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Original Article

Effect of Depsides Salts from Salvia Miltiorrhiza on cognitive function and serum Hcy, D-dimer and apoA1 in patients with cerebral infarction

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Abstract: Objective: To study the effects of Depsides Salts from Salvia Miltiorrhiza on cognitive function and serum Hcy, D-dimer and apoA1 in patients with cerebral infarction. Methods: A total of 120 patients with cerebral infarction were enrolled, and patients were divided into 2 groups based on a random number table. Sixty patients treated with a conventional regimen were selected as the observation group, 60 patients treated with the conventional regimen combined with Depsides Salts from Salvia Miltiorrhiza were selected as the experimental group. After 14 days of treatment, the clinical efficacy, as well as the serum homocysteine (Hcy), D-dimer and apolipoprotein A1 (apoA1) were compared between the groups; the score of National Institutes of Health Stroke Scale (NIHSS), the score of Mini-Mental State Exam (MMSE), and the score of Montreal Cognitive Assessment (MoCA) were also compared between the two groups. Results: The total effective rate of the experimental group was 81.67%, which is higher than that of the control group (61.67%) ($P<0.05$). The serum Hcy and D-dimer were lower in the experimental group than in the control group ($P<0.05$). The serum apoA1was higher in the experimental group than in the control group ($P<0.05$). The improvement of the score of NIHSS, MMSE and MoCA of the experimental group was better than that of the control group ($P<0.05$). Conclusion: Depsides Salts from Salvia Miltiorrhiza can lower serum Hcy and D-dimer levels, and increase serum apoA1 level in cerebral infarction patients, as well as improve the clinical efficacy. Depsides Salts from Salvia Miltiorrhiza can also repair neural damage and improve cognitive function, it is highly recommended to be used in clinical practice and future research.

Keywords: Depsides Salts from Salvia Miltiorrhiza, cerebral infarction, clinical efficacy, homocysteine, D-dimer, apolipoprotein A1

Introduction

Cerebral infarction is a kind of ischemic cerebrovascular disease, it is also called cerebral ischemic stroke (CIS) in clinical practice. Cerebral infarction is mainly caused by cerebral ischemia and hypoxia due to insufficient blood and oxygen supply to the brain. The fundamental pathological change is the stenosis or occlusion of the cerebral artery; it often leads to brain tissue damage and necrosis, which eventually causes the loss of brain function [1, 2]. The annual incidence of cerebral infarction is on the rise, and acute onset accounts for 75% of total cases [3]. About 30% of patients with cerebral infarction are elderly patients [4], and 2/3 of all lethal and disabled patients are elderly [5, 6]. It's reported that cerebral infarction has become the leading cause of death in China [7]. At present, the main principle for the treatment of cerebral infarction is anticoagulation, anti-thrombosis, and anti-platelet aggregation [8], but the clinical efficacy of the conventional treatment regimen is often unsatisfactory [9]. Previous studies have found that a series of pathophysiological changes can occur during the development of cerebral infarction, such as aggravation of oxidative st-

ress, damage of vascular endothelial cells, increased blood viscosity, etc., which are involved in the failure of conventional treatment regimen [10]. Cerebral infarction belongs to the category of "stroke disease" in the diagnosis of traditional Chinese medicine. The pathogenesis is due to the endogenous liver wind and impeded circulation of Qi and blood; the treatment is based on the principle of promoting blood circulation to remove blood stasis [11]. Depsides Salts from Salvia Miltiorrhiza is a traditional Chinese medicine for promoting blood circulation and removing blood stasis. It has been proven to be effective in multiple cardiovascular diseases [12]. Previous studies have shown that Depsides Salts from Salvia Miltiorrhiza is effective in the treatment of cerebral infarction, but the mechanism is still unclear. Some studies have shown that the active ingredient of Depsides Salts from Salvia Miltiorrhiza is magnesium acetate, which is beneficial to the reduction of infarction area and the restoration of blood circulation in the ischemic penumbra [13].

Homocystein (Hcy) is a metabolite in the human body. It is produced by methionine and has a certain toxicity. It is a risk factor for atherosclerosis and an independent risk factor for stroke [14, 15]. D-dimer is one of the indicators of the coagulation function. Elevated D-dimer indicates a hyper coagulation state, which is related to the severity of the disease and the prognosis of the patient [16]. Apolipoprotein A1 (apoA1) is an apoptotic factor in the tumor necrosis factor receptor family [17]. Studies have shown that apoA1 is present in high-density lipoprotein, which inhibits low-density lipoprotein, regulates inflammatory factor levels, and inhibits atherosclerosis. Increased apoA1 is considered to be a protective factor for cerebral infarction [18]. In this study, Depsides Salts from Salvia Miltiorrhiza was added to the treatment regimen for cerebral infarction patients. The changes of serum Hcy, D-dimer, and apoA1, as well as the clinical efficacy and improvement of neurological function were observed and compared, to provide clinical evidence for the use of Depsides Salts from Salvia Miltiorrhiza in cerebral infarction patients.

Materials and methods

Patients

A total of 120 patients with cerebral infarction admitted to Laiyang Central Hospital of Yantai from January 2017 to June 2018 were enrolled. Patients were divided into 2 groups based on a random number table. Sixty patients treated with a conventional regimen were selected as the observation group, 60 patients treated with conventional regimen combined with Depsides Salts from Salvia Miltiorrhiza were selected as the experimental group. This study was approved by the ethics committee of the Laiyang Central Hospital of Yantai. All patients provided informed consent prior to this study.

Inclusion criteria: Patients diagnosed with cerebral infarction based on the guidelines for the diagnosis and treatment of acute ischemic stroke in China (2014) [19]; patients were diagnosed with cerebral infarction for the first time; patients aged between 18 and 76 years; the score of National Institutes of Health Stroke Scale (NIHSS) was between 5-15 points [20].

Exclusion criteria: Patients were allergic to Depsides Salts; patients had a history of craniocerebral trauma, epilepsy, or cerebrovascular disease; patients could not cooperate in cognitive function evaluation; patients with abnormal coagulation function or using heparin or other anticoagulants before treatment; patients who had cardiopulmonary insufficiency; patients with malignant tumors; patients who were lactating or pregnant; or patients that had digestive tract or urinary tract bleeding.

Methods

The control group was treated with a conventional regimen according to the guidelines for the diagnosis and treatment of acute ischemic stroke in China (2014) [19]. Patient received inhaled oxygen, and had monitoring of vital signs, blood pressure, and blood glucose. Mannitol (Zhengda Tianqing Pharmaceutical Group Co., Ltd., China) 0.5-2 g/kg was added to 100 mL of normal saline, and given intravenously once a day to reduce intracranial pressure; aspirin enteric-coated tablet (Bayer, Germany) 100 mg was given orally once a day for anti-platelet treatment; atorvastatin calcium tablet (Pfizer Pharmaceutical Co., Ltd., USA) 20 mg was given orally once a day, to lower blood cholesterol and stabilize plaque; edaravone injection 30 mg was added to 100 mL of saline, and given intravenously twice a day to remove oxygen free radicals.

The experimental group was treated with Depsides Salts from Salvia Miltiorrhiza (Shanghai

Green Valley Pharmaceutical Co., Ltd., China) combined with the conventional treatment regimen as given to the control group. Depsides Salts from Salvia Miltiorrhiza 200 mg was added to 250 mL 5% glucose or normal saline, given once a day. The treatment lasted for 14 days in both groups.

Observation indices

The score of NIHSS was evaluated after 14 days of treatment [19]. The clinical efficacy was determined according to the degree of decline of the NIHSS score: 90-100% decline is defined as healed; 46-91% as significantly improved; 18-45% as improved; ≤17% as unchanged. Total effective rate = (healed + significantly improved + improved)/total×100%.

A volume of 5 mL of venous blood was obtained at 8 a.m. both at admission and after treatment. The blood was drawn into EDTA tubes and stored in a refrigerator at 4°C for 15 min. The serum was separated by a centrifuge at a speed of 3,300 rpm and mixed with 40 μL protease inhibitor with phosphate buffer. The samples were stored in a freezer at -80°C before the detection of D-dimer, homocysteine (Hcy), and apolipoprotein A1 (apoA1) by serum enzyme-linked immunosorbent assay in a microplate reader (Thermo, USA).

The NIHSS score was compared between the two groups before and after the treatment. The NIHSS score ranged from 0 to 42 points and was used to assess the neurological damage. The higher the score, the more severe the neurological damage: 0-1 point is classified as normal; 2-4 points as mildly damaged; 5-15 points as moderately damaged; 16-20 points as moderately-to-severely damaged; and >21 points as severely damaged [20].

The Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) were used to assess the cognitive function before and after treatment. The MMSE has 19 items with a total score of 30 points. The MoCA has a total score of 30 points. The lower the score, the worse the cognitive function [21].

The adverse reactions were recorded and compared between the two groups of patients, including cerebral hemorrhage, hematuria, skin irritation, nausea and vomiting during the treatment.

Statistical analysis

All data were analyzed with SPSS 17.0 statistical package. Quantitative values were expressed as mean ± sd and differences between groups were evaluated using independent or paired t-test. Enumeration data were expressed as number/percentage (n/%) and compared by χ^2 test. A *P* value less than 0.5 is considered significant.

Results

Comparison of baseline conditions

There were no significant differences in gender, age, education level, BMI, onset-admission interval, stroke location, and comorbidities between the two groups (all P>0.05). See **Table 1**.

Comparison of total efficacy

There were significant differences between the two groups regarding the number of healed, significantly improved, improved and unchanged patient outcomes (all P<0.05). The total effective rate of the experimental group was 81.67%, higher than that of the control group (61.67%), as shown in **Table 2**.

Comparison of serum Hcy, D-dimer and apoA1

There were no significant differences in serum Hcy, D-dimer and apoA1 between the two groups before treatment (all P>0.05). The serum Hcy and D-dimer decreased in both groups after treatment (all P<0.05). Serum apoA1 increased in both groups after treatment (both P<0.05); However, the decrease of Hcy and D-dimer, and the increase of apoA1 were more pronounced in the experimental group than in the control group (all P<0.05). See **Table 3**.

Comparison of NIHSS score

There was no significant difference in NIHSS score between the two groups before treatment (P>0.05). After treatment, the NIHSS score of both groups was lower than that before treatment (both P<0.05). In addition, the NIHSS score of the experimental group was lower than

Table 1. Comparison of baseline conditions

Group	Experimental Group (n=60)	Control Group (n=60)	χ^2/t	P
Gender (Male/Female)	34/26	28/32	1.201	0.273
Age (year)	68.5±7.1	67.4±5.9	0.692	0.492
Education (year)	12.5±3.9	11.9±4.0	0.627	0.533
BMI (kg/m^2)	25.71±3.76	25.59±4.28	0.110	0.913
Onset to admission (hour)	3.12±0.76	3.21±0.66	0.234	0.786
Stroke location				
Brain stem	7	5	1.382	0.710
Brain lobes	13	10		
Cerebellum	6	9		
Basal ganglia	34	36		
Hyperlipidemia	-	-	-	-
Yes	34	32	0.135	0.714
No	26	28		
Hypertension				
Yes	40	34	1.269	0.260
No	20	26		
Coronary heart disease				
Yes	20	24	0.574	0.449
No	40	36		
Obesity				
Yes	20	26	1.269	0.260
No	40	34		
Hyperhomocysteinaemia				
Yes	44	48	0.745	0.388
No	16	12		
Hyperuricemia				
Yes	38	44	1.386	0.239
No	22	16		

Note: BMI: Body Mass Index.

that of the control group after treatment (P< 0.001). See **Table 4**.

Comparison of MMSE and MoCA score

There was no significant difference in MMSE and MoCA scores between the two groups before treatment (both P>0.05). The experimental group showed significantly greater improvement in MMSE and MoCA scores after treatment (both P<0.05). The two groups both had significant MMSE and MoCA scores after treatment (all P<0.05), see **Table 5** and **Figure 1**.

Comparison of adverse reactions

There was no mortality during the treatment period. In the experimental group, 1 patient developed cerebral hemorrhage, 1 patient developed hematuria, and 1 patient had nausea and vomiting. The total incidence of adverse reactions was 5.00% (3/60). While in the control group, 2 patients developed cerebral hemorrhage, 2 patients had nausea and vomiting; the total incidence of adverse reactions was 6.67% (4/60). There was no statistical difference between the two groups (χ^2=0.154, P=0.695).

Discussion

By studying the pathophysiology of cerebral ischemic stroke (CIS), we found that oxidative stress induced by CIS leads to the production of inflammatory factors and hemodynamic changes, which ultimately leads to local blood circulation disorders and damage to neurons [22, 23]. Depsides Salts from Salvia Miltiorrhiza is extracted from traditional Chinese medicine Salvia Miltiorrhiza, with the effect of promoting blood circulation and removing blood stasis. Further studies have found that Depsides Salts from Salvia Miltiorrhiza could inhibit platelet aggregation, which increased the blood supply to the brain tissue in the ischemic area and had the effect of protecting against oxygen free radicals [24]. Another study showed that Depsides Salts from Salvia Miltiorrhiza could counteract the oxidative stress response of endothelial cells, increase endothelial cell viability and the production of vascular endothelial growth factor [25, 26]. Moreover, Depsides Salts from Salvia Miltiorrhiza has a defined composition, which is easy for quality control, and has a more stable therapeutic effect and less side effects compared with traditional Chinese medicine Salvia Miltiorrhiza [27]. This study found that the total effective rate of the experimental group after treatment was 81.67%, which was significantly higher than that of the control group (61.67%), and there was no significant difference in the incidence of adverse reac-

Table 2. Comparison of clinical efficacy

Group	Healed	Significantly improved	Improved	Unchanged	Total effective rate (%)
Experimental group (60)	6 (10.00)	28 (46.67)	15 (25.00)	11 (18.33)	49 (81.67)
Control group (n=60)	3 (5.00)	17 (28.33)	17 (28.33)	23 (38.33)	37 (61.67)
χ^2		8.049			5.910
P		0.045			0.015

Table 3. Comparison of Hcy, D-dimer and apoA1

Group	Hcy (μmol/L)	D-dimer (mg/L)	apoA1 (g/L)
Before treatment			
Experimental group	20.56±2.28	2.27±0.38	1.06±0.18
Control group	20.48±2.23	2.29±0.40	1.09±0.18
t	0.154	0.234	0.917
P	0.878	0.786	0.363
After treatment			
Experimental group	13.63±1.99#	1.51±0.38#	1.22±0.15#
Control group	15.83±2.02#	2.07±0.45#	1.18±0.15#
t	4.269	4.890	4.153
P	<0.001	<0.001	<0.001

Note: #P<0.05, compared with before treatment in the same group, Hcy: homocysteine; apoA1: apolipoprotein A1.

Table 4. Comparison of NIHSS score

Group	NIHSS (points)
Before treatment	
Experimental group	9.6±3.6
Control group	9.9±3.7
t	0.917
P	0.363
After treatment	
Experimental group	4.8±1.5#
Control group	5.6±1.5#
t	4.153
P	<0.001

Note: #P<0.05, compared with before treatment in the same group, NIHSS: National Institutes of Health Stroke Scale.

tions between the two groups. It is speculated that many of the advantages of Depsides Salts from Salvia Miltiorrhiza are related to its anti-platelet aggregation and antioxidant effects.

Serum homocysteine (Hcy) is considered to be an independent risk factor for stroke [28]. Hcy promotes oxidative stress and release of inflammatory factors in the human body, and stimulates immune responses to damage vascular endothelial cells, eventually leading to atherosclerosis [29]. In this study, serum Hcy was also found to be elevated in patients with CIS before treatment, and decreased in both groups after treatment; and the decrease is more pronounced in the experimental group treated with Depsides Salts from Salvia Miltiorrhiza, which may be related to the improvement of oxidative stress in the body. In previous studies, D-dimer was found to be elevated in the serum of patients with ischemic stroke, and the degree of elevation was correlated with the prognosis of patients [16, 30]. The rise of D-dimer indicates the blood of patients is in a hypercoagulable state and prone to thrombosis. This study also found that D-dimer increased before treatment and decreased after treatment in cerebral infarction patients, but the experimental group decreased more significantly, which can be explained by the anti-platelet aggregation effect of Depsides Salts. Apolipoprotein A1 (apoA1) is mainly present in high-density lipoprotein. A 10 year follow-up study showed that low levels of apoA1 and high-density lipoprotein are risk factors for all stroke patients [31]. In the present study, apoA1 decreased before treatment and increased after treatment in both groups, while the increase in the experimental group was more apparent, which may be related to the inhibition effect of atherosclerosis by Depsides Salts from Salvia Miltiorrhiza.

Studies have shown that Depsides Salts from Salvia Miltiorrhiza could significantly relieve the hypoxic state of brain tissue, minimize the damage of glial cells and neuronal cells, and ultimately reduce brain function damage [32]. The NIHSS score provides a reliable tool for assessing the neurological impairment through quantitative indicators [33]. MMSE and MoCA are commonly used evaluation tools to reflect

Table 5. Comparison of MMSE and MoCA score

Group	MMSE (points)	MoCA (points)
Before treatment		
Experimental group	25.42±1.22	22.50±1.94
Control group	25.37±1.16	22.20±2.35
t	0.108	0.538
P	0.914	0.592
After treatment		
Experimental group	27.83±0.9#	23.73±2.03#
Control group	25.70±1.80	22.23±2.18
t	5.201	2.759
P	<0.001	0.008

Note: #P<0.05, compared with before treatment in the same group, MMSE: Mini-Mental State Exam; MoCA: Montreal Cognitive Assessment.

patients' cognitive function [20, 21]. In this study, after treatment with Depsides Salts from Salvia Miltiorrhiza, the experimental group showed significantly better scores compared with the control group, which is consistent with previous studies.

There are certain limitations of this study, such as the small sample size and short observation period. In future studies, a larger sample size is required and the results should be confirmed by a randomized controlled trial with a long-term follow-up.

In conclusion, Depsides Salts from Salvia Miltiorrhiza can lower serum Hcy and D-dimer level, increase serum apoA1 level in cerebral infarction patients, as well as improve the clinical efficacy. Depsides Salts from Salvia Miltiorrhiza can also repair neural damage and improve cognitive function, it is highly recommended to be used in clinical practice and future research.

Disclosure of conflict of interest

None.

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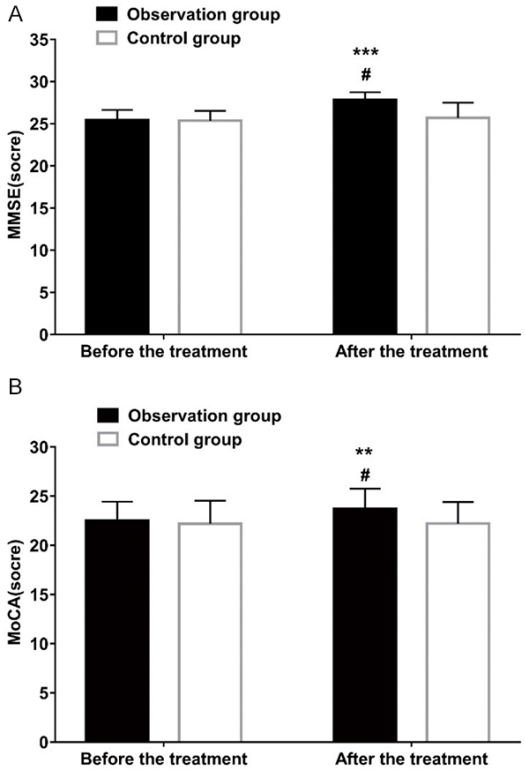

Figure 1. Comparison of MMSE and MoCA score. *P<0.05, **P<0.01, ***P<0.001, compared with the control group; #P<0.05, compared with before treatment, MMSE: Mini-Mental State Exam; MoCA: Montreal Cognitive Assessment.

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