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Original Research Article

Effects of atorvastatin and rosuvastatin on blood lipids, platelet aggregation rate and inflammatory factors in patients with cerebral infarction

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Abstract

Purpose: *To investigate the effects of atorvastatin and rosuvastatin on blood lipids, platelet aggregation rate (PAR) and inflammatory factors in patients with cerebral infarction.*
Methods: *Patients (n = 120) with cerebral infarction treated in Feng Hua People's Hospital, Jiang Feng Hua, China from January 2014 to October 2016 were randomly divided into control group (clopidogrel combined with atorvastatin, 60 cases) and observation group (clopidogrel combined with rosuvastatin, 60 cases). Blood lipids, PAR, inflammatory factors and carotid atherosclerotic plaque were recorded and compared.*
Results: *Following treatment, total cholesterol (TC), triglycerides (TG) and low density lipoprotein cholesterol (LDL-C) in the observation group were significantly lower ($p < 0.05$) than in the control group, while high density lipoprotein cholesterol (HDL-C) was significantly higher ($p < 0.05$). C-reactive protein (CRP), tumor necrosis factor-α (IL-6) and interleukin-6 (IL-6) were significantly decreased in the two groups after treatment ($p < 0.05$). Plaque area, intima-media thickness (IMT) and number of plaques in the two groups were significantly lower after treatment than before treatment ($p < 0.05$). Plaque area, IMT and number of plaques in the observation group were significantly lower than those in the control group ($p < 0.05$).*
Conclusion: *Atorvastatin and rosuvastatin have no significant effect on the antiplatelet function of clopidogrel, but rosuvastatin shows better control of blood lipids, carotid atherosclerosis and inflammatory factors.*

Keywords: *Atorvastatin, Rosuvastatin, Cerebral infarction, Blood lipids, Platelet aggregation rate, Inflammatory factors*

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INTRODUCTION

Cerebral infarction is one of the common cerebrovascular diseases. With rising aging population in China, improvement in living standards and changes in work pressure, morbidity and mortality of stroke are on the increase [1]. Acute ischemic stroke refers to a cerebrovascular disease or recurrence of pathological blood disorder based on localized or diffuse brain dysfunction, and is the most common type of cerebral infarction (accounts for about 50 ~ 80 %). Its main clinical manifestations are hemiplegia, aphasia, and nerve function deficiency syndrome consciousness disorder [2,3].

In the acute stage of ischemic stroke, the main treatment measures are aimed at thrombolysis to restore blood circulation, protect nerve function

and save the life of patient. There are many reports about the treatment measures in the acute phase; there are no controversies about these treatments. Related studies show that after the onset of cerebral infarction, the patient has a higher recurrence rate, up to 13.4 % for 1-year recurrence rate [4], 26 % for 5-year recurrence rate and 39 % for 10-year recurrence rate [5]. Thus, high recurrence rate is a serious problem in current treatment of cerebral infarction. Treatment measures for ischemic stroke in the acute stage include antiplatelet therapy, regulation of blood lipids and blood pressure; and treatment of primary diseases [6]. Statins as lipid-lowering drugs are widely used in the later treatment of ischemic stroke. Studies have shown that statins not only play a role in regulating lipids, they also reduce inflammatory effects, reduce atherosclerotic plaque, and exert anti-platelet aggregation effect, all of which improve the prognosis of cerebral infarction [7,8].

The commonly used drugs in late post-ischemic stroke include statins and clopidogrel. Atorvastatin is metabolized by cytochrome P450 (CYP3A4) and causes competitive inhibition leading to clopidogrel resistance, decreased anti-platelet activity and increased risk of cardiovascular and cerebrovascular events [9]. Rosuvastatin is metabolized by cytochrome P450 2C9 (CYP2C9), and has no significant effect on anti-platelet activity of clopidogrel. However, some studies reported that statins have no effect on the origin of clopidogrel resistance, and the impact of its anti-platelet effect remains controversial [9-11] .
The research aimed to investigate the effects of atorvastatin and rosuvastatin on blood lipids, platelet aggregation rate (PAR) and inflammatory factors in patients with cerebral infarction.

METHODS

Study subjects

Patients with cerebral infarction (120) treated in Feng Hua People's Hospital of Zhe Jiang Province, Zhe Jiang Feng Hua, from January 2014 to October 2016, were selected. Inclusion criteria were: (1) Patients with clinical symptoms in line with "Clinical diagnostic criteria for stroke" by WHO [12]; (2) patients confirmed for presence of infarction by head CT or MRI examination; (3) patients aged 30 to 79 years with complete clinical data; (4) patients who did not take antiplatelet drugs or statins 3 months before the study; and (5) patients and their families who gave informed consent and signed consent form. The exclusion criteria were:

(1) patients with severe heart, kidney, liver and other vital organ dysfunction; (2) Patients with mental illness (3) Patients with contra-indications to clopidogrel, rosuvastatin and atorvastatin as well as patients allergic to pharmaceutical ingredients, pregnant patients and lactating patients. This study was approved by the ethics committee of Feng Hua People's Hospital (no. ZFH2013032), and followed the guidelines of Helsinki Declaration [13]. The recruited patients were divided into the control group and the observation group by random number table method, with 60 cases in each. In the control group, 35 cases were male and 25 were female. They ranged in age from 32 to 79 years (mean age, 45.83 ± 7.49 years). There were 28 cases with hypertension, 15 cases of hyperlipidemia, 10 cases of diabetes mellitus and 7 cases with smoking history. In the observation group, 30 cases were male and 30 were female. They were aged 33 to 77 years (mean age, 46.75 ± 7.51 years). There were 25 cases of hypertension, 16 cases of hyperlipidemia, 11 cases of diabetes mellitus and 8 cases wih smoking history. The differences in sex, age and basic disease between the two groups had no statistical significance ($p > 0.05$).

Treatment protocol

The two groups of patients received conventional treatment in accordance with recent "Chinese ischemic stroke and transient ischemic attack secondary prevention guidelines" [14]. This included blood glucose and blood pressure control, antiplatelet therapy and primary disease treatment. In the control group, patients were given clopidogrel combined with atorvastatin [clopidogrel (Sanofi Winthrop Industries) at a dose of 75 mg orally once daily; and 20 mg atorvastatin (Pfizer Ireland Pharmaceuticals) orally once a day. The patients in the observation group were given clopidogrel combined with rosuvastatin [clopidogrel (drug as in control group) 75 mg once daily, orally; rosuvastatin (strength, 10 mg/tablet, approval number: J20120006; Astra Zeneca UK limited) 10 mg, once a day, orally. The two groups of patients were treated continuously for 6 months.

Observation parameters

Levels of serum lipids, inflammatory factors and carotid atherosclerosis were measured 6 months before and after treatment. Fasting venous blood was taken early in the morning 1, 2, 3 and 6 months before and after treatment for PAR test. Total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) levels of

patients were measured by TBA-40FR fully automatic biochemical analyzer (Toshiba, Japan). Platelet aggregation rates were measured before treatment and after 1, 2, 3, and 6 months of treatment using Sonoclot coagulation and platelet function analyzers (Sienco Inc, USA). Immuno-turbidimetry was used for determination of C-reactive protein (CRP) levels. Interleukin -6 (IL-6) and tumor necrosis factor –α (TNF-α) were determined on double antibody enzyme linked immunosorbent assay (ELISA) kits (Shanghai Senxiong Technology Industrial Co., Ltd).

The area and number of carotid plaque and carotid intima-media thickness (IMT) were determined on Color Doppler ultrasound (PHILPS, Holland). Bilateral common carotid artery (CCA), internal carotid artery (ICA) and plaques in the bifurcation of the CCA were recorded. Qualitative and quantitative records of ultrasound echo characteristics and plaque morphology were kept. Blood levels of LDH, CK-MB, ALT, AST, and total bilirubin were assayed in the two groups.

Statistical analysis

Statistical analysis is analyzed by SPSS version 20.0 and the data are presented as mean ± standard deviation (SD) and, were compared between the two groups using t-test. Enumeration data are presented as frequency or percentage (%), and were compared using χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Blood lipid levels

There were no statistically significance in TC, TG, HDL-C and LDL-C levels between the two groups before the treatments ($p > 0.05$). However, after the treatments, TC, TG and LDL-C levels were significantly decreased ($p < 0.05$), while HDL-C levels increased significantly ($p < 0.05$) in the two groups. The levels of TC, TG and LDL-C in the observation group after treatment were significantly lower than corresponding values in the control group ($p < 0.05$). HDL-C was significantly higher than in the control group ($p < 0.05$; Table 1).

Platelet aggregation rate

There was no significant difference in PAR between the two groups before treatment ($p > 0.05$), but PAR in the two groups decreased significantly ($p < 0.05$) after treatment. However, PAR values (in the two groups) after treatment for 1, 2, 3 and 6 months were similar ($p > 0.05$; Table 2).

Levels of inflammatory factors

As shown in Table 3, differences in the levels of inflammatory factors between the two groups before treatment was not statistically significant ($p > 0.05$).

Table 1: Blood lipid levels (mmol/L) of the patients

Group	Time	TC	TG	HDL-C	LDL-C
Control group (60)	Before treatment	5.88 ± 1.09	2.07 ± 0.37	0.87 ± 0.22	3.75 ± 0.77
	After treatment	5.11 ± 1.01	1.67 ± 0.21	1.11 ± 0.34	2.91 ± 0.61
	T	4.014	7.283	4.591	6.624
	P	0.000	0.000	0.003	0.011
Observation group (60)	Before treatment	5.97 ± 1.12	2.11 ± 0.42	0.84 ± 0.21	3.88 ± 0.79
	After treatment	4.52 ± 0.73*	1.34 ± 0.19*	1.35 ± 0.42*	2.31 ± 0.47*
	T	7.011	1.989	8.413	13.230
	P	0.000	0.000	0.000	0.000

*Values are expressed as mean ± SD; *p < 0.05, compared to control group after treatment*

Table 2: Platelet aggregation rate (%) of the patients

Group	Before treatment	1-month treatment	2-month treatment	3-month treatment	6-month treatment
Control group (60)	70.32 ± 14.01	50.87 ± 13.95*	48.11 ± 12.43*	43.54 ± 13.07*	41.47 ± 13.04*
Observation group (60)	71.17 ± 14.88	51.34 ± 13.07*	47.35 ± 12.12*	41.18 ± 12.84*	39.71 ± 12.94*
T	0.322	0.190	0.339	0.998	0.742
P	0.748	0.849	0.735	0.320	0.460

*Values are expressed as mean ± SD; *p < 0.05 compared with values before treatment*

Table 3: Levels of inflammatory factors in the patients

Group	Time	CRP (mg/L)	TNF-α (pg/mL)	IL-6 (pg/mL)
Control (60)	Before treatment	14.87 ± 2.97	185.74 ± 27.41	139.88 ± 16.89
	After treatment	8.68 ± 1.45	90.14 ± 25.17	108.74 ± 13.71
	T	14.507	19.899	11.088
	P	0.000	0.000	0.000
Observation (60)	Before treatment	15.11 ± 3.07	190.17 ± 26.33	140.58 ± 17.47
	After treatment	5.79 ± 1.31*	80.04 ± 19.25*	100.97 ± 9.87*
	T	21.629	26.154	15.291
	P	0.000	0.000	0.000

*Values are expressed as mean ± SD; *p < 0.05, compared with control group after treatment*

Table 4: Carotid atherosclerotic plaques in the patients

Group	Time	Plaque area (mm^2)	IMT(mm)	Number of plaques (个)
Control (n = 60)	Before treatment	15.74 ± 2.14	1.74 ± 0.67	2.63 ± 1.07
	After treatment	11.14 ± 1.87	1.34 ± 0.51	1.74 ± 0.84
	T	12.538	3.680	3.665
	P	0.000	0.008	0.008
Observation (n = 60)	Before treatment	16.41 ± 2.42	1.68 ± 0.61	2.35 ± 1.14
	After treatment	10.37 ± 1.74*	1.01 ± 0.37*	1.42 ± 0.24*
	T	1.982	7.274	8.547
	P	0.000	0.000	0.000

*Values are expressed as mean ± SD; *p < 0.05, compared with control group after treatment*

After treatment, CRP, TNF- and IL-6 levels in the two groups were significantly lower than the corresponding values before treatment ($p < 0.05$), while the levels of CRP, TNF- and IL-6 in the observation group were significantly lower than those in the control group ($p < 0.05$).

Carotid atherosclerotic plaques

Plaque area, IMT and number of plaques were similar in the two groups before treatment. However, after treatment, the plaque area, IMT and number of plaques decreased significantly in the two groups ($p < 0.05$), while in the observation group, plaque area, IMT and number of plaques were significantly lower than those in the control group ($p < 0.05$; Table 4).

Recurrence rate and complications

After 6 months of treatment in the control group, one case of recurrent cerebral infarction (1.67 %; 1/60); one case of liver injury (1.67 %; 1/60) and 2 cases of increased myocardial enzymes (3.33 %; 2/60) were seen, along with 1.67 and 5 % recurrence rate and complication rate, respectively. There was no recurrence in the observation group, but 2 cases of liver injury (3.33 %; 2/60) and 3 cases of elevated myocardial enzymes (5 %; 3/60) occurred, while the total incidents of complications was 8.33 % (5/60). Adverse reactions of the two groups got better after their respective treatments, and no other serious adverse reactions were observed. Differences in recurrence rate and total incidence of complications between the two groups did not show statistical significance ($p > 0.05$).

DISCUSSION

Cerebral infarction is a common disease in neurology, with acute onset and speedy development. In recent years, the incidence has increased in younger populations, seriously affecting the health and quality of life of patients [15]. Atherosclerosis is the pathological basis of cerebral infarction, and the main risk factor of atherosclerotic plaque formation is high blood lipids. Thus, lipid-lowering therapy can effectively reduce atherosclerosis and the incidence of cerebral infarction [16]. Clopidogrel combined with statins has become a routine treatment for prevention of cerebral infarction. It can effectively reduce the risk of recurrence and improve prognosis in patients with cerebral infarction [17]. Clopidogrel, one of the most common anti-platelet agents, is metabolized by the CYP450 enzyme system to form an active component, which can irreversibly bind to the ADP receptor on the platelet membrane surface, thereby exerting its antiplatelet aggregation effect[18].

CRP, TNF- alpha and IL-6 belong to non-specific markers of the acute stage of systemic inflammatory response, which increase blood viscosity, promote plaque formation and accelerate atherosclerosis [19]. They are risk factors for atherosclerosis. CRP is an acute phase protein synthesized in the liver. It is involved in the inflammatory process of

atherosclerosis, by inducing increases in intimal thickness and rupture of plaques, which result in acute cerebral infarction. Statins are hydroxymethylglutaryl coenzyme A reductase (HMG-CoA) inhibitors which can block cholesterol biosynthesis and lipid peroxidation, stabilize atherosclerotic plaque and increase cerebral blood flow [20,21].

It has been reported that 30 % of ischemic stroke are caused by carotid artery diseases, and that cerebral infarction is closely related to carotid atherosclerosis [22]. Atherosclerosis involves the intracranial and external arteries. Lipids gradually accumulate in the arterial smooth muscle cells in the vascular smooth muscle, leading to intimal hyperplasia and plaque formation. Inflammation and oxidative stress lead to plaque rupture and arterial invasion, blockage of the lumen by thrombosis and ischemic cerebral infarction [23,24]. Thus, there is a complementary relationship between the level of inflammation and carotid atherosclerotic plaque formation. This implies that plaque formation can be controlled by reducing the level of inflammation, thereby preventing cerebral infarction.

In the current study, the level of inflammatory factors and carotid atherosclerosis were significantly decreased in the observation group, when compared with their corresponding values before treatment. This finding is due to the fact that statins can lower the level of CRP, inhibit platelet aggregation, promote fibrinolysis and stabilize atherosclerotic plaque. Besides, rosuvastatin suppresses aggregation of inflammatory cells and the formation of foam cells and oxygen free radical produced by macrophages [25,26].

Comparison of the two kinds of statin in patients with cerebral infarction revealed that platelet aggregation rate and blood lipid levels were lower than those before treatment, suggesting that the two statins had lipid-lowering and antiplatelet effects. However, the data showed that blood lipid levels in the observation group changed greatly when compared with the control group, while in the two groups, platelet aggregation rate declined to the same extent. This shows that rosuvastatin was more effective than atorvastatin in reducing blood lipids in cerebral infarction. The mechanism of action is based on the lipid-lowering effect of statins and their inhibitory effects on the key enzymes of cholesterol biosynthesis, thereby regulating the rate of synthesis of cholesterol and inhibiting atherosclerosis [27].

Rosuvastatin has a stronger inhibitory effect on HMG-CoA reductase than any other statin; it has a long half-life, low hepatic first pass effect, and better pharmacokinetic properties [28]. Studies by Johansen *et al* [29] and Wang *et al* [30] demonstrated that agents metabolized by CYP3A4 (such as atorvastatin) are lipophilic, and so promote clopidogrel resistance, while rosuvastatin which is not metabolized by CYP3A4, is hydrophilic, and has obvious influence on the platelet aggregation effect of clopidogrel. This study found that the platelet aggregation functions of clopidogrel in the patients with secondary prevention of cerebral infarction in the two groups may be similar, possibly due to multiple metabolic pathways of clopidogrel.

Study limitations

There are some deficiencies in this study. All subjects were in-patients admitted to the hospital, and the sample size was small. Thus, there may be selective bias. Future studies should use an expanded sample size, stratify the patients, and extend follow-up to obtain more reliable conclusions.

CONCLUSION

The results obtained in this study indicate that atorvastatin and rosuvastatin have good lipid-lowering and anti-inflammatory effects in patients with cerebral infarction, without significant effects on the platelet aggregation function of clopidogrel. The results also revealed that rosuvastatin displays better control of blood lipids, atherosclerosis and levels of inflammatory factors, and thus possesses distinct therapeutic benefits.

DECLARATIONS

Acknowledgement

None.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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