients received no treatment (group 2). First group included 13 males and 12 females with mean age of 63.36 ± 10.75 years, while group 2 was consisted of 16 males and 14 females with the mean age of 68.33 ± 10.72. There was no statistical difference between two groups considering sex (*P*-value=0.92) and age (*P*=0.69). Previous history of diabetes Mellitus, hypertension, Hyperlipidemia and smoking was identical among group 1 and 2 [Table 1]. Whether right or left MCA was affected, we could not find any considerable difference, among both groups (*P*=0.72). One patient with prior consumption of statins was found in group 1; however, it did not reach statistical significance when compared by group 2 with no consumption of statins earlier than stroke occurrence. NIHSS score measured in first day immediately after stroke attack and following 7 days as described in Table 2, did not differ significantly in two groups. Moreover, BARTHEL index recorded within 90 days was not also different comparing group 1 and 2 [Table 2]. After 90 days, no mortality was recorded in group 2, while one patient expired in group treating with statins. Yet mortality rate was identical statistically in both groups (*P*=0.26).

DISCUSSION

No significant difference was found in NIHSS score among patients and controls in the 1st and 7th days after stroke attack. Moreover, comparing of BARTHEL index in both patients and controls, after 3 months later than stroke incidence difference was not statistically considerable. Accordingly, we did not find statins administration to play any role in stroke recovery and consequent long term prognosis. NIHSS score recorded in the very first day of stroke occurrence did not differ statistically between 2 groups which indicated that both group are identically selected. The other characteristics among patients and controls were comparable while no difference was seen in their age and sex distributions and previous risk factors attributed to ischemic stroke. Although a few studies have been established to evaluate the outcome of ischemic stroke among patients who received statins, their results showed improvement in stroke prognosis.[22-24] The Stroke Prevention with Aggressive Reduction of Cholesterol Level (SPARCL) trial, demonestrated a better outcome in recurrent ischemic cerebrovascular events when statin is used versus patients who were not administered with HMG-COA reductase inhibitors, even though this trend was not statistically significant.[24] Patients included in both our survey and SPARCL's, had no past history of coronary artery diseases whereas there was not enough evidence for statins benefits in stroke prevention among patients who had no previous history of CAD.[7] Nevertheless, the SPARCL was a longitudinal trial study enrolled patients with recent ischemic or hemorrhagic stroke or TIA (within 1-6 months), and randomized them in 2 atrovastatin and placebo-receiving group. This trial was performed to evaluate severity of consequent stroke attacks in patients receiving atrovastatin prior to stroke occurrence. They assessed Modified ranking scale score (MRSs), Barthel index and NIHSS score, at the study initiation and 90 days after subsequent stroke. Conversely, we conducted a clinical trial among patients who didn't have recent stroke attack, receiving lovastatin or no treatment immediately after stroke occurrence and following 90 days. Patients who were not treated with lovastatin did not receive any placebo that was considered as one of our study limitations, we also measured BARTHEL index 90 days post-stroke, which is regarded as reliable, although

Table 1: Frequency of risk factors within group 1, who received lovastatin and group 2, having no treatment

	Group 1	Group 2	*P*-value
Sex	Male=13, Female=12	Male=16, Female=14	0.92
Mean age	63.36 ± 10.75	68.33 ± 10.72	0.69
Hypertention	n =13 (52%)	n =20 (66.6%)	0.26
Diabetes melitus	n =4 (16%)	n =5 (16.6%)	0.94
Hyperlipidemia	n =4 (16%)	n =6 (20%)	0.70
Smoking	n =9 (36%)	n =8 (26.6%)	0.45

Group 1: Subjects received lovastatin; Group 2: Patients received no treatment

Table 2: NIHSS and BARTHEL index within group 1 and 2

	Group1	Group2	*P*-value
1st day NIHSS	15.96 ± 4.30	14.46 ± 4.31	0.52
7th day NIHSS	15.75 ± 4.20	13.46 ± 5.56	0.10
90th day BARTHEL index	77.29 ± 10.31	70.83 ± 23.71	0.22

Group 1: Subjects received lovastatin; Group 2: Patients received no treatment; NIHSS: National Institutes of Health Stroke Scale

its application in stroke trials is inconsistent.[25] This was another limitation of our survey that was due to impossibility of face-to-face visit for all patients after 90 days post-stroke. On the other hand, Moonis *et al*. treated patients with acute ischemic stroke with statins, for 4 weeks and demonstrated an improved stroke outcome after 90 days. They employed all kind of statins but there were insufficient number of subjects treated with each statin type for concluding if one type of statin was better than others. It was in contrast to our survey and SPARCL's in which only Lovastatin and atrovastatins effects was observed respectively. General mechanism for all statin types is HMG-CoA reductase inhibition, regardless of their pharmacokinetical difference including absorption, binding, excretion, and solubility which lead to variable dose-related effectiveness in reducing LDL-cholesterol levels. Pravastatin and rosuvastastin barely penetrate into cell membranes and are mostly absorbed by liver cells because of their hydrophilic properties. Nevertheless Lovastatin and Simvastatin are more lipophilic and can surpass the the blood–brain barrier (BBB), which could be a possible relevant explanation for their cholesterol-independent neuroprotective actions.[26]

CONCLUSION

However, whether statins have pleiotropic effects or not, we could not find any enhancement in post-stroke ability of the patients with statins therapy. Although futher studies with larger samples are needed to establish the possible favorable outcome of statins when administered in cerebrovascular diseases.

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