Original Article

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Short-term clinical outcome of stroke patients with or without prior statin treatment

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Abstract

This study evaluated the impact of statin on the severity and outcome of stroke among patients who had taken it prior to the stroke onset and compared to patients who had not received it before the stroke. We included 261 consecutive patients with acute ischemic stroke who admitted in Namazee hospital affiliated to Shiraz University of Medical Sciences from 2018-2019. We recorded demographic data, vascular risk factors, history of previous statin treatment, and National Institutes of Health Stroke Scale (NIHSS) score at time of hospital admission and modified Rankin Scale (MRS) 3 months after stroke onset. The dependent variables were initial severity of stroke as measured by National Institute of Health Scoring System (NIHSS) and good outcome defined as modified Rankin Scale (MRS) 0 to 1. Among 261 patients with acute ischemic stroke, 76 were using statins (52.6% of users were women). Among all the subjects, 175 (67.6%) had history of hypertension, 78 (30.1%) had history of diabetes mellitus, 87(33.5%) had history of hyperlipidemia, 63 (24.3%) were smokers. Admission NIHSS and MRS were not statistically different in statin users and non-statin users (P=0.12 and P=0.08, respectively). Adjusted Odds Ratios for poor functional outcome and 90-day mortality according to previous statin use were 0.87 (95% CI 0.37-2.05), P=0.54) and 0.75(95% CI 0.31-1.81, P=0.52) which were not statistically significant. This study showed that pre-stroke statin therapy did not affect the initial clinical severity, short-term functional outcome and 90-day mortality after ischemic stroke.

Keywords: Stroke, Ischemic stroke, Statin

1. Introduction

Ischemic stroke is a major cause of disability and mortality in developing and developed countries (1, 2). Two-thirds of all strokes occur in the middle and low income countries which is increasingly becoming a major health problem (3). Therefore, more attention to preventive methods should be prioritized in these countries. HMG CoA reductase inhibitors (statins) with intensive lipid-lowering effects are recommended for secondary prevention of stroke (4). There is some evidence that shows an effect on neurological injury which could be mediated by antithrombotic and anti-inflammatory effects that improve neuroprotection, neurogenesis, restoration of endothelial function, anti- oxidative stress effects, decreased vascular inflammation, and enhanced angiogenesis (5). Also, it has been shown that statins reduce Coenzyme Q10 levels which act as a lipid soluble endogenous antioxidant in the brain. Recent preclinical examinations on stroke rats have shown

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abrogating impact of atorvastatin in stroke rats and they showed that adding Coenzyme Q10 to atorvastatin pretreatment improves stroke outcomes (6).

The beneficial effect of statins on patients with stroke is well known, notably their effect on stroke prevention (7). However, the effect of statins usage prior to onset of stroke on the severity and outcome of stroke is not well known (8). Different studies reported different results based on the nature of their population and methodology of their survey (9). Some observational studies showed that statins taken prior to the stroke can improve stroke initial severity and also stroke outcome evaluated by Modified Ranking Scale (MRS) (7, 10). Contrary to these findings, Cordenier A et al. in a systematic review and meta-analysis showed that preemptive statins did not improve 90-day post stroke outcome (8). Also, in a new meta-analysis Keun-Sik Hong et al showed that pre stroke statin use was associated with milder initial stroke severity and slightly better functional outcome (11). In addition, there is no study about this matter in Middle-eastern population.

Accordingly, we investigated the effect of preemptive stroke treatment on initial stroke severity and 90-day stroke outcome in an Iranian population.

2. Materials and methods

This is a retrospective cohort study based on prospectively collected data of a stroke registry performed in Namazee hospital affiliated to Shiraz University of Medical Sciences from 2018 to 2019. This is a high volume referral centers for stroke in southwestern Iran.

We included consecutive patients who were admitted to the neurology ward fulfilling all inclusion and exclusion criteria. Ischemic stroke was screened according to the Recognition of Stroke in the Emergency Room (ROSIER) scale as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients, and confirmed by a brain CT or an MRI indicating the presence of infarction and the absence of hemorrhage.

Inclusion criteria were first ever ischemic stroke according above-mentioned definition, age between 18 and 90 years, modified Ranking scale (MRS) score of 0 before stroke and signing the informed consent. Exclusion criteria were intracranial tumor, Moya Moya disease, any known vasculitic disease, varicella zoster, malaria, neurosyphilis or any other infection-related vasculopathy, radiation induced vasculopathy, fibromuscular dysplasia, sickle cell disease, neurofibromatosis, primary central nervous system vasculitis, postpartum angiopathy, reversible vasoconstriction syndrome, migraine, epilepsy and patients who were taking anti-inflammatory medications or supplements.

Demographic data (age and sex) of recruited patients were recorded. Major cerebrovascular risk factors were investigated for all subjects. They included current, or previous cigarette smoking, hypercholesterolemia (positive history, fasting total cholesterol level >200 mg/dL, LDL >130 mg/dL), hypertriglyceridemia (fasting triglycerides level >150 mg/dL), arterial hypertension (positive history, systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg, out of the acute phase, treated or not), and diabetes mellitus (positive history and /or fasting plasma glucose greater than 126 mg/dL out of the acute phase).

The first outcome of interest and dependent variable were initial severity of stroke as measured by National Institute of Health Scoring System (NIHSS) which obtained on admission by trained neurology residents. Prior use of statin was defined as continuous administration of any type of statin with any dose scheduled for at least 6 weeks before stroke.

Ninety days after stroke, functional outcome of stroke patients were investigated by Modified Ranking Scale (MRS) which was assessed by a neurology resident with phone conversation. NIHSS and MRS assessments were performed by neurology residents blinded to preemptive statin usage.

This study was approved by Institutional Review Board of Shiraz University of Medical Sciences (No. HP-12-89). All participants gave the written informed consent All participant completed and signed informed consent before their participation in the study.

2.1. Statistical analysis

Frequency (%), mean±standard deviation and Median (IQR) were used as descriptive indices. Odds ratio (OR) and corresponding confidence interval (%95 C.I) were used to assess the multivariate relationships between independent variables and dependent variable using a multiple logistic regression as a full model to control the effect of possible confounders. The significance level was set at 0.05. Statistical Package for the Social Sciences Version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Also we used Kolmogorov–Smirnov test for normality test. In order to investigate the effect of risk factors on the outcome of the disease, we used logistic regression model. First, independent variables entered into the model, and the crude OR for each variable was evaluated, then variables which had the P value<0.2 entered the multivariate model and their effect was measured simultaneously on the dependent variable.

3. Results

Two hundred and sixty patients were recruited (58.5% male, mean age 67.95±13.71, range of age; 23-96). Among all the subjects, 175 (67.6%) had history of hypertension, 78 (30.1%) had history of diabetes mellitus, 87(33.5%) had history of hyperlipidemia, 63 (24.3%) were smokers. 36 (47.4%) of statin users were male and 40 (52.6%) were female. 19.6% of patients died within 90 days after stroke onset.

Not to use statins were more common among the male patients (P=0.02). Meanwhile, history of hyperlipidemia, hypertension, and diabetes mellitus were significantly more common in statin users (P=0.001, P=0.001 and P=0.03, respectively), and average value of LDL was significantly lower in statin users too (P=0.01).

Figure 1 Shows the distribution of modified Rankin scale (MRS) at admission and 90 days after stroke in statin users and non-statin users.

Table 1 shows associations between initial stroke severity (measured by admission NIHSS) and clinical and laboratory characteristics. Female sex, history of hypertension, history of myocardial infarction, increased triglyceride was significantly associated with higher admission NIHSS (Respectively, p=0.004, P= 0.006, P=0.048, P=0.032).

Table 2 shows unadjusted Odds Ratios of 90-day poor outcome and 90-day mortality according to baseline characteristics and previous statin use. In this analysis, the results showed that women are twice as likely to die from ischemic stroke as men, which was statistically significant (P=0.023). Patients over 65 years of age were also 2.49 times more likely to be at risk of mortality than patients under the age of 65, which was statistically significant (P=0.009). It is also notable that the risk of death in patients with previous statin use was approximately 17% lower than those who did not use statin, but this observed risk reduction was not statistically significant(P=0.532). History

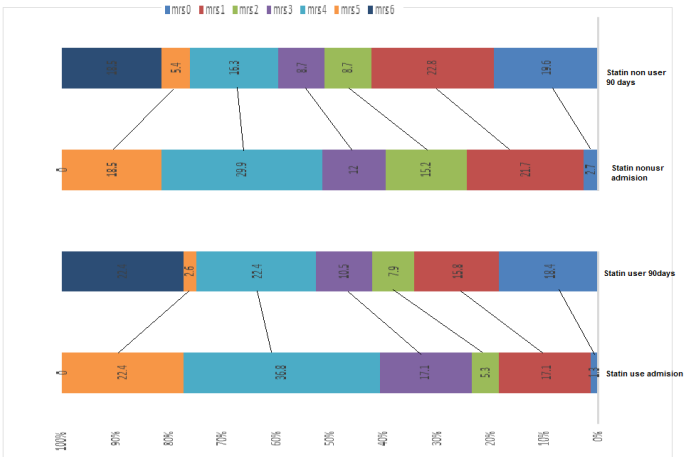

Figure 1. Distribution of modified Rankin Scale (MRS) at discharge according to statin use in 260 ischemic stroke patients.

Table 1. Associations between initial stroke severity (NIHSS) and different demographic, clinical and laboratory characteristics

Variable	category	Mean NIHSS	SD	Pvalue
Sex	MALE	7.65	7.345	**0.004**
	FEMALE	11.06	10.472	
Age*	<65	7.88	8.013	0.053
	>65	10.01	9.509	
History of hypertension	YES	10.00	9.755	**0.006**
	NO	7.12	6.508	
History of Diabetes Mellitus	YES	8.32	9.140	0.381
	NO	9.40	8.840	
History of Hyperlipidemia	YES	8.61	9.405	0.566
	NO	9.30	8.696	
History of Smoking	YES	8.68	8.248	0.623
	NO	9.20	9.157	
MI	YES	12.21	10.322	**0.048**
	NO	8.68	8.686	
LDL**	normal	9.06	8.566	0.814
	abnormal	8.77	9.821	
TOTALCHOL**	normal	9.48	8.948	0.154
	abnormal	7.69	9.017	
TG**	normal	6.76	7.749	**0.032**
	abnormal	9.65	9.249	
HDL**	normal	8.09	9.778	0.421
	abnormal	9.24	8.739	

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of hypertension, history of diabetes, history of hyperlipidemia, history of previous stroke, LDL, TOTALCHOL, TG and HDL measures, and NIHSS above 10 increases the risk of death, but this increase was not significant (Respectively P=0.442, P=0.248, P=0.912, P=0.209, P=0.809, P=0.825, P=0.063 P=0.792). Smoking history reduces the risk of mortality, but this observation was not statistically significant too (P=0.081).

As shows in Table 3, variables which had the P value<0.2 entered the multivariate model and their effect was measured simultaneously on the dependent variable. The results of the regression model show that, after eliminating the gender bias effect, the age of >65 years old increases the risk of mortality, but this increase was not statistically significant (P=0.052). NIHSS >10 also increases the risk of mortality, which was statistically significant (P<0.001). However, previous statin use, smoking, history of myocardial infarction and TG measures reduce the risk of mortality, which were not statistically significant (Respectively P=0.679 P=0.285, P=0.873, P=0.604).

Also after eliminating the gender bias effect, we found that NIHSS >10 significantly increased the risk of poor outcome (P<0.001). Female gender, history of smoking, history of MI and high TG concentrations increase the risk of poor outcome, but these findings were not significant (Respectively, P=0.152, P=0.067, P=0.104, P=0.438). But previous statin use decreases the risk of poor outcome which was not statistically significant (P=0.771).

4. Discussion

In current study statin users and non-statin users did not differ according to NIHSS at admission, 90-day mortality and 90-day poor outcome. Female patients, higher age and higher admission NIHSS was associated with more risk of 90-day

Table 2. Risk of favorable90-day poor outcome and 90-day mortality according to different demographic, clinical and laboratory characteristics.

Variable	90-day Mortality (N=51)	90-day Poor outcome* (MRS≥2) (N=165)
	Crude OR(95% CI)	Crude OR(95% CI)
Sex(Female)	2.06 (1.1-3.84) P=0.023	1.45(0.86-2.45) P=0.157
Age(>65)	2.49(1.25-4.957) P=0.009	1.92(1.15-3.21) P=0.015
Statin user	0.83(0.43-1.61) P=0.532	0.86(0.49-1.51) P=0.612
History of hypertension	1.30 (0.65 - 2.57) P=0.442	1.08(0.63-1.86) P=0.774
History of Diabetes Mellitus	1.52(0.75-3.117) P=0.248	1.12(0.65-1.94) P=0.671
History of Hyperlipidemia	1.03(0.5- 1.972) P=0.912	1.57 (0.93-2.67) P=0.098
History of Smoking	0.46(0.19- 1.09) P=0.081	0.75(0.41-1.38) P=0.364
MI	1.77(0.72-4.31) P=0.209	3.06(1.12-8.32) P=0.026
LDL	1.08(0.55-2.1) P=0.809	1.60(0.90-2.82) P=0.102
TOTALCHOL	1.08(0.54-2.15) P=0.825	1.43(0.80-2.58) P=0.224
TG	2.25(0.95-5.33) P=0.063	1.47(0.81-2.47) P=0.203
HDL	1.10(0.53-2.29) P=0.792	1.65(0.90-3.01) P=0.107
NIHSS on admission>10	10.22(4.99-20.92) P<0.001	15.27(5.89-39.62) P<0.001

*MRS after 90 days

mortality and poor functional outcome.

The effect of statin pre-treatment on stroke severity and outcome still remains unknown (4, 5, 7, 8, 10-17). Hong et al. analyzed 70 observational studies in a systematic review and showed that pre-treatment with statins might provide slightly better functional outcome in ischemic stroke after 90 days. Also, it might reduce the initial stroke severity. Pre-treatment of stroke with statins was associated with better initial stroke severity (Odds Ratio (OR) 1.24, CI (1.05-1.48); P=0.013), better functional outcome (OR 1.50, CI (1.29-1.75); P=0.001), and lower mortality (OR 0.42, CI (0.21-0.82), P=0.0108) (16). In contrast to these findings, Cordenier et al showed that pre-treatment of stroke with statins was associated with a lower risk of in-hospital mortality (OR 0.56; CI (0.40-0.78), P≤0.0006), but there was no difference between pre-stroke statin users and non-users in functional outcome after 3 months (OR 1.01; CI (0.64 -1.61), P=0.96) (8). The discrepancy between these reviews may be explained by the different inclusion criteria, different end points or different follow-up times. Furthermore, Alonzo et al showed that although patients under statin treatment before stroke had higher prevalence of metabolic factors, they had better functional outcomes one-month after the event. (OR 2.9, CI (2.07-3.46); P=0.001) (18).

The underlying mechanisms of the po-

Table 3. Risk of favorable90-day poor outcome and 90-day mortality according to different demographic, clinical and laboratory characteristics (multivariate analysis).

Variable	90-day Mortality(N=51)	90-day Poor outcome* (MRS≥2)(N=165)
	adjusted OR(95% CI)	adjusted OR(95% CI)
Sex(Female)	1.493 (0.69-3.19) P=0.324	2.16(1.16-4.02) P=0.152
Age(>65)	2.21(0.98-4.95) P=0.052	1.92(1.15-3.21) P=0.01
Statin user	0.84(0.38-1.86) P=0.679	0.90(0.45-1.79) P=0.771
History of Smoking	0.57(0.21-1.57) P=0.285	2.07(0.96-4.45) P=0.067
MI	1.09(0.35-3.33) P=0.873	2.51(0.81-7.76) P=0.104
TG	0.99(0.99-1.005) P=0.604	1.002(0.99-1.007) P=0.438
NIHSS on admission>10	9.60(4.50-20.47) P<0.001	16.58 (5.66-48.53) P<0.001

*MRS after 90 days

tential effectiveness of statin treatment on stroke outcomes are hypothetical. Some studies found that statins have many effects beyond lowering the cholesterol and Serum LDL levels (19, 20). However, in our study, we did not find any reduction in the initial stroke severity or any improvement in 90-day function in patients pre-treated with statins, but it does not mean that there was no neuroprotective effect. It could be explained that the NIHSS is not sensitive enough to detect minimal differences, and it is noteworthy that imaging-based studies in humans have provided evidence, showing that smaller ischemic lesions have been found in stroke patients on statins (21). Also, the cause of stroke is multifactorial including age, sex, ethnicity, hypertension, ischemic heart disease, etc. (22). So, it is likely that statins cannot prevent all of the pathophysiological underlying mechanisms involved in the stroke occurrence and neurological deterioration. Furthermore, Statins have been revealed to reduce Coenzyme Q10 levels which act as a lipid soluble endogenous antioxidant in the brain. Recent preclinical examinations on stroke rats have shown abrogating impact of atorvastatin in stroke rats and they showed that Adding Coenzyme Q10 to atorvastatin pretreatment improves stroke outcomes (6).

Our study had some limitations. Firstly, our sample size was rather small, so the power of our results was limited. Secondly, we used arbitrary cut-off values for MRS. Probably; different cut-off values cause different results. Thirdly, in our study different stroke subtypes were not analyzed differently. In addition, the duration of statin therapy and also the dose of statins were not measured as a variable.

In conclusion, our study showed that pre-stroke statin therapy is not associated with a better initial clinical severity and midterm functional outcome after ischemic stroke. We suggest further studies on the effectiveness of pre-stroke use of statin with larger sample size, especially in other Middle East countries.

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Conflict of Interest

None declared.

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