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ORIGINAL ARTICLES

Regulation of lipid levels after ischemic stroke and an analysis of the associated factors in China

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Abstract

Background and Objectives: Stroke is the most common neurological disease in China and regulation of lipid levels is important for secondary prevention. This study aimed to investigate the practice of lipid lowering agents immediately after and one month following ischemic stroke in China, and to determine the factors affecting the practice. *Methods:* A total of 857 patients with acute ischemic stroke were enrolled from 11 hospitals in the Qingdao area, Northern China. Data pertaining to the patients' demographic, clinical data, and treatment before and after the stroke were recorded. Univariate and multivariate logistic regression analyses were used to determine the factors associated with the treatment at two time points: at the acute stage and at one month follow-up. *Results:* The frequency of lipid lowering therapy was 50.3% (431/857) at acute stage and 41.5% (306/738) at one month. Lipid lowering therapy at acute stage was independently and positively associated with a history of hyperlipidemia((*P*=0.002, *OR* (95%*CI*): 3.784 (1.610-8.898)) and excess alcohol consumption (*P*=0.005, *OR* (95%*CI*): 1.928 (1.214-3.062)), partial anterior circulation infarct classification (*P*=0.000, *OR* (95%*CI*): 1.974 (1.370-2.767)), and low-density lipoprotein levels ((*P*=0.000, *OR* (95%*CI*): 1.426 (1.170-1.739)). Lipid lowering therapy at one month follow-up was independently and positively associated with lipid lowering therapy at acute stage ((*P*=0.000, *OR* (95%*CI*): 18.275 (11.476-29.101)), and negatively with the Modified Rankin Scale ≥4 at follow-up ((*P*=0.030, *OR* (95%*CI*): 0.568 (0.341-0.948)).

Conclusions: Lipid lowering therapy was found to be used in about half of patients during acute and early secondary prevention of ischemic stroke in the Qingdao area of Northern China. There should be more education efforts to the health care professionals and public to increase its use.

INTRODUCTION

Cerebrovascular disease is the third leading cause of death and the number one cause of major long-term disability worldwide[1] and in China. In China, approximately 80% of strokes are ischemic, and approximately one-third are recurrent. Atherosclerotic stenosis of cerebral vessels is a common cause of stroke worldwide, and intracranial stenosis is more common in Asians, accounting for 30% - 50% of strokes[2], which is associated with a higher risk of recurrent stroke.[2-3] With regards to stroke prevention, as the mechanisms underlying clinical stroke syndrome vary, the preventative measures should be tailored to the disease mechanism.[1] Lipid lowering agents , mainly 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors (statins), which reduce the levels of low-density lipoprotein (LDL) cholesterol, has become the most important advancement in stroke prevention since the introduction of aspirin and blood pressure lowering therapies, with each 10% reduction in LDL cholesterol estimated to decrease stroke risk by 15%.[4] The effect has been proven to be more important in large artery disease.[5] Therefore stroke guidelines from many of the Asian countries have recently recommended the use of statins for recurrent stroke prevention in patients with previous ischaemic stroke or transient ischaemic attack.[6]

Since the publication of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial[7], statins have been increasingly used throughout China; but the exact current practice is unknown. Previous studies of statins use have been restricted to long-term secondary

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stroke prevention, particularly in patients treated in urban hospitals[8], thus limiting the conclusions that can be drawn. However, early rather than late prevention is more important because of the higher recurrence that occurs during the early stages after stroke.[9-11] The objective of this study was to investigate the current status of statins use immediately after ischemic stroke in the Qingdao area of Northern China, including both urban and rural areas, and to determine the factors and potential barriers that affect its use.

METHODS

This is the substudy of a multicentre, prospective study on acute therapy and secondary prevention of stroke that includes 11 hospitals in the Qingdao area of China. The subjects were patients admitted with a diagnosis of acute ischemic stroke from January to October 2011. The inclusion criteria were: (1) Age ≥18 years; (2) Diagnosis of acute ischemic stroke confirmed by clinical presentations and computerised tomography (CT) or magnetic resonance imaging (MRI) brain scan; (3) Onset of symptoms within the past 7 days; and had given written informed consent for the study. Patients were excluded if the CT or MRI brain showed a cerebral haemorrhage.

The baseline characteristics included the age, sex, marital status, living status (whether living alone or with relatives), education ("higher" with secondary school education or above, or "lower" with primary school education or below), income ("higher" with income > RMB >1500 /month, or "lower" with RMB < CNY1500/month), medical insurance ("higher" with labour insurance or commercial insurance, or "lower" with rural insurance or no insurance), and hospital level. The hospitals were classified as "Level 1" (rural hospital with only the most basic facilities and very limited inpatient capacity, with patients treated by general practitioners); "Level 2" (semi-rural hospital with at least 100 inpatient beds, providing preventive and acute medical care, with patients treated by Neurologists); or "Level 3" (urban tertiary referral centre, with a stroke unit and patients treated by a team of specialists). A trained Neurologist was responsible for the data collection using a standardised questionnaire for all the patients recruited.

The risk factors for stroke recorded included history of hypertension, coronary heart disease, diabetes mellitus, hyperlipidemia, stroke or transient ischemia attack (TIA), and current smoking and excessive alcohol intake. Excessive alcohol consumption was defined as drinking more than 20g alcohol intake per day. The severity of the neurological deficits and the disability levels of the study subjects were assessed using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Strokes were classified as follows: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), or posterior circulation infarct (POCI) according to the OCSP (Oxfordshire Community Stroke Project) classification. Strokes were also classified as large artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), and other types according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. Details of the lipid adjustment therapies were obtained from the medical records. The one month follow-up data were collected from either patients or their caregivers during the face-to-face interviews at the first outpatient clinic visit. We also recorded the use of statins at two specific time points; during the acute stage after the current stroke in the hospital and at the one month follow-up.

Statistical analysis

All of the data were analysed using the SPSS 18.0 software. The continuous variables were expressed as the mean ± standard deviation (SD) and median (range), and the categorical variables were expressed as percentages. A univariate analysis was performed using the two sample *t*- test or Mann-Whitney *U* test depending on the distribution of the data and the chi-square test or Fisher's exact test. A logistic regression analysis was then performed to determine the associations between the significant variables identified in the univariate analysis and the use of statins in the acute stage and at the one-month follow-up. All of the *P*-values and confidence intervals (*CI*s) were estimated in a two-tailed fashion. The differences were considered to be statistically significant when $P < 0.05$.

RESULTS

A total of 1114 stroke patients from 11 sites were assessed for study eligibility, with an age range of 22 to 98 years (mean 67.0 ± 12.4 years). Of the 1114 patients, 257 were excluded from the study for the following reasons: intracranial haemorrhaging (134, 52.1%), did not have a recent acute stroke (67, 26.1%), and no consent (56, 21.8%). This resulted in a final sample size of 857 patients, with a mortality rate of 3.2%

Table 1: Factors associated with use of lipid lowering therapy during acute stage of stroke using univariate analysis

	Statins	No statins	*P*	*OR*
Demographic factors				
N	431(50.3%)	426(49.7%)		
Hospital levels			<0.001*	
Rural (Level 1)	16 (3.7%)	69 (16.2%)		
Semirural (Level 2)	164 (38.1%)	121 (28.4%)	<0.001**	5.845 (3.232-10.570)
Urban (Level 3)	251 (58.2%)	236 (55.4%)	<0.001***	4.587 (2.588-8.128)
Sex (male)	253 (58.7%)	239 (56.1%)	0.442	0.899 (0.686-1.179)
Age			0.003	2.159 (0.500-3.819)
Mean±SD	66.0±11.9	68.1±12.8		
Median (range)	67 (29-92)	70 (22-98)		
Marriage (single)	22 (5.1%)	33 (7.7%)	0.117	1.557 (0.892-2.718)
Living alone	16 (3.7%)	21 (5.0%)	0.831	1.345 (0.692-2.615)
Education (Lower)	215 (50.5%)	223 (52.5%)	0.559	1.083 (0.828-1.418)
Medical insurance (Lower)	208 (48.4%)	197 (46.2%)	0.553	0.918 (0.702-1.201)
Occupation(lower)	206(48.0%)	210 (49.6%)	0.635	1.067 (0.816-1.396)
Vascular Risk factors(previous history)				
Hypertension	278(64.5%)	259(60.9%)	0.281	1.165 (0.883-1.537)
Coronary heart disease	111(25.8%)	120(28.2%)	0.426	0.885 (0.654-1.196)
Diabetes mellitus	97(22.5%)	74(17.4%)	0.060	1.381 (0.986-1.936)
Hyperlipidemia	42(9.7%)	11(2.6%)	0.000	4.073 (2.068-8.025)
Stroke history	78(18.1%)	67(15.9%)	0.388	1.171 (0.818-1.675)
Smoking	110(25.5%)	77(18.1%)	0.008	1.553 (1.119-2.157)
Excessive alcohol consumption	94(21.9%)	49(11.5%)	<0.001	2.152 (1.479-3.133)
Clinical assessment				
Diagnosis			0.624	1.114 (0.724-1.714)
TIA	49 (11.4%)	44 (10.3%)		
Infarction	382 (88.6%)	382 (89.7%)		
OCSP classification			0.026	
Total anterior circulation infarct	74 (20.6%)	81 (25.6%)	1	
Part anterior circulation infarct	152 (42.2%)	99 (31.2%)	0.012	0.595 (0.397-0.891)
Lacunar Infarct	68 (18.9%)	75 (23.7%)	0.974	1.008 (0.639-1.588)
Posterior circulation infarct	66（18.3%）	62 (19.6%）	0.522	0.858 (0.537-1.371)
NIHSS at onset			0.080	1.036 (0.138-1.934)
Mean±SD	5.7±6.1	6.7±7.1		
Median(range)	4(0-32)	4(0-32)		
TOAST classification			<0.001§	
Large artery atherosclerosis	216 (50.2%)	125 (29.5%)		
Small vessel occlusion and others	181 (42.1%)	245 (57.8%)	<0.001§§	0.428 (0.319-0.573)
Cardioembolism	33 (7.7%)	54 (12.7%)	<0.001§§§	0.354 (0.218-0.575)
LDL			<0.001	-0.284 (-0.424—0.144)
Mean±SD	3.3±1.12	3.0±0.80		
Median(range)	3.2(0.04-12.73)	3.0(1.04-7.55)		

TIA: transient ischemic attack; OCSP classification: Oixfordshire Community Stroke Project classification; NIHSS: National Institutes of Health Stroke Scale; TOAST classification: Trial of Org 10172 in Acute Stroke Treatment classification; LDL:low-density lipoprotein

*p-value of comparison among the three groups; **p-vale of comparison between rural and semirural; ***p-value of comparison between rural and urban; § p-value of comparison among the three groups; §§p-vale of comparison between large artery atherosclerosis and small vessel occlusion; §§§ p-value of comparison between large artery atherosclerosis and cardioembolism.

(27/857). At one month, 92 patients did not attend the follow-up. The data for statin use at one month was thus obtained from 738/857 (86.1%) of patients. The median time between stroke onset and the one month follow-up was 32 days (range 25 to 40 days). The baseline demographic data of the 857 study patients is shown in Table 1. Of the study patients, 50.3% (431/857) received statins after stroke in the hospital. At the one month follow-up, 41.5% (306/738) were on lipid lowering therapy.

Table 1 shows the factors associated with lipid lowering therapy at acute stage. The factors identified by univariate analysis as having a potential association were included in the model of the multivariate analysis. The results of multivariate analysis showed that lipid lowering therapy at acute stage was independently and positively associated with a history of hyperlipidemia ((*P*=0.002, *OR* (95%*CI*): 3.784 (1.610-8.898)), excessive alcohol consumption (*P*=0.005, *OR* (95%*CI*): 1.928 (1.214-3.062)), PACI stroke (*P*<0.001, *OR* (95%*CI*): 1.974 (1.370-2.767)), and raised LDL levels ((*P*=0.000, *OR* (95%*CI*): 1.426 (1.170-1.739)) (Table 2).

The results of univariate analysis of the factors associated with lipid lowering therapy one month after stroke is shown in Table 3. The factors identified by univariate analysis as having a potential association were included in the model of multivariate analysis. The results of multivariate analysis showed that lipid lowering therapy at one month follow-up was independently and positively associated with lipid lowering therapy at acute stage ((P=0.000, OR (95%CI): 18.275 (11.476-29.101)), and negatively with mRS ≥4 at follow-up ((P=0.030, OR (95%CI): 0.568 (0.341-0.948))(Table 4).

DISCUSSION

Intracranial atherosclerosis causes 30% - 50% of strokes in Asia[2], and symptomatic intracranial stenosis is associated with a higher risk of recurrent stroke.[2-3] Studies have demonstrated that a decrease in LDL concentrations with HMG-CoA reductase inhibitors (statins) can reduce the incidence of stroke in high-risk populations.[13-16] Besides decreasing LDL level, statins also posses other mechanisms, such as improving endothelial function and cerebrovascular reactivity, stabilisation of microvascular integrity, anti-inflammatory and immunomodulatory properties.[17-18] Therefore, lipid lowering therapy is an important advancement in stroke prevention, especially to patients with large artery disease.[5] Like other countries, the Chinese Stroke Prevention and Treatment Guideline in 2009 also recommended the use of statins in stroke patients. This prospective, multicentre study provided an overview of the current status of lipid lowering treatment after ischemic stroke in urban and rural China, aiming to complement the urban data obtained in previous studies.[20-21] We selected two time points to reflect acute stage therapy and early secondary prevention.

Previous studies have suggested that statins are effective in the acute phase of ischemic stroke[22-24], including improving outcome and decreasing mortality.[26-28] Our study found that the frequency of statins use at the acute stage was only 50.3%, which is lower than 83.5% from the studies performed in developed countries.[29] We found the statins use during acute stroke while the patients were still in hospital was associated with a history of hyperlipidemia, excessive alcohol consumption, PACI stroke, and raised LDL levels. Patients with a history of excessive alcohol consumption often displayed disturbances in lipid metabolism, and were probably thus prescribed statins by their physicians. Patients with TACT had more severe disease than PACT. They were more likely to have disturbance of consciousness and dysphagia, probably thus less likely to receive oral drugs including statins. Previous studies have reported

Table 2: Factors associated with use of lipid lowering therapy during acute stage of stroke using multivariate analysis

	B	S.E.	P	Exp(B)	95%CI
Hyperlipidemia (with vs. without)	1.331	0.436	0.002	3.784	1.610-8.898
Alcohol (with vs. without)	0.656	0.236	0.005	1.928	1.214-3.062
OCSP (PACI vs. TACI)	0.666	0.179	0.000	1.974	1.370-2.767
LDL	0.355	0.101	0.000	1.426	1.170-1.739

OCSP: Oxfordshire Community Stroke Project classification; PACI: partial anterior circulation infarct ; TACI: total anterior circulation infarct; LDL: low-density lipoprotein

Table 3: Factors associated with use of lipid lowering therapy during follow-up at one month of stroke using univariate analysis

	Statins	No statins	*P*	*OR*
Demographic characteristics				
N	306(41.5%)	432(58.5%)		
Hospital levels			<0.001*	
Rural (Level 1)	10 (3.3%)	75 (17.4%)		
Semi-rural (Level 2)	111 (36.3%)	174 (40.3%)	<0.001**	0.209(0.104-0.422)
Urban (Level 3)	185 (60.5%)	183 (42.4%)	<0.001***	0.132(0.066-0.263)
Sex (male)	187 (61.1%)	231 (53.5%)	0.039	0.731(0.543-0.985)
Age			0.084	1.560(-0.528-3.648)
Mean±SD	66.4±12.1	67.9±12.9		
Median (range)	67 (32-94)	69 (22-92)		
Marriage (single)	17 (5.6%)	26 (6.0%)	0.785	1.091(0.581-2.048)
Living state (alone)	10 (3.3%)	23 (5.3%)	0.185	1.661(0.779-3.543)
Education (lower)	140 (46.4%)	226 (52.6%)	0.099	1.282(0.955-1.722)
Medical insurance (lower)	145 (47.4%)	254 (58.9%)	0.002	1.593(1.186-2.141)
Occupation (lower)	139 (45.7%)	256 (59.7%)	<0.001	1757(1.305-2.364)
Risk factors				
Hypertension	201 (65.7%)	255 (59.2%)	0.072	1.321(0.975-1.791)
Coronary heart disease	78 (25.5%)	112 (25.9%)	0.894	0.977(0.699-1.367)
Diabetes mellitus	69 (22.5%)	74 (17.1%)	0.066	1.408(0.976-2.033)
Hyperlipidemia	27 (8.8%)	18 (4.2%)	0.009	2.226(1.203-4.119)
Stroke history	52 (17.0%)	65 (15.1%)	0.484	1.153(0.774-1.717)
Smoking	91 (29.7%)	82 (19.0%)	0.001	1.807(1.282-2.547)
Excessive alcohol consumption	79 (25.9%)	54 (12.5%)	0.000	2.447(1.668-3.590)
Clinical assessment				
Diagnosis			0.305	1.277(0.800-2.040)
TIA	37 (12.1%)	42 (9.7%)		
Infarction	269 (87.9%)	390 (90.3%)		
OCSP classification			0.551	
Total Anterior Circulation Infarct	59 (22.9%)	67 (21.5%)		
Part Anterior Circulation Infarct	110 (42.6%)	120 (38.5%)		
Lacunar Infarct	43 (16.7%)	63 (20.2%)		
Posterior circulation infarc	46（17.8%）	62（19.9%）		
TOAST classification			<0.001§	
Large Artery Atherosclerosis	160(52.5%)	143(33.3%)		
Small Vessel Occlusion and others	123 (40.3%)	237 (55.1%)	<0.001§§	0.464(0.339-0.635)
Cardioembolism	22 (7.2%)	50 (11.6%)	<0.001§§§	0.393(0.227-0.681)
Statins in hospital	274 (89.5%)	124 (28.7%)	<0.001	21.268(13.956-32.412)
LDL			0.037	-0.103(-0.299—0.926)
Mean±SD	3.2±1.0	3.1±0.9		
Median(range)	3.1(0.04-12.7)	3.0(0.7-7.9)		
NIHSS at follow-up			0.243	1.312(0.299-2.325)
Mean±SD	3.0±4.3	4.3±6.2		
Median(range)	1(0-18)	1(0-28)		
mRS: at follow-up			0.030	0.633(0.419-0.958)
0-3	259 (86.6%)	324 (80.4%)		
≥4	40 (13.4%)	79 (19.6%)		

TIA: transient ischemic attack; OCSP classification: Oixfordshire Community Stroke Project classification; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LDL: low-density lipoprotein; mRS: modified Rankin Scale.
*p-value of comparison among the three groups; **p-vale of comparison between rural and semirural; ***p-value of comparison between rural and urban; § p-value of comparison among the three groups; §§p-vale of comparison between large artery atherosclerosis and small vessel occlusion; §§§ p-value of comparison between large artery atherosclerosis and cardioembolism.

Table 4: Factors associated with use of lipid lowering therapy during one month follow-up of stroke using multivariate analysis

	B	S.E.	P	Exp(B)	95%CI
mRS* at follow up(≥4 vs. ≤3)	-0.565	0.261	0.030	0.568	0.341-0.948
Statins in hospital (with vs without)	2.906	0.237	0.000	18.275	11.476-29.101

mRS:modified Rankin Scale

factors such as female gender and geography as important factors related to the use of statins in hospital.[29]

The SPARCL study was the first to show the beneficial effect of statins on secondary stroke prevention.[7] Taking account of all of the major statins trials, it has been estimated that each 1-mmol/L (39-mg/dL) decrease in the concentration of LDL cholesterol resulted in a relative risk reduction for stroke of 21.1% (95% CI, 6.3%–33.5%; P=0.009).[4] In this study, we found that the frequency of statins use was 41.5% during one month follow-up, at the beginning of secondary prevention. This was similar to reports from other countries (approximately 36.5%)[30] and was higher than other previous reports in China (approximately 20%).[31] Our results showed that statins treatment at the one month follow-up was associated with mRS≥4. Patients with more disability (mRS≥4) may have more complications, such as a dysfunction of the liver and kidney, and may be fed by a nasogastric tube, which limits their use of statins. We also found that the patients who used statins during acute stroke while in hospital were more likely to also use statins during follow-up. Thus, statins use during the acute stage is particularly important as it affects the subsequent long term use.

This study has several limitations. Firstly, we selected fewer patients (only 9.9%) from Level 1 rural hospitals because of inadequate imaging facilities (CT and MRI), although there were more stroke patients in the rural than urban areas of China. As we have shown that there were less use of statin in the rural as compared to the urban hospitals (Table 1), the frequency of statins use in China may be lower than that reported in this study. Secondly, we did not collect the longer term follow-up data, and thus the long-term practice of secondary prevention remained unknown. Thirdly, this study was limited by its moderate sample size and limited location. The study would be more representative if we could recruit more patients from wider distributions in China. Lastly, there were about ten percent of patients who were lost to follow-up. As these patients may be less adherent to statins, the non-adherence to secondary prevention could thus be higher than estimated.

In conclusion, this study reported the use of lipid lowering therapy during acute and early secondary prevention of ischemic stroke in the Qingdao area of Northern China, in both urban and rural hospitals. It was , found to be used in about half of the patients, less during follow-up. There should be more education efforts to the health care professionals and public to increase its use.

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DISCLOSURE

Conflicts of interest: None

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