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Original Article

Therapeutic effects of aspirin combined with atorvastatin on ischemic strokes

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Abstract: Objective: The aim of this study was to investigate the efficacy of aspirin combined with atorvastatin in the treatment of ischemic stroke. Methods: A total of 127 patients with ischemic strokes, admitted to The Fifth Affiliated Hospital, Harbin Medical University, from January 2016 to December 2017, were randomly divided into an observation group (n=66) and control group (n=61). In the control group, patients were treated with aspirin alone. Patients in the observation group were treated with aspirin combined with atorvastatin. Oxidized low-density lipoprotein (OX-LDL), transforming growth factor-β1 (TGF-β1), vascular cell adhesion molecule-1 (VCAM-1), high-sensitivity C-reactive protein (hs-CRP), and lipid levels in serum were measured before treatment and at 6 months after treatment. Modified RANKIN scale (mRS) scores, modified Barthel index (MBI) scores, carotid intimal plaque area, and carotid intima-media thickness were compared before treatment and 6 months after treatment for the two groups. Recurrence rates of ischemic strokes, incidence of cerebrovascular disease, and incidence of adverse reactions were compared between the two groups. Results: After 6 months of treatment, levels of OX-LDL, VCAM-1, hs-CRP, total cholesterol, low-density lipoprotein cholesterol, and triglycerides in serum in the observation group were significantly lower than those before treatment (all P<0.05). Levels of serum TGF-β1 and high-density lipoprotein cholesterol were significantly higher than those before treatment (both P<0.05). Serum levels of OX-LDL, TGF-β1, hs-CRP, VCAM-1, and lipids were not significantly different before and after treatment in the control group as well as between the two groups before treatment (all P>0.05). However, there were significant differences in serum levels of the above five indicators between the two groups at 6 months after treatment (all P<0.05). There were no significant differences in mRS scores, MBI scores, carotid intimal plaque area, and carotid intima-media thickness between the two groups before treatment (all P>0.05). After 6 months of treatment, mRS scores of the observation group were significantly lower than that of the control group. MBI scores were significantly higher than that of the control group. Carotid intimal plaque area and carotid intima-media thickness were both less than those of the control group. Differences were statistically significant (all P<0.05). Recurrence rate of ischemic stroke and incidence of cerebrovascular disease in the observation group were significantly lower than those in the control group (both P<0.05). There were no significant differences in incidence of adverse reactions between the two groups (P>0.05). Conclusion: Aspirin combined with atorvastatin has synergistic effects in the treatment of ischemic stroke. It has significant effects on regulating lipids, improving atherosclerotic plaque, and improving quality of life. It is also safe and worthy of clinical application.

Keywords: Aspirin, atorvastatin, ischemic stroke, statins

Introduction

Ischemic stroke is an acute cerebrovascular disease with cerebral tissue ischemia, hypoxic necrosis, and a series of clinical signs and symptoms [1, 2]. At present, scholars generally believe that carotid atherosclerosis, stenosis, platelet activation, and thrombosis are the main pathological mechanisms leading to ischemic stroke, clarifying the role of antithrombosis in preventing and treating ischemic stroke [3, 4]. In addition, inflammatory response, as an independent factor, can affect the stability of atherosclerotic plaque, cause thrombosis, and cause cerebrovascular occlusion, indicating that inhibition of inflammatory response can play a role in brain protection [5]. Aspirin is a commonly used drug for inhibiting platelet aggregation. Studies have shown that continuous application of aspirin can produce strong

platelet aggregation inhibitory effects, inhibiting the formation of atherosclerosis [6]. Atorvastatin is a classical drug among statins. It plays an important role in the prevention and treatment of ischemic strokes due to its significant lipid-lowering and anti-inflammatory effects, along with stabilization of atherosclerotic plaque [7-9]. The efficacy of aspirin alone in the treatment of ischemic strokes has been confirmed. However, there are differences in results of reports on the efficacy of aspirin in combination with atorvastatin in the treatment of ischemic strokes. There is a lack of systematic evaluation and a general conclusion has not yet been reached [10]. Other studies have reported that aspirin and statins are both metabolized through the cytochrome P_{450}3A4 enzyme, which has the possibility of competitive inhibition and reduces efficacy [11, 12]. Therefore, this study selected 127 patients with ischemic strokes as study subjects. This study analyzed the differences in efficacy between aspirin plus atorvastatin and aspirin alone, providing guidance and experimental basis for clinical treatment of ischemic strokes.

Materials and methods

General data

A total of 127 patients with ischemic strokes, admitted to The Fifth Affiliated Hospital, Harbin Medical University, from January 2016 to December 2017, were randomly divided into an observation group and control group. Based on conventional treatment, patients in the control group were treated with aspirin alone. Patients in the observation group were treated with aspirin plus statins. All patients signed informed consent and this study was approved by the Ethics Committee of The Fifth Affiliated Hospital, Harbin Medical University.

Inclusion criteria: In accordance with diagnostic criteria for ischemic strokes, confirmed by CT or MRI, and carotid plaques were confirmed by color doppler ultrasonography and CTA examination of the neck; First episode, no history of ischemic strokes; Complete clinical data, coordinated with drug treatment, follow up and regular return visits, and older than 18 years of age [13].

Exclusion criteria: Combined severe heart, liver, and kidney dysfunction, acute or chronic infection, autoimmune disease, malignant tumors; Combined cerebral hemorrhage, intracranial space-occupying lesions, and other brain organic diseases; Allergic to aspirin or statins and use of immunosuppressants or inflammatory inhibitor drugs.

Treatment methods

Both groups of patients strictly controlled blood pressure, blood glucose, and blood lipid levels. Mannitol was applied to reduce intracranial pressure and an edaravone intravenous infusion was applied for brain protection. On this basis, patients in the control group were treated with 100 mg aspirin alone (Harbin Pharmaceutical Group General Pharmaceutical Factory), orally once daily. Patients in the observation group were treated with aspirin and statins. Aspirin was taken orally once a day for 100 mg. Atorvastatin (Beijing Jialin Pharmaceutical Co., Ltd.) was taken orally once a night, 20 mg each time, before going to bed. The duration of continuous medication in both groups was 6 months.

Observation indicators

Before and 6 months after treatment, oxidized low density lipoprotein (OX-LDL), transforming growth factor β1 (TGF-β1), vascular cell adhesion molecule-1 (VCAM-1), high-sensitivity C-reactive protein (hs-CRP), and lipid levels in serum of both groups were measured and compared. Modified RANKIN scale (mRS) scores and modified Barthel index rating scale (MBI) scores were compared before and after 6 months of treatment for the two groups. Carotid intimal plaque area and carotid intima-media thickness were compared before and after treatment for the two groups.

The incidence of stroke recurrence, incidence of cerebrovascular disease, and incidence of adverse reactions were compared between the two groups. For stroke recurrence rate, head MRI scans were repeated 48 hours after onset of stroke symptoms to exclude new strokes. Occurrence of cerebrovascular disease referred to transient ischemic attacks, cerebral hemorrhage, and recurrence and progression of cerebral infarction within 6 months of follow up. Adverse reactions were defined as patient gastrointestinal response, abnormal liver function, skin rash, muscle pain, epistaxis, or bleeding gums within 6 months after treatment.

Table 1. Comparison of basic data between two groups of patients

Item	Male/female (case)	Age (year)	Diabetes (case)	Hypertension (case)
Control group (n=61)	40/21	65.9±1.8	25	22
Observation group (n=66)	43/23	64.6±2.1	28	24
t/X^2	0.002	0.267	0.027	0.001
P	0.960	0.741	0.869	0.972

Detection methods

Before treatment and 6 months after treatment, 5 mL of fasting cubital venous blood was collected, placed in a special anticoagulant test tube, and centrifuged at 3,000 r/min for 10 minutes. Serum was stored at -20°C for preservation. Serum OX-LDL, TGF-β1, VCAM-1, and hs-CRP were measured by enzyme-linked immunosorbent assay. OX-LDL, TGF-β1, VCAM-1, and hs-CRP kits were provided by R&D science (USA) and operated strictly in accordance with manufacturer instructions. Serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels in the two groups of patients were measured using Beckman Coulter AU5800 automatic biochemical analyzer.

Rating criteria

MRS scores were based on patients with ischemic strokes. It was rated as 0 if they were completely asymptomatic. If there were symptoms but the functional disorder was lighter and did not affect daily work or life, 1 point was rated. If mild disability affected daily work and life but did not require help, 2 points were rated. If there was a moderate disability needing some assistance but they could walk independently, then the score was 3 points. If moderate or severe disability required help and the patient could not walk independently, the score was 4 points. If there was severe disability, the patient was bed-ridden, and daily work and life depended entirely on others for help, 5 points were rated. Death was rated as 6 points. Higher scores indicated worse patient prognosis.

MBI scores contained 10 items, including eating, dressing, toileting, urinary control, stool control, climbing and descending stairs, bathing, bed and chair transfers, and flat ground walk, for a total of 100 points. Higher scores indicated higher degrees of independence.

Carotid endometrial plaque assessment

Carotid examinations were performed with a Siemens X700 Color Doppler Ultrasound with a probe frequency of 10 MHz. Intima-media thickness of carotid arteries was measured on a section of 1.0 cm from the intamescentia of the common carotid artery and on the section of the common carotid artery. The product of the longest carotid artery diameter and maximum medial thickness was taken as the carotid intimal plaque area.

Data processing

SPSS 18.0 software was used to process experimental data. Measurement data in accordance with normal distribution and variance homogeneity are expressed as mean ± standard deviation. An independent sample t-test was used for comparisons between groups. Comparisons before and after treatment used a paired t-test. Counting data are expressed as a percentage. X^2 test was used for comparisons between the two groups. $P<0.05$ indicates that differences are statistically significant.

Results

Comparison of basic data between the two groups of patients

There were no statistically significant differences between the observation group and control group in basic information such as gender, age, diabetes, and hypertension (all $P>0.05$) a shown in **Table 1**.

Comparison of serum levels of OX-LDL, TGF-β1, VCAM-1, and hs-CRP between the two groups

After 6 months of treatment, serum levels of OX-LDL ($P=0.028$), VCAM-1 ($P=0.017$), and hs-CRP ($P=0.003$) were significantly lower than those before treatment in the observation group, while serum TGF-β1 levels were higher

Table 2. Comparison of serum OX-LDL, VCAM-1, hs-CRP, and TGF-β1 levels before and after treatment in both groups

Item	OX-LDL (ng/mL)	VCAM-1 (ng/mL)	hs-CRP (mg/L)	TGF-β1 (pg/mL)
Control group				
Before treatment	117.45±56.32	8.63±3.58	5.03±0.52	198.17±63.58
6 months after treatment	99.63±42.87	7.74±2.74	4.96±0.46	207.84±55.14
t	2.295	1.835	2.021	1.984
P	0.149	0.208	0.181	0.186
Observation group				
Before treatment	116.58±57.14	8.84±3.23	5.09±0.48	196.15±64.61
6 months after treatment	81.02±46.64*,#	7.11±2.03*,#	1.56±0.14*,#	239.02±58.71*,#
t	5.866	3.509	17.983	12.585
P	0.028	0.017	0.003	0.006

Note: Compared with before treatment in the same group, *P<0.05; compared with 6 months after treatment in the control group, #P<0.05. OX-LDL: t=5.625, P=0.046; VCAM-1: t=7.825 P=0.039; hs-CRP: t=12.247, P<0.001; TGF-β1: t=5.524, P=0.048. OX-LDL, oxidized low-density lipoprotein; TGF-β1, transforming growth factor-β1; VCAM-1, vascular cell adhesion molecule-1; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Comparison of serum TC, TG, LDL-C, and HDL-C levels before and after treatment in both groups (mmol/L)

Item	TC	TG	LDL-C	HDL-C
Control group				
Before treatment	4.86±0.16	2.02±0.09	2.40±0.18	1.19±0.05
6 months after treatment	4.77±0.20	1.98±0.13	2.32±0.17	1.20±0.06
t	3.897	1.732	3.592	1.732
P	0.060	0.225	0.070	0.225
Observation group				
Before treatment	4.99±0.21	2.07±0.06	2.45±0.13	1.26±0.07
6 months after treatment	4.10±0.13*,#	1.67±0.04*,#	1.86±0.11*,#	1.52±0.08*,#
t	4.534	34.641	51.095	45.033
P	0.045	0.001	<0.001	<0.001

Note: Compared with before treatment in the same group, *P<0.05; compared with 6 months after treatment in the control group, #P<0.05. TC: t=8.562, P=0.035; TG: t=5.966, P=0.027; LDL-C: t=9.052, P=0.031; HDL-C: t=27.713, P=0.001. TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

than that before treatment (P=0.006). Serum levels of OX-LDL (P=0.149), TGF-β1 (P=0.186), hs-CRP (P=0.181), and VCAM-1 (P=0.208) before and after treatment in the control group were not significantly different (all P>0.05). Compared with patients in the control group after treatment, OX-LDL (P=0.046), VCAM-1 (P=0.039), and hs-CRP (P<0.001) levels were significantly decreased in the observation group and TGF-β1 (P=0.048) levels were significantly increased. Differences were statistically significant (all P<0.05) as shown in **Table 2**.

Comparison of serum levels of TC, TG, LDL-C, and HDL-C in the two groups

After 6 months of treatment, serum TC (P=0.045), TG (P=0.001), LDL-C (P<0.001), and HDL-C (P<0.001) levels in the observation group were significantly decreased compared to before treatment. Levels of TC, TG, LDL-C, and HDL-C in the control group before and after treatment were not significantly different. There were no significant differences in serum TC, TG, LDL-C, and HDL-C levels between the two groups before treatment. Levels of TC (p=0.035), TG (p=0.027), LDL-C (p=0.031), and HDL-C (p=0.001) after treatment between the two groups were statistically significant as shown in **Table 3**.

Comparison of mRS scores and MBI scores between the two groups

Differences in mRS and MBI scores between the two groups before treatment were not sig-

Table 4. Comparison of mRS scores and MBI scores before and after treatment in the two groups of patients

Item	Control group	Observation group	t	P
mRS score				
Before treatment	2.35±0.82	2.45±0.78	0.524	0.476
6 months after treatment	1.87±0.33	1.34±0.31	10.452	0.028
t	2.683	6.468		
P	0.044	0.001		
MBI score				
Before treatment	88.12±0.41	88.71±0.56	0.632	0.374
6 months after treatment	92.40±0.39	97.59±0.45	11.245	0.023
t	370.659	139.824		
P	<0.001	<0.001		

Note: mRS, modified RANKIN scale; MBI, modified Barthel index.

Table 5. Comparison of carotid intimal plaque area and carotid intima-media thickness before and after treatment in the two group patients

Item	Control group	Observation group	t	P
Carotid intimal plaque area (cm^2)				
Before treatment	0.82±0.08	0.80±0.09	0.725	0.274
6 months after treatment	0.76±0.04	0.48±0.06*,#	11.854	0.016
t	2.598	18.475		
P	0.122	0.003		
Carotid intima-media thickness (mm)				
Before treatment	1.41±0.13	1.42±0.11	0.762	0.236
6 months after treatment	1.31±0.08	1.01±0.09*,#	12.692	0.012
t	3.464	3.943		
P	0.074	0.011		

Note: Compared with the same group before treatment, *P<0.05; compared with 6 months after treatment in the control group, #P<0.05.

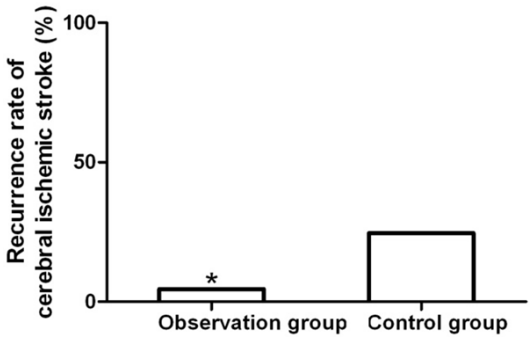

Figure 1. Comparison of recurrence rates of ischemic strokes between the two groups of patients. Compared with the control group, *P<0.05.

nificant. After 6 months of treatment, mRS scores in the observation group were significantly lower than the control group (P=0.028) and MBI scores were significantly higher than the control group (P=0.023). Data in the two groups were significantly different as shown in **Table 4**.

Comparison of carotid intimal plaque area and carotid intima-media thickness between the two groups of patients

There were no significant differences in carotid intima plaque area and carotid intima-media thickness before treatment. After 6 months of treatment, carotid intimal plaque area (P=0.016) and carotid intima-media thickness (P=0.012) were both lower in the observation group than in the control group. There were statistically significant differences in carotid intimal plaque area and carotid intima-media thickness between the two groups as shown in **Table 5**.

Comparison of recurrence rate of ischemic stroke, incidence of cerebrovascular disease, and incidence of adverse reactions between the two groups

Recurrence rates of ischemic stroke in the observation group were significantly lower than the control group. Differences were statistically significant (4.55% vs. 24.59%, X^2= 5.417, P=0.016) as shown in **Figure 1**.

Compared to the control group, incidence of cerebrovascular disease in the observation group was significantly lower, with statistically significant differences (9.09% vs. 22.95%, X^2= 4.625, P=0.025).

Adverse reaction rate in the observation group was 6.06%, including 1 case of gastrointestinal

Table 6. Comparison of cerebrovascular disease occurrence and adverse reactions between the two groups of patients (case)

Item	Control group (n=61)	Observation group (n=66)	X^2	P
Cerebrovascular disease			4.625	0.025
Transient ischemic attack	6	3		
Cerebral hemorrhage	2	1		
Recurrent cerebral infarction	5	1		
Progression of cerebral infarction	1	1		
Adverse reactions			1.245	0.106
Gastrointestinal reaction	1	1		
Muscle pain	0	1		
Abnormal liver function	1	1		
Gingival/nasal bleeding	1	1		

reaction, 1 case of muscle pain, 1 case of abnormal liver function, and 1 case of gingival/nasal bleeding. Adverse reaction rate in the control group was 4.92%, including 1 case of gastrointestinal reaction, 1 case of abnormal liver function, and 1 case of gingival/nasal bleeding. There were no significant differences in incidence of adverse reactions between the two groups (X^2=1.245, P=0.106) as shown in **Table 6**.

Discussion

Ischemic strokes are caused by damage to brain tissue due to local blood flow disorders and secondary neurological deficits. If blood flow reperfusion can be resumed as soon as possible through collateral circulation of the lesion, then restoration of nerve function and reduction of the degree of neurological deficit can be of great significance. Carotid atherosclerosis is one of the main causes of ischemic strokes. The pathological processes of carotid atherosclerotic plaque stenosis, thrombosis, thrombus shedding, and platelet activation are all closely related to inflammatory reactions. OX-LDL is one of the biomarkers that initiate carotid atherosclerosis inflammation. hs-CRP is a sensitive indicator that reflects the degree of inflammation. VCAM-1 is an index involved in the chemotaxis of macrophage adhesion. Animal experiments have confirmed that the atherosclerotic progression of VCAM-1 deficiency in rats is significantly inhibited [14]. Absence of TGF-β1 in peripheral circulation in patients with ischemic strokes can further inhibit regeneration of vascular endothelial cells [15]. Aspirin is an anti-platelet aggregation agent that can be used to prevent and treat ischemic strokes with the support of evidence-based medicine. It can inhibit cyclooxygenase and has the function of resisting platelet function, thereby preventing platelet adhesion, activation, aggregation, and thrombosis. Studies have reported that oral aspirin can significantly reduce the recurrence rate of ischemic strokes within 48 hours of treatment [16]. Other studies have shown that if aspirin alone was used to treat ischemic strokes, more than half of ischemic stroke patients have recurrence, with unsatisfactory effects. Results of this present study showed that serum levels of OX-LDL, TGF-β1, hs-CRP, VCAM-1, and lipids in the control group were not significantly different before and after treatment (all P>0.05). Moreover, after 6 months of follow up, recurrence rates of ischemic strokes and incidence of cerebrovascular disease events were as high as 20%, indicating that with aspirin therapy alone it is difficult to achieve effective treatment. This difficulty may be related to factors such as poor responsiveness or compliance with aspirin in some patients, polymorphisms in the genes for cyclooxygenase, and pharmacological effects of other drugs that affect aspirin [17].

Recent studies have found that statin drugs can selectively inhibit hydroxymethylglutaryl coenzyme A reductase, increase LDL-C receptors, lower serum LDL-C levels, and inhibit carotid atherosclerotic plaque formation. At the same time, statin drugs also reduce various inflammatory mediators generated during the formation of carotid atherosclerotic plaques and play a role in suppressing inflammatory reactions and stabilizing carotid atherosclerotic plaques [18]. The results of this study show that 6 months after treatment, serum levels of OX-LDL, VCAM-1, hs-CRP, and blood lipids in the observation group were significantly lower than those before treatment (all

P<0.05). Serum TGF-β1 and HDL-C levels were significantly higher than those before treatment (both P<0.05). These results suggest that statins may reduce the synthesis of rate-limiting enzymes in cholesterol synthesis, promote the decomposition of LDL-C, inhibit inflammation, and stabilize carotid atherosclerotic plaque. Changes in serum levels of OX-LDL, VCAM-1, hs-CRP, and TGF-β1 in the observation group may be because statins coordinate the release of cytokines, prompt the immune system to return to homeostasis, and suppress inflammatory response. In addition, the results of this study show that recurrence rates of ischemic stroke and incidence of cerebrovascular disease in the observation group were significantly smaller than those in the control group. There were no significant differences in incidence of adverse reactions between the two groups, however, which suggests that aspirin and statins have a synergistic effect on the treatment of ischemic strokes, with high safety. These results are consistent with results reported by Montaner et al. [19].

Statins have a lipid regulating effect and multiple functions, including anti-oxidant capability, inhibition of inflammation, stabilization of plaques, and improvement of vascular endothelial cell function. They are independent of lipid-regulating therapy, resulting in strong brain tissue protection [20]. Studies have reported that early use of statins to treat ischemic strokes can significantly improve endothelial function and neurological function [21]. In addition, statins have been shown to have an inhibitory effect on inflammatory response and increase the number of endothelial progenitor cells in the collateral circulation of the lesion, having positive effects on the promotion of angiogenesis [22]. In the present study, after 6 months of treatment, carotid intimal plaque area and carotid intima-media thickness in the observation group were all smaller than those in the control group. There were significant differences between the two groups (both P<0.05). This may be closely related to the anti-oxidation and inhibition of inflammatory reactions of statins. In addition, after 6 months of treatment, mRS scores of the observation group were significantly lower than the control group and MBI scores were significantly higher than the control group. Differences were statistically significant (both P<0.05). These results show that aspirin combined with statins for treatment of ischemic strokes can improve the prognosis of patients.

In summary, there are synergistic effects between aspirin and statins in the treatment of ischemic strokes. They play significant roles in regulating lipids, reducing and stabilizing atherosclerotic plaques, improving prognosis, and improving quality of life. This combination therapy is also safe and worthy of clinical application. However, the number of samples in this present study was small and there was no long-term follow up data. Future studies may confirm these results by increasing sample sizes and extending follow up periods.

Disclosure of conflict of interest

None.

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