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Original Article

Clinical study of double anti-platelet therapy combined with different doses of statin in the treatment of acute cerebral infarction complicated with microhemorrhage

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Abstract: Objective: To assess the clinical effect and safety of double anti-platelet therapy combined with different doses of statins for acute cerebral infarction complicated with microhemorrhage. Methods: A total of 312 patients who had acute cerebral infarction complicated with microhemorrhage in our hospital were randomly allocated into two groups: the experimental group (n=164) and group for control (n=148). Those in the group for experiment received dual antiplatelet rosuvastatin tablets (20 mg QN), while the control group received dual antiplatelet rosuvastatin tablets (10 mg QN). After 30 days of treatment, blood biochemistry and brain magnetic resonance imaging were performed to record the serum lipid levels, liver transaminase, inflammatory and oxidative stress indicators and other biochemical indicators as well as the number of cerebral microhemorrhage foci. Results: Serum lipids in both groups after intervention were decreased compared to those without intervention ($P < 0.05$). Furthermore, after receiving the intervention, the HCY and inflammatory indicators (such as hs-CRP) of the two groups were improved compared to before intervention ($P < 0.05$). The safety index (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Creatine kinase (CK), creatinine (Cr)) had no statistically significant difference than those without intervention in the two groups ($P > 0.05$). Conclusion: Rosuvastatin can effectively regulate blood lipids and Hcy levels in patients with acute cerebral infarction and microbleeds, and it can reduce blood lipids and inflammation; furthermore, high dose rosuvastatin has better improvement effects and higher safety in a shorter period time.

Keywords: Different doses of statin, acute cerebral infarction complicated with microhemorrhage, clinical effect, safety

Introduction

Acute cerebral infarction is a common cerebrovascular disease, which is mainly caused by cerebral blood supply disorders and vascular occlusions. The characteristic of this disease are its high disability rate and mortality rate [1, 2]. It is one of the main diseases that seriously threaten human health [3]. Cerebral microbleeds (CMBs) are a complication of cerebral infarction with brain parenchyma damage, which are caused by intracranial microvascular lesions. At present, clinical research shows that reasonable control of blood lipid levels can maintain the integrity of the microvascular walls and reduce the risk of cerebral hemorrhage [4, 5]. At present, for acute cerebral infarction, double antiplatelet therapy is advised to be carried out as early as possible without contraindications, and the bleeding risk of patients' needs to be closely observed; moreover, antiplatelet drugs alone are used as the first-line drug for the prevention of cerebral infarction, and anti-platelet aggregation therapy has become a key link in the prevention and treatment of acute cerebral infarction [6].

Rosuvastatin is a selective inhibitor of HMG CoA reductase. It can reduce the level of serum lipids through the synthesis of HMG CoA reductase and cholesterol in the liver. It can effectively improve the vascular endothelial function and blood supply disorders in the brain. At the same time, it can also antagonize oxidative

Table 1. Comparison of clinical characteristics of acute cerebral infarction complicated with microhemorrhage patients between both groups

	Experimental group (n=164)	Control group (n=148)	t/χ^2	*P*
Age (years)	54±4.15	55±2.75	2.25	0.61
Sex				
Male (n %)	89 (54.3%)	77 (52%)	4.68	0.58
Female (n %)	75 (45.7%)	71 (48%)	4.49	0.43
BMI	22.5±3.16	23.35±2.43	1.39	0 .34
Smoking	78 (47.6%)	72 (48.6%)	6.71	0.55
Alcohol intake				
More than 14 alcohol units	75 (45.7%)	69 (46.6%)	2.96	0.42
Less than 14 alcohol units	89 (54.3%)	79 (53.4%)	6.18	0.37
Hypertension	67 (40.9%)	59 (39.9%)	1.79	0.16
Diabetes	58 (35.4%)	49 (33.1%)	1.29	0.49
Coronary heart disease	48 (29.3%)	44 (29.7%)	0.63	0.51

stress reactions as well as protect the ischemic brain tissue [7-9]. At present, there is no conclusion on whether antiplatelet, thrombolytic and anticoagulant therapy increases the risk of hemorrhagic transformation in patients with acute cerebral infarction complicated with CMBs. Research has shown that the use of antithrombotic drugs was correlated with CMBs, and the incidence of CMBs increases with the prolongation of antithrombotic drugs [10]. However, some researchers suggest that statins drugs can increase the risk of CMBs in patients with acute cerebral infarction [11, 12].

In this study, we compared serum lipids, hs-CRP, HCY, liver transaminase and other biochemical indicators and cerebral microbleeds in patients with acute large artery atherosclerotic cerebral infarction combined with cerebral microbleeds under different doses of rosuvastatin combined with dual antiplatelet therapy; furthermore, we explored the effect of intensive lipid-lowering therapy on CMBs on the basis of dual anti platelet therapy to investigate the influence and safety of these drugs in patients with the acute cerebral infarction complicated with microhemorrhage.

Data and methods

Clinical data

This study was performed at the People's Hospital of Dongxihu District and The First Hospital of Wuhan City from July 2018 and July 2020. A total of 312 patients with acute cerebral infarction complicated with microhemorrhage in our hospital were included as the research subjects. The enrolled patients were randomly allocated into two groups: the experimental group (164 cases) and the control group (148 cases). This study was approved by the ethics committee of the People's Hospital of Dongxihu District and the ethics committee of The First Hospital of Wuhan City.

Inclusion and exclusion standards

Inclusive standards: ① The infarct onset was less than 72 h prior to admission; ② According to the clinical symptoms, clinical signs and auxiliary examination, the patients were diagnosed with acute ischemic stroke; ③ According to toast standards, large artery atherosclerotic (LAA) cerebral infarction was observed, moreover, all CMBS were found by SWI; ④ Patients and their families voluntarily signed the informed consent.

Exclusion standards: ① Patients who were treated with intravenous thrombolysis after admission; ② Had a history of malignant tumors; Had a history of mental disease or disturbance of consciousness; Had a history of blood system diseases; pregnant and lactating women; had a history of liver, kidney and heart disorders; ③ Had a history of intractable hypertension; ④ Had a history of Cerebral vascular malformation, brain tumor or brain trauma; ⑤ Patients who had contraindications to MRI examination; ⑥ Patients who were allergic to statins.

The criteria for drug withdrawal: ① ALT/AST > 3 times the normal value; ② creatinine clearance rate < 30 ml/min; ③ serum creatine kinase (CK) levels was increased above normal values; ④ patients had a new onset of intracerebral hemorrhage.

Method

The Experimental group: The patients received dual antiplatelet (aspirin enteric coated tablets (Bayer medical and health care Co., Ltd.,

Table 2. Comparison of serum lipids between the two groups before and after intervention ($\bar{x}$ ± sd)

	Experimental Group (n=164)	Control group (n=148)	t/χ^2	*P*
TC (mmol/L)				
Before intervention	6.5±1.0	6.4±1.3	4.76	0.17
After intervention	4.8±0.7	5.9±0.7	7.25	0.000
TG (mmol/L)				
Before intervention	2.8±0.8	2.6±0.7	4.43	0.34
After intervention	1.9±0.5	2.3±0.7	3.69	0.000
LDL-C (mmol/L)				
Before intervention	4.7±0.9	4.6±0.8	0.21	0.87
After intervention	2.9±0.5	3.5±0.6	7.94	0.000

Note: Significant difference as P < 0.05. TC: total cholesterol; TG: triglyceride; LDL-C: Low density lipoprotein cholesterol.

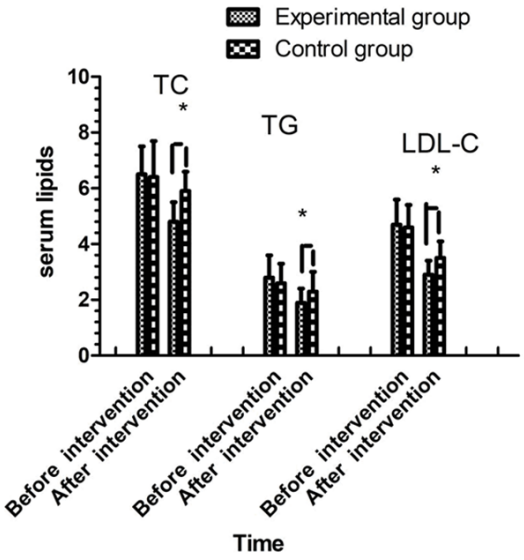

Figure 1. Comparison of serum lipids between the two groups before and after intervention. *P < *0.05.*

Guoyao Zhunzi: j20171021) 100 mg QD + clopidogrel sulfate tablets (Sanofi (Hangzhou) Pharmaceutical Co., Ltd., batch number: 170306) 75 mg QD) and rosuvastatin tablets (AstraZeneca Pharmaceutical Co., Ltd., Guoyao Zhunzi: j20090092) 20 mg QN). Meanwhile, we controlled the blood pressure and blood sugar of patients, and gave symptomatic treatment such as improving circulation and nourishing nerves. The treatment lasted for 30 days.

The Control group: The patients received dual antiplatelet (aspirin enteric coated tablets (Bayer medical and health care Co., Ltd., Guoyao Zhunzi: j20171021) 100 mg QD + clopidogrel sulfate tablets (Sanofi (Hangzhou) Pharmaceutical Co., Ltd., batch number: 170306) 75 mg QD) and rosuvastatin tablets (AstraZeneca Pharmaceutical Co., Ltd., Guoyao Zhunzi: j20090092) 10 mg QN). Meanwhile, we controlled the blood pressure and blood sugar of patients, and gave symptomatic treatment such as improving circulation and nourishing nerves. The treatment lasted for 30 days.

Observation index

① Inflammatory and oxidative stress indicators: we recorded high sensitivity C-reactive protein (hs-CRP) as inflammatory and oxidative stress indicators before and after treatment. ② Prognostic indicators: we recorded homocysteine (HCY) as a prognostic indicator before and after treatment. ③ Cerebral microbleeds (*CMBS)*: We recorded the number of cerebral microbleeds of both groups before and after treatment to compare the clinical efficacy. ④ The levels of serum lipids: Serum total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) were recorded as serum lipids in both groups before and after treatment. ⑤ Adverse reactions: We recorded liver and kidney function such as Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Creatine kinase (CK) and creatinine (Cr) to assess its adverse reactions.

Statistical analysis

All data were analyzed by SPSS 22.0. Among them (n, %) refers to the calculated data. The comparison of relevant data between groups and within groups was performed by chi square test, and the measurement data was applied (mean ± sd). The comparison between groups was conducted by t test. P < 0.05 indicated statistical significance.

Results

Clinical characteristics

Table 1 shows the characteristics of the participants. This study included 312 patients after follow-up, with 164 patients in the experimental group, with a mean age (54±4.15) years old; while in the control group, had a

Table 3. Comparison of inflammatory and oxidative stress indicators between the two groups before and after intervention ($\bar{x}$ ± sd)

	Experimental Group (n=164)	Control group (n=148)	t/χ^2	*P*
hs-CRP (mg/L)				
Before intervention	5.09±1.03	4.97±1.03	3.26	0.08
After intervention	4.08±1.06	4.60±0.99	10.75	0.000
HCY (μmol/L)				
Before intervention	13.36±3.09	13.25±3.41	2.23	0.63
After intervention	10.12±2.39	12.7±3.06	4.54	0.000

Note: Significant difference as P < 0.05. hs-CRP: High sensitivity C-reactive protein; HCY: Homocysteine.

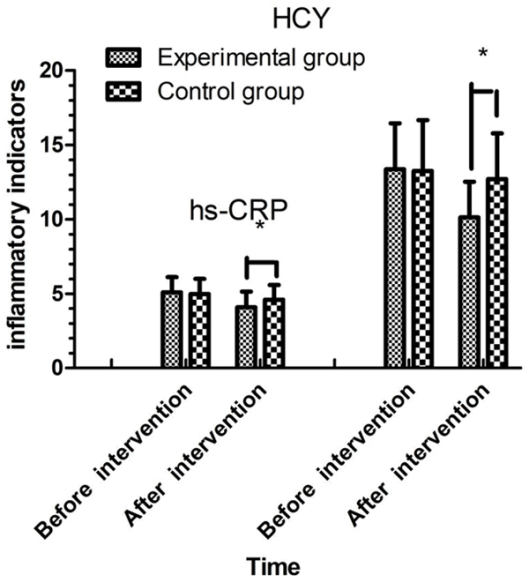

Figure 2. Comparison of inflammatory and oxidative stress indicators between two groups. *P < *0.05.*

mean age (55±2.75) years old. The BMI in the experimental group was (22.5±3.16) kg/m^2, and in the control group it was (23.35±2.43) kg/m^2, there was no statistical significance between two groups (P=0.34 > 0.05). The smokers in the experimental group were 78 (47.6%), and that in the control group was 72 (48.6%). The alcohol intake of which was more than 14 alcohol units in experimental group was 75 (45.7%), and in control group it was 69 (46.6%), there was no statistical significance between the two groups (P=0.42 > 0.05). The number of patients who had a history of hypertension in the experimental group was 67 (40.9%), and in the control group it was 59 (39.9%). The number of patients who had a history of diabetes in the experimental group was 58 (35.4%), and in the control group it was 49 (33.1%). The number of patients who had a history of coronary heart disease in the experimental group was 48 (29.3%), and that in the control group was 44 (29.7%). The two groups were similar in demographics, clinical characteristics, and there was no statistical significance in the general data between the two groups.

Comparison the levels of serum lipids between both groups

As shown in **Table 2** and **Figure 1**, the level of serum total cholesterol (TC) before and after intervention in the experimental group respectively was (6.5±1.0) and (4.8±0.7) mmol/L; while that in the control group respectively was (6.4±1.3) and (5.9±0.7) mmol/L. The level of serum triglyceride (TG) before and after intervention in the experimental group respectively was (2.8±0.8) and (1.9±0.5) mmol/L; and that in the control group respectively was (2.6±0.7) and (2.3±0.7) mmol/L. The level of low density lipoprotein cholesterol (LDL-C) before and after intervention in the experimental group respectively was (4.7±0.9) and (2.9±0.5) mmol/L; and that in the control group respectively was (4.6±0.8) and (3.5±0.6) mmol/L. There was a statistically significant difference between the two groups in TC, TG and LDL-C after intervention (P < 0.05) (**Table 2** and **Figure 1**).

Comparison of inflammatory and oxidative stress indicators between both groups

The level of high sensitivity C-reactive protein (hs-CRP) before intervention in the experimental group was (5.09±1.03) mg/L, and that in the control group was (4.97±1.03) mg/L, and there was no statistically difference between two groups (P=0.08 > 0.05). While the level of hs-CRP after intervention in the experimental group was (4.08±1.06) mg/L, and that in the control group was (4.60±0.99) mg/L, with a statistically significant difference between the two groups (P < 0.05) (**Table 3** and **Figure 2**).

Comparison of prognostic indicators between both groups

The level of homocysteine (HCY) before and after intervention in the experimental group respectively was (13.36±3.09) and (10.12±2.39) μmol/L, while that in the control group

Table 4. *Number of CMBS in* two groups ($\bar{x}$ ± sd)

Group	Number of cases	Before intervention	After intervention
Experimental group	164	4.02±1.22	4.19±1.71
Control group	148	3.99±1.79	4.01±1.81
t	-	2.168	7.866
P	-	0.45	0.03

Note: Significant difference as P < 0.05.

respectively was (13.25±3.41) and (12.7±3.06) μmol/L, there was a statistically significant difference between two groups after intervention (P < 0.05) (**Table 3** and **Figure 2**).

Number of CMBS in both groups

The number of CMBS before intervention in the experimental group was (4.02±1.22), and that in the control group was (3.99±1.79), there was no statistically difference between two groups (P=0.45 > 0.05). While the number of CMBS after intervention in the experimental group was (4.19±1.71), and that in the control group was (4.01±1.81), and there was a statistically significant difference between the two groups (P < 0.05) (**Table 4**).

Comparison of adverse reactions between bith groups

After intervention, the liver and kidney function (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Creatine kinase (CK), creatinine (Cr)) of patients had no statistically significant difference than those who did not accept intervention in the two groups (P > 0.05). Therefore, this treatment is safe for participants (**Table 5**).

Brain magnetic resonance imaging of patient in the experimental group

After the intervention, cerebral microbleeds of patients in the experimental group were improvement after double anti-platelet combined with rosuvastatin 20 mg treatment compared with before treatment (**Figure 3**).

Discussion

In this study, different doses of rosuvastatin were used to treat cerebral microbleeds in patients with acute cerebral infarction. The results showed that the effect of treatment for the high-dose atorvastatin group on regulating blood lipids, Hcy and hs-CRP was better than that of the low-dose atorvastatin group, and the lipid-lowering effect was higher than that of the low-dose treatment. Moreover, the results suggested that high-dose atorvastatin in the treatment of acute cerebral infarction microbleeds could reduce inflammatory reactions and the improve lipid-lowering effect. Furthermore, there was no significant difference in the incidence of adverse reactions between the two groups, which indicated that high-dose atorvastatin drug treatment in a short period of time had high safety.

Acute cerebral infarction is the necrosis of brain tissue caused by sudden interruption of blood supply to the brain. Its pathogenesis is complex and it has various inducing factors, such as hypertension, coronary heart disease and hyperlipidemia [13]. This disease is difficult to cure, which brings heavy economic and mental pressure to the patient's family and society. Cerebral microbleeds are more insidious under conventional conditions, lacking typical clinical symptoms and signs, the causes of hemorrhagic transformation after cerebral infarction are unclear in clinical medicine. It is reported that the area of cerebral infarction, the location of cerebral infarction, the etiology of cerebral infarction and reperfusion time have certain effects on the transformation of hemorrhage [14].

Rosuvastatin, is among the third generation statins, it is a HMG CoA reductase inhibitor blocking the metabolic pathway which can prevent the synthesis of cholesterol in hepatocytes, reduce the expression of plasma cholesterol and lipoproteins, inhibit the formation of low-density lipoprotein cholesterol, and lower the levels of blood lipids. At the same time, it can reduce inflammatory mediators, stabilize plaques, resist oxygen free radicals, improve the survival of neurons and reduce brain edema [15-17]. As shown in our results, the high dose atorvastatin drugs treatment is effective.

The therapeutic mechanism of the effectiveness of the high dose of atorvastatin treatment maybe due to the fact that it can enhance the lipid-lowering and anti-inflammatory effects, with a dose-response relationship. High-dose

Table 5. *Comparison of safety index* between two groups ($\bar{x}$ ± sd)

Group	time	AST	ALT	CK	Cr
Experimental group (n=164)	Before intervention	29.63±5.62	29.38±6.20	82.04±5.97	80.48±6.84
	After intervention	29.92±5.52	29.84±5.54	82.61±7.03	81.94±7.05[a]
	t	2.458	3.071	1.837	4.972
	P	0.86	0.79	0.88	0.24
Control group (n=148)	Before intervention	29.27±5.21	30.04±4.97	79.83±6.38	80.03±5.97
	After intervention	29.67±4.97	30.64±6.48	79.46±6.58	81.31±4.39
	t	1.278	2.131	1.921	4.549
	P	0.63	0.45	0.83	0.19

Note: Compared with the control group, *P < 0.05. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatine kinase; Cr: creatinine.*

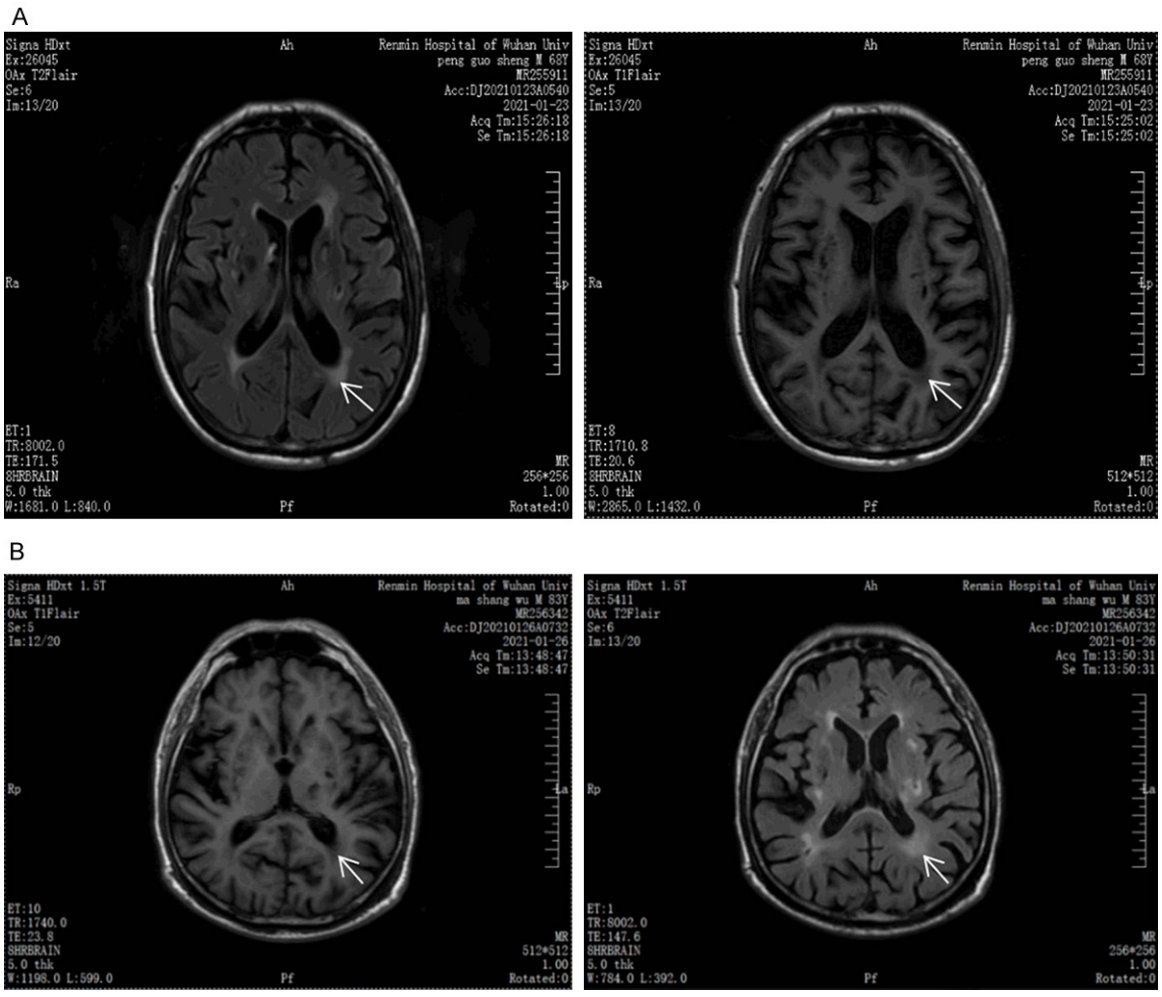

Figure 3. Brain magnetic resonance imaging of patient in experimental group. The arrow demonstrated the changes of microbleeds before and after treatment. A: Brain magnetic resonance imaging of patient before treatment in the experimental group. B: Brain magnetic resonance imaging of patient after treatment in the experimental group.

atorvastatin drugs have a significant inhibitory effect on the inflammatory response, and it also could improve the early microvascular atherosclerosis and change the clinical outcome of patients. Some studies have found that the combination of double antibody and lipid-lower-

ing therapy is better than double antibody therapy in patients with acute cerebral infarction complicated with CMBs, and it does not significantly increase the number of CMBs and the risk of bleeding transformation. Thus, it can better play the role of dual antiplatelet therapy, and has a high safety [18-21]. In clinical work, in order to better control blood lipids, patients are required to use statins drugs in sufficient quantity and standards. The influence of lipid-lowering therapy on CMBs needs further study. At the same time, the sample size needs expansion for further study, and the follow-up time needs to be extended to observe whether the patients are safe in the long-term use of oral statins.

Statins, as the first-line drug for lipid-lowering, did not show serious adverse events in the application process. The adverse reactions related to statins treatment were relatively mild, such as gastrointestinal symptoms, headache, rash, muscle symptoms or increased levels of CK and liver enzymes [22]. This study found that the levels of AST, ALT, CK and Cr in both experimental and control groups were not significantly increased, which indicated that statins drugs have high safety in liver function, renal function and inn muscles, and intensive lipid-lowering in the short-term does not increase the incidence of adverse events.

There were limitations in our study. First, the cases included were small in number, and we didn't carry out large sample experiments. Second, the observation time was short, and we didn't observed the long-term efficacy and recurrence of the patients. A larger, placebo-controlled, perspective study is needed to evaluate the efficacy and mechanism of double anti-platelet therapy combined with different doses of statin on the acute cerebral infarction complicated with microhemorrhage.

In conclusion, high dose rosuvastatin combined with double anti-platelet therapy can effectively improve serum lipids, inflammatory and oxidative stress indicators and the condition of microbleeding foci. Therefore, relevant research is needed to assess the long-term efficacy and safety of high dose statin drugs in patients with acute cerebral infarction complicated with microhemorrhage.

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Disclosure of conflict of interest

None.

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