Efficacy comparison of rosuvastatin and atorvastatin in the treatment of atherosclerosis and drug safety analysis

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Abstract: Previous studies have shown that the commonly used statin lipid lowering drugs can delay the progression of atherosclerotic plaque. Atorvastatin can stabilize atherosclerotic plaque, but it can not reverse atheromatous plaque. This study will compare the efficacy of rosuvastatin and atorvastatin in the treatment of atherosclerosis and try to prove that the use of statins can improve peripheral atherosclerosis and reverse atherosclerotic plaque. The results showed that 10 mg rosuvastatin was more effective than 20 mg atorvastatin in lowering serum lipid level and elevating ABI index, ABI as rosuvastatin group(0.782±0.236) and atorvastatin group(0.541±0.196). After 6 months of treatment, the carotid artery IMT in rosuvastatin group and atorvastatin group decreased compared with before treatment, and the difference was statistically significant ($P<0.05$). The TC/mmol·L^{-1} is 2.83±0.56 in rosuvastatin group and 3.24±0.71 in atorvastatin group. In addition, rosuvastatin did not increase the risk of adverse reactions compared with atorvastatin. The results confirm that statin therapy can improve peripheral atherosclerosis and reverse atherosclerotic plaques.

Keywords: Rosuvastatin, lipid-lowering drug, safety index, reverse plaque, adverse drug reaction.

INTRODUCTION

In recent years, the diet structure of Chinese people has changed significantly, and the incidence of atherosclerosis has increased. Atherosclerosis is a chronic progressive disease that can involve arteries of all important organs in the body (Mellotte *et al.,* 2015). Further development of atherosclerosis can lead to the serious consequences including: arterial lumen occlusion, rupture and bleeding (Ostojic *et al.,* 2015). Statins can be used in a variety of ways: reducing platelet aggregation and promoting its fibrinolysis, thus keeping atherosclerotic plaque stable, or likely to promote its reversal. Ankle-brachial index (ABI) is a simple and convenient means to predict cardiovascular accident and mortality, and their clinical value has been widely recognized.

Previous studies have shown that the commonly used statins can slow the progression of atherosclerotic plaques, and rosuvastatin can stabilize atherosclerotic plaque, but it cannot reverse the plaque. According to the present research data, rosuvastatin is obviously superior to atorvastatin in reducing LDL-C and reversing plaque, but there is no significant difference in the effect of anti-inflammatory (Parvathy *et al.,* 2013). In addition, rosuvastatin did not increase the risk of adverse reactions compared with atorvastatin. However, the adverse reactions of rosuvastatin and atorvastatin were not identical in different studies (Tomotaka *et al.,* 2010; Ray *et al.,* 2014). The incidence of total adverse events of statins is relatively low. The current adverse reaction data are obtained from large clinical trials and FDA database of adverse reporting systems in various countries (Wu *et al.,* 2015; Daniel *et al.,* 2011). There may be bias and more confounding factors in the data of the adverse reporting system (Tural *et al.,* 2015). Careful and prudent evaluation is needed before the conclusion is reached. Randomized controlled trials (RCT) often have more restrictive conditions, lower overall incidence of adverse events, and relatively limited clinical value (Zhu *et al.* 2015). In this study, carotid ultrasound and ABI were used as indicators to assess atherosclerotic improvement. It was confirmed that statin therapy could improve peripheral atherosclerosis and reverse atherosclerotic plaques.

MATERIALS AND METHODS

General information

A total of 240 patients with acute cerebral infarction who were hospitalized in Weifang YiDu Central Hospital from January 2016 to September 2017 were randomly selected. Randomly divided all patients into three groups, 80 cases in each group, including 80 cases as rosuvastatin group (40 men, 40 women), 80 cases as atorvastatin group (39 men, 41 women) and 80 cases as control group (42 men and 38 women). The research plan was approved by the hospital ethics committee with the approval number 14WGYDH16.

Inclusion criteria: (1) Diagnostic criteria set up by the Academic Conference on cerebrovascular; (2) Hospitalized patients aged 35~75 years. (3)Cerebral

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infarction within 3 d after first onset and cerebral infarction were excluded by cerebral CT scan. (4) A letter of informed consent has been signed. (5) There are risk factors for cerebrovascular diseases such as hypertension, diabetes and smoking.

Exclusion criteria: (1) There are obvious diseases of heart, liver, kidney and blood system. (2) Patients who have been treated with thrombolytic therapy after the onset of the disease. (3) Allergic to statins. (4) Pregnant women and breast-feeding women. (5) In the past 1 months, other blood lipid lowering drugs were used. (6) Patients with mental disorders. (7) Patients with obvious abnormalities in laboratory examination include aspartate aminotransferase (AST), alanine aminotransferase (ATL), serum total bilirubin serum creatine kinase (CK), and so on. There was no significant difference in gender, age, past history, blood pressure and blood lipid level, mRS score and NIHSS score before treatment, and there was no difference between the 3 groups, as shown in table 1.

Treatment plan

All patients were treated with standard ischemic stroke after admission, including antiplatelet aggregation, hypoglycemic therapy and blood pressure control. Rosuvastatin group was added with rosuvastatin tablet 10 $mg \cdot d^{-1}$ (specification: 10 mg per tablet, drug batch number: JC880).Atorvastatin group was added with atorvastatin tablet 20 $mg \cdot d^{-1}$ (specification: 20mg per tablet, drug batch number: 1237253), continuous treatment for 6 months.

Laboratory evaluation index

Before and 6 months after medication, 4 blood lipids were detected in all patients, including plasma triglyceride (TG0), total cholesterol (TC), high density lipoprotein cholesterol (high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C). Carotid ultrasound was performed before and sixth months after treatment to observe the qualitative and quantitative changes of plaques and plaques. The ankle-brachial index (ABI) value was measured at the same time.

Carotid plaque detection

The color Doppler ultrasound diagnostic system is employed by full-time staff to reduce system errors. The location, size, echo characteristics and surface morphology of plaques and plaques of common carotid artery, common carotid artery and internal carotid artery were recorded. At the same time, the plaques were qualitatively and quantitatively recorded. The diagnostic criterion of carotid plaques was IMT (intima-media thickness) of common carotid artery, common carotid artery bifurcation and internal carotid artery. The characteristics of the plaque were divided into 3 categories: hypoechoic, mixed echo and strong echo, which have the following characteristics: low echo plaque lipid composition, less collagen fiber content, mixed echo plaque lipid and collagen composition, high echo plaque mainly calcium salt deposition. Quantitative analysis was made by recording the number of plaques in each patient and measuring plaque IMT. ABI measurement: the automatic arteriosclerosis instrument was used and measured according to the operation instructions of the instrument. The ABI value was measured before and 6 months after treatment.

Safety index

6 months after the treatment, the patients were tested for liver function and renal function. During the treatment, there were no serious adverse reactions such as liver failure and rhabdomyolysis.

STATISTICAL ANALYSIS

A simple random sampling method was used to analyze the data with SPSS 19 statistical software. The measurement data was expressed as $x \pm s$. The paired t test was used in the group. The variance analysis was used in the group. The comparison of the two groups was compared with the $\chi 2$ test and the Fisher precision probability method, and the difference of $P<0.05$ was statistically significant.

RESULTS

Changes of blood lipid level and IMT of carotid atherosclerotic plaques

Features before treatment are compared as shown in table 1. After treatment, lipid levels (including TC, TG and LDL-C) in rosuvastatin group and atorvastatin group were all decreased, the difference was statistically significant ($P<0.05$).Blood lipid levels (including TC, TG and LDL-C) were not changed before and after treatment in the control group. The difference was not statistically significant ($P>0.05$). Compared with the Atorvastatin group, the levels of TC, TG and LDL-C in the rosuvastatin group were significantly lower than those in the Atorvastatin group ($P<0.05$).There was no significant difference in the level of HDL-C between the 3 groups before and after treatment ($P>0.05$). Rosuvastatin group, atorvastatin group and control group has 52, 58 and 55 patients with carotid artery plaque before treatment, with no statistically significant difference ($P>0.05$). There was no significant difference in IMT between the 3 groups before treatment ($P>0.05$).After 6 months of treatment in rosuvastatin group and atorvastatin group, there was a significant difference in carotid IMT between before and after treatment ($P<0.05$). The IMT of carotid artery was significantly decreased in rosuvastatin group ($P<0.01$). There was no significant difference in IMT between the control group before and after treatment ($P>0.05$), and the results were shown in table 2.

Change and comparison of patch properties

According to carotid ultrasound results, rosuvastatin group, atorvastatin group and control group had 52 cases of carotid plaques, 58 cases, 55 cases. There was no significant difference in IMT between the 3 groups before treatment, and at 6 months, the IMT of rosuvastatin and atorvastatin group was significantly lower than that before and in the control group (P<0.05). Before treatment, there was no significant difference in the ratio of hypoechoic plaque, hyperechoic plaque and mixed echo plaque between the 3 groups. Compared with pre treatment and control group, the rate of low echo plaque in rosuvastatin group and atorvastatin group decreased significantly at 6 months, and the rate of hyperechoic plaque increased significantly (P<0.05). The proportion of low echo plaque and hyperechoic plaque among the two groups was not statistically significant. The results are shown as shown in table 3

Quantitative analysis of ankle brachial index

The pre treatment ABI index of rosuvastatin group, atorvastatin group and control group were (0.535±0.151), (0.546±0.173) and (0.538±0.173), respectively, with no significant difference. The ABI index of rosuvastatin group was higher than that before treatment, and the difference was statistically significant. Compared with the Atorvastatin group, the ABI index increased significantly in rosuvastatin group compared with that in the Atorvastatin group (P<0.05). There was no significant difference in the ABI index between the Atorvastatin group and the control group before and after treatment, as shown in table 4.

Analysis of the result of safety index

All the patients were selected before and 6 months after medication. All the patients were examined for renal function, liver function and creatine phosphokinase. The 3 groups were not statistically significant before treatment. After 6 months of treatment, the liver function damage increased in the rosuvastatin group and atorvastatin group. There were statistical differences compared with the control group ($\chi2$=0.317, $\chi2$=0.378, P=0.003, P=0.002). In the two treatment group, there was no significant difference in the proportion of liver function damage ($\chi2$= 0.445, P=0.252), and there was no statistical difference between the 3 groups of CK and the renal function (P> 0.05), as shown in table 5.

DISCUSSION

Statins are different in their structure; their drug generation and efficacy are different. The intensity of HMG-Co A reductase inhibition, rosuvastatin is stronger than atorvastatin and simvastatin, and so on. It is the strongest in lipid lowering drugs (Bihlet *et al*., 2017). In this study, the results showed that 10 mg rosuvastatin was more effective than 20 mg atorvastatin in lowering serum lipid level and elevating ABI index (Cahill *et al*., 2015). The effect of statins on lipid lowering was increased with the increase of dose. The study showed that 10~40 mg of rosuvastatin could reduce low density lipoprotein cholesterol (LDL-C) 55% ~ 65%, and atorvastatin 10~80 mg could reduce LDL-C 40% ~ 50% (Dimitry *et al*., 2017). The effects of two statins on lipid lowering were significantly higher than fluvastatin, pravastatin, simvastatin and lovastatin (Daniel *et al*., 2011). A number of clinical trials showed that rosuvastatin was significantly less LDL-C than atorvastatin in patients with hyperlipidemia, metabolic syndrome, diabetes, or coronary heart disease. The study also found that, regardless of the patient's basic blood lipid level, the rosuvastatin treatment could cause more than 82% of the patients to reach a target level of less than 100 mg $d{\cdot}L^{-1}$, which was significantly higher than the other statins (Foody *et al*., 2014).

In recent years, numerous studies have found that carotid atherosclerotic plaques, especially unstable plaques, are closely related to the occurrence of cerebral infarction. Unstable plaque (vulnerable plaque) suddenly ruptured bleeding, platelets activated; resulting in thrombosis is one of the pathogenesis of ischemic stroke (Finnerup *et al*., 2015). Carotid atherosclerotic plaque is one of the most important risk factors for acute cerebral infarction. If we have early treatment of carotid atherosclerotic plaques, we can effectively prevent and control the occurrence and development of ischemic stroke (Feig *et al*., 2011). At present, many studies at home and abroad have confirmed that statin lipid-lowering drugs can reduce the incidence of stroke events, which may be related to the above mechanisms. A large meta - Analysis of various lipid - lowering treatments (such as statins, beetle, nicotinic acid, diet) shows that only statins can prevent the progression of systemic atherosclerotic lesions and reduce the risk of recurrence of first stroke and stroke. The study suggests that atherosclerotic plaques can be used as an important indicator of the risk of cerebral infarction, and the carotid intima medium thickness (IMT) is considered as a marker of atherosclerosis and can be used as an observation indicator to measure the decline of atherosclerosis (Ghoneum *et al*., 2015). After 6 months of treatment, there were statistically significant differences between the rosuvastatin and atrovastatin carotid artery IMT before and before treatment (P<0.05). The two groups of carotid plaques were more stable than before treatment, the proportion of hypoechoic plaques decreased (P<0.05), and the proportion of hyperechoic plaque increased (P<0.05). It is confirmed that rosuvastatin and atorvastatin play a role in stabilizing and subsiding plaque in carotid atherosclerotic plaques. However, there was no significant difference between the two groups. It was not confirmed that the difference in the efficacy between the two drugs may be related to the lack of sample size (Heeba *et al*., 2015).

Table 1: Comparison of characteristics before treatment

Project	Rosuvastatin group	Atorvastatin group	Control group	P value
Average age	58.3±6.4	60.1±7.1	58.9±6.8	0.316
Male / female	40/40	39/41	42/38	0.681
Past medical history				
Hypertension	32	35	30	0.418
Diabetes	12	14	10	0.571
Blood pressure				
Systolic pressure /mm Hg	155±16	156±15	155±17	0.728
Diastolic pressure /mm Hg	89±7	91±6	90±7	0.784
Blood lipid level				
TC / mmol·L^{-1}	5.42±1.06	5.56±1.13	5.48±1.24	0.472
TG / mmol·L^{-1}	2.83±0.56	2.76±0.71	2.75±0.66	0.821
LDL-C/mmol·L^{-1}	3.54±0.51	3.60±0.55	3.62±0.48	0.731
NIHSS score	7.26±1.18	7.34±1.54	7.31±1.26	0.816
MRS score	3.27±0.68	3.14±0.71	3.35±0.69	0.641

Table 2: IMT comparison of blood lipids and carotid atherosclerotic plaques

Group	Time	TC/mmol·L^{-1}	TG/mmol·L^{-1}	LDL-C/mmol·L^{-1}	HDL-C/mmol·L^{-1}	IMT/mm
Rosuvastatin group	Before treatment	5.64±1.31	2.84±0.79	3.82±1.10	1.08±0.45	2.61±0.82
	After treatment	2.83±0.56	1.92±0.63	1.84±0.45	1.10±0.51	1.69±0.71
Atorvastatin group	Before treatment	5.83±1.46	2.91±0.74	3.72±0.91	1.04±0.38	2.54±0.72
	After treatment	3.24±0.71	1.85±0.62	2.36±0.52	1.08±0.24	1.76±0.65
Control group	Before treatment	5.79±1.14	2.85±0.76	3.69±0.83	0.95±0.42	2.57±0.65
	After treatment	5.14±1.15	2.91±0.77	3.75±0.74	1.05±0.53	2.55±0.74

Table 3: Changes in the properties of carotid atherosclerotic plaque

Group	Time	Cases	Hypoechoic plaque/case	Mixed echo plaque/case	Hyperechoic plaque /case
Rosuvastatin group	Before treatment	52	18(34.61%)	27(51.92%)	32(61.53%)
	After treatment	52	9(17.30%)	20(38.46%)	35(67.30%)
Atorvastatin group	Before treatment	58	19(32.75%)	28(48.27%)	31(53.44%)
	After treatment	58	10(17.24%)	21(36.20%)	37(63.79%)
Control group	Before treatment	55	20(36.36%)	28(50.90%)	32(58.18%)
	After treatment	55	21(38.18%)	30(54.54%)	32(58.18%)

Table 4: ankle-brachial index

Group	Time	Cases	Ankle-brachial Index
Rosuvastatin group	Before treatment	80	0.542±0.127
	After treatment	80	0.782±0.236
Atorvastatin group	Before treatment	80	0.562±0.164
	After treatment	80	0.541±0.196
Control group	Before treatment	80	0.551±0.132
	After treatment	80	0.589±0.216

Table 5: Comparison of biochemical indexes before and after treatment

Group	Time	CK/U·L^{-1}	ALT / U·L^{-1}	Cr /μmol·L^{-1}	BUN / mmol·L^{-1}
Rosuvastatin group	Before treatment	61.24±28.77	24.62±12.64	95.71±15.28	5.23±1.07
	After treatment	53.67±24.12	57.12±25.59	92.14±16.17	5.64±1.56
Atorvastatin group	Before treatment	59.13±27.64	23.14±12.07	96.18±18.65	4.92±1.04
	After treatment	55.21±31.01	54.28±19.24	101.87±22.14	5.82±1.35
Control group	Before treatment	58.79±25.14	22.16±11.34	96.13±15.14	5.11±1.09
	After treatment	55.47±29.31	18.72±9.46	94.27±16.87	5.62±1.84

ABI (Ankle-brachial Index) is the highest ratio of the ankle artery to the brachial artery systolic pressure. The monitoring of ABI has the advantages of simple operation and noninvasive (Liu *et al*., 2016). It is one of the tools to predict the cardiovascular and peripheral vascular lesions. The study confirmed that the sensitivity, specificity and accuracy of ABI in diagnosing peripheral vascular diseases can be compared with angiography (Kaplan *et al*., 2014). The results of this study showed that the ABI in the rosuvastatin group improved significantly in the 6 months after treatment. The difference was statistically significant compared with that before treatment and the difference was statistically significant compared with the Atorvastatin group in the same period (Kenichi *et al*., 2014). There was no significant difference in the overall level of ABI between the Atorvastatin group and the control group during the whole treatment period. Therefore, we believe that rosuvastatin can improve peripheral atherosclerosis.

During the 6 months of treatment, the increase of transaminase in rosuvastatin group and atorvastatin group was significantly higher than that in the control group ($P < 0.05$). There was no significant difference between the rosuvastatin group and the atorvastatin group ($P > 0.05$). When the transaminase increased more than 3 times, the statin transaminase could be reduced to normal. During the treatment, no serious adverse reactions such as liver and kidney failure and rhabdomyolysis were found. The results suggest that statins are safe.

CONCLUSION

To sum up, from the current research data, rosuvastatin is obviously superior to atorvastatin in reducing LDL-C and reversing plaque, but there is no significant difference in the effect of anti-inflammatory. There is no strong clinical evidence for the prevention of cardiovascular disease. In addition, rosuvastatin did not increase the risk of adverse reactions compared with atorvastatin. However, the adverse reactions of rosuvastatin and atorvastatin were not identical in different studies. In primary prevention, long-term statins can make the heart and brain blood vessels benefit significantly and do not increase the risk of cerebral hemorrhage. The recommended long-term use of statins is generally safe, and the results of this study coincide.

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