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Effect of salvia miltiorrhiza and ligustrazine hydrochloride injection combined with hydroxyethyl starch injection on serum BNP, Hcy, MMP−2, S100B protein and hemorheology in patients with acute cerebral watershed infarction

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ABSTRACT

Objective: To study the effect of salvia miltiorrhiza and ligustrazine hydrochloride injection combined with hydroxyethyl starch injection on serum BNP, Hcy, MMP-2, S100B protein and hemorheology in patients with acute cerebral watershed infarction. **Methods:** A total of 90 patientswith acute cerebral watershed infarction in our hospital from August 2014 to December 2016 were enrolled in this study. The subjects were divided into the control group (n=45) and the treatment group (n=45) randomly. The control group was treated with hydroxyethyl starch injection, the treatment group was treated withsalvia miltiorrhiza and ligustrazine hydrochloride injection combined with hydroxyethyl starch injection, and both the two groups were treated for 2 weeks. The serum BNP, Hcy, MMP-2, S100B protein and hemorheology of the two groups before and after treatments were compared. **Results:** There were no significantly differences of the serum BNP, Hcy, MMP-2, S100B protein and hemorheology of the two groups before treatment. The serum BNP, Hcy, MMP-2, S100B proteinlevels of the two groups after treatment were significantly lower than before treatment, and that of the treatment group after treatment were significantly lower than the control group. The PV, Lr, Mr, Hr and RE of the two groups after treatment were significantly lower than before treatment, and that of the treatment group after treatment were significantly lower than the control group. **Conclusion:** Salvia miltiorrhiza and ligustrazine hydrochloride injection combined with hydroxyethyl starch injectioncan significantlyimprovetheneurological function and hemorheology, reduce inflammation of the patients with acute cerebral watershed infarction, and it was worthy clinical application.

1. Introduction

Cerebral watershed infarction (CWI) is a cerebral infarction that occurs at the junction of two areas of the aorta in the brain, imaging showed that it was located in the cortical artery supply area or the larger basal nucleus area, and the marginal zone of the blood supply zone between the small arteries could be unilateral or bilateral, which accounted for more than 10% of the cerebral infarction, the main clinical manifestations were spasticity, muscle tension, muscle strength, and coordination disturbance among muscle groups[1]. ACWI occurs frequently in the elderly population, which is progressing rapidly. The condition is dangerous. It has higher disability rate and fatality rate, and more than 50% of the patients have different degrees of physical disability, which seriously threatens the health of the patients[2]. At present, the clinical treatment of ACWI mainly uses anticoagulant, anti-platelet aggregation, fibrinolysis, free radical scavenging and microcirculation improvement, but the clinical efficacy is not satisfactory[3]. In recent years, Chinese medicine treatment of acute cardiovascular and cerebrovascular diseases in clinical widely used, based on this idea; this study explored the use of proprietary Chinese medicine combined with western medicine for the treatment of ACWI. This research was to study the effect of salvia

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miltiorrhiza and ligustrazine hydrochloride injection combined with hydroxyethyl starch injection on serum BNP, Hcy, MMP-2, S100B protein and hemorheology in patients with acute cerebral watershed infarction. The results are as follows.

2. Informations and methods

2.1. General information

We selected 90 patients with ACWI treated in our hospital from August 2014 to December 2016 as the subjects. Case inclusion criteria: (1) In line with the "Fourth National Conference on cerebrovascular diseases criteria" in the diagnostic criteria for ACWI[4]. (2) The diagnosis was ACWI by cranial CT and magnetic resonance imaging; (3) The incidence of hospitalized patients in 2 h. Case exclusion criteria: (1) Patients with intracerebral hemorrhage and intracranial occupying lesions; (2) patients with dysphagia or severe impairment of consciousness (3) Bleeding prone patients; (4) Patients with hepatic or renal dysfunction; (5) Patients who have been treated with anti-platelet aggregation, thrombolysis, fibrinolysis, anticoagulation and so on; (6) Patients with mental disorders.

The 90 subjects included in this study were randomly divided into two groups: the control group and the experimental group, each with 45 cases. In the control group, 30 cases were male, 15 were female, aged 55-78 years old, and the average age of the patients was (62.41±5.39) years; The course of disease was 4-29 h, and the average course of disease was (13.11 ± 6.10) h; Types of infarction: 9 cases of cortical type, 31 cases of subcortical type, 5 cases of mixed type. In the experimental group, 31 cases were male, 14 were female, aged 55-79 years old,and the average age of the patients was (63.18±5.10) years; The course of disease was 4-30 h, and the average course of disease was (14.25 ±5.84) h. Types of infarction: 8 cases of cortical type, 30 cases of subcortical type, 7 cases of mixed type. There was no significant difference between the two groups in sex, age, course of disease, infarction type and so on (P>0.05), and they were comparable.All patients in the two groups were informed of the study before the treatment and signed the informed consent with consent. The study was approved by the medical ethics committee of our hospital.

2.2. Experimental method

All patients were given basic treatment measures such as anticoagulation, anti-platelet aggregation, lowering blood pressure, lowering blood sugar, intracranial pressure and fluid replacement after the intervention. The control group were treated with Hydroxyethyl Starch Injection (purchased from Nanjing cttq Pharmaceutical Co. Ltd., specifications of 500 mL/bottle, National Drug Certificate H20065430), intravenous drip, 500 mL/time, 1 time/d, for continuous treatment of 2 W.

2.3 Detection index

The venous blood 5mL of the two groups before and after treatment in the morning fasting state was collected. The supernatant was centrifuged and the serum was kept at -70 centigrade freezer. The serum levels of brain natriuretic peptide (BNP), homocysteine (Hcy), matrix metalloproteinase-2 (MMP-2) and S100B protein were detected and compared between the two groups before and after treatment. The blood rheology indexes of two groups before and after treatment were detected and compared, which includes PV, Lr, Mr, Hr and RE.

Using double antibody sandwich enzyme-linked immunosorbent assay (ELISA) method for detection of serum BNP, Hcy, MMP-2 and protein levels of S100B, kit were purchased from Shanghai Xinyu Biotechnology Co. ltd.; SH211A type blood rheology analyzer was used to detect PV, Lr, Mr and Hr, and the instruments were purchased from Chongqing racing science and Technology Development Co., Ltd.RE= Lr/Hr.

2.4 Data processing

We Used SPSS 19.0 software package to process the test result data, mean ± standard deviation (Mean ± SD) represents measurement data, the use of t test was to compare the difference between groups; The clinical average data were expressed by % and chi square test was used, with P<0.05 as a statistically significant.

3. Results

3.1. Comparison of serum BNP, Hcy, MMP–2 and S100B protein levels in the two groups before and after treatment

Before treatment, the serum levels of BNP, Hcy, MMP-2 and S100B protein in the control group were (451.48±29.87) ng/mL, (16.33±1.25) μ mol/L, (348.26±31.40) μ g/L and (0.49±0.12) ng/mL, that in experimental group were (448.31±30.54) ng/mL, (16.40±1.30) umol/L, (351.17±33.52) μ g/L and (0.51±0.15) ng/mL. The difference between the two groups was not statistically significant (P>0.05). After treatment, the serum levels of BNP, Hcy,

Table 1.
Comparison of serum BNP, Hcy, MMP-2 and S100B protein levels in the two groups before and after treatment.

Group	n	Time	BNP (ng/mL)	Hcy (μ mol/L)	MMP-2 (μ g/L)	S100B protein (ng/mL)
Control group	45	Before treatment	451.48±29.87	16.33±1.25	348.26±31.40	0.49±0.12
		After treatment	214.87±22.60*	12.61±1.04*	286.10±25.35*	0.31±0.09*
Experimental group	45	Before treatment	448.31±30.54	16.40±1.30	351.17±33.52	0.51±0.15
		After treatment	140.35±17.86*#	9.17±0.83*#	210.74±21.28*#	0.18±0.06*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

Table 2.
Comparison of hemorheology indexes between two groups before and after treatment.

Group	*n*	Time	PV (mPa·s)	Lr (mPa·s)	Mr (mPa·s)	Hr (mPa·s)	RE
Control group	45	Before treatment	1.89±0.43	12.65±2.25	7.15±0.72	5.05±1.31	3.50±0.20
		After treatment	1.50±0.31*	9.30±1.67*	5.33±0.61*	4.16±0.77*	2.23±0.09*
Experimental group	45	Before treatment	1.84±0.39	12.17±2.10	7.24±0.80	5.10±1.35	3.39±0.18
		After treatment	1.12±0.17*#	7.02±1.08*#	3.98±0.35*#	3.27±0.54*#	2.14±0.05*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

MMP-2 and S100B protein in the control group were (214.87±22.60) ng/mL, (12.61±1.04) umol/L, (286.10±25.35) ug/L and (0.31±0.09) ng/mL, that in experimental group were (140.35±17.86) ng/mL, (9.17±0.83) umol/L, (210.74±21.28) ug/L and (0.18±0.06) ng/mL. Those levels in two groups were lower than before treatment, and the experimental group after treatment, the serum levels of BNP, Hcy, MMP-2 and S100B protein in the experimental group were lower than those in the control group, and the differences were statistically significant (P<0.05).Please look at table 1.

3.2. Comparison of hemorheology indexes between two groups before and after treatment

Before treatment,the levels of PV, Lr, Mr, Hr and RE in the control group were (1.89±0.43) mPa·s, (12.65±2.25) mPa·s, (7.15±0.72) mPa·s, (5.05±1.31) mPa·s and (3.50±0.20) mPa·s, that in experimental group were (1.84±0.39) mPa·s, (12.17±2.10) mPa·s, (7.24±0.80) mPa·s, (5.10±1.35) mPa·s and (3.39±0.18) mPa·s. The difference between the two groups was not statistically significant (P>0.05). After treatment, the he levels of PV, Lr, Mr, Hr and RE in the control group were (1.50±0.31) mPa·s, (9.30±1.67) mPa·s, (5.33±0.61) mPa·s, (4.16±0.77) mPa·s and (2.23±0.09) mPa·s, that in experimental group were (1.12±0.17) mPa·s, (7.02±1.08) mPa·s, (3.98±0.35) mPa·s, (3.27±0.54) mPa·s and (2.14±0.05) mPa·s. The PV, Lr, Mr, Hr and RE in the two groups were smaller than before treatment, and the PV, Lr, Mr, Hr and RE in the experimental group were smaller than those in the control group, and the differences were statistically significant (P<0.05). Please look at Table 2.

4. Discussion

Studies[5] have shown that the pathogenesis of ACWI is unclear, it is believed that its development is related to many factors, such as low circulation, low blood volume, carotid stenosis or occlusion, microvascular embolization, atherosclerosis and hemodynamic changes. ACWI is most likely to occur when the patient has a stenosis of more than 50% and is accompanied by hemodynamic disturbances or decreased blood pressure throughout the blood[6]. Therefore, it is now believed that the earlier thrombolysis and the timely improvement of blood volume are of important clinical significance for the treatment and prognosis of ACWI. The clinical treatment of ACWI is mostly anticoagulant, anti-platelet aggregation, reducing fibrinolysis and so on, however, few patients can receive treatment in time window, the clinical efficacy is not satisfactory, and the prognosis is poor, which has great damage to the patient's living ability and neurological function[7]. Traditional Chinese medicine believes that cerebral infarction is a category of "apoplexy", which is caused by the emptiness of meridians, the deficiency of Qi, the invasion of meridians and collaterals, the loss of meridians and the obstruction of Qi and blood, so that the treatment should be based on dredging collaterals, activating blood circulation and removing stasis[8]. The main components of Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection are Danshensu and ligustrazine, among them, danshensu has the effect of dredging collaterals, activating blood circulation, removing blood stasis and relieving pain, and ligustrazine has the effect of promoting qi and activating blood circulation; The combination of two ingredients can enhance the effect of promoting blood circulation and removing blood stasis. At present, it is mostly used for the treatment of myocardial infarction, coronary heart disease, angina pectoris, ischemic stroke, cerebral insufficiency and so on[9]. Hydroxyethyl Starch Injection is a commonly used plasma volume expander. It can increase blood volume, inhibit the formation of cerebral atherosclerosis, and improve the blood viscosity. It is mainly used in the treatment of ACWI[10]. This research was to study the effect of salvia miltiorrhiza and ligustrazine hydrochloride injection combined with hydroxyethyl starch injection on serum BNP, Hcy, MMP-2, S100B protein and hemorheology in patients with acute cerebral watershed infarction, so as to provide some guidance for the clinical treatment of ACWI.

The results showed that the serum levels of BNP, Hcy, MMP-2 and S100B protein in the two groups after treatment were lower than before treatment, and that in the experimental group were lower than those in the control group, and the difference was statistically significant (P<0.05). The results suggest that Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection combined with Hydroxyethyl Starch Injection can significantly reduce the serum levels of BNP, Hcy, MMP-2 and S100B in patients with ACWI.BNP is a secreted neurohormone in ventricular myocytes, ischemia and hypoxia affect the hypothalamus, medulla oblongata and striatum in patients with cerebral infarction, resulting in increased secretion of BNP[11]. Studies have shown that high levels of BNP indicate severe brain damage in patients, so serum BNP levels can be used to assess the severity of ACWI[12]. Hcy, a metabolic intermediate product of sulfur-containing amino acids, is a nonspecific acute phase response protein, which is markedly elevated in the organism when it has acute infection or tissue damage[13]. MMP-2 is a matrix metalloproteinase, which participates in the secondary cascade injury of cerebral infarction and can be used as a molecular marker for the analysis of the prognosis and the prognosis of patients with cerebral infarction[14]. S100B protein is mainly secreted by glial cells, ACWI occurs when nerve cells are necrotic or damaged, and the integrity of the neuronal cell membrane is disrupted, and the S100B protein leaks

through the compromised blood-brain barrier into the intercellular space,and then enter the cerebrospinal fluid and blood circulation, causing significant increases in serum S100B protein level[15]. The Danshensu in Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection can improve microcirculation, Ligustrazine can dilate venule, arteriole caliber, dredge microcirculation, protect brain tissue, prevent platelet aggregation, and have the effect of promoting blood circulation and removing blood stasis, it combined with hydroxyethyl amylase treatment of ACWI, can play a synergistic role, the effect is significant, and can reduce inflammation and improve the nervous function of patients[16]. In addition, the results of this study show that the PV, Lr, Mr, Hr and RE were smaller in the two groups than before treatment, and the PV, Lr, Mr, Hr and RE in the experimental group were smaller than those in the control group, and the difference was statistically significant (P<0.05). It is indicated that Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection combined with Hydroxyethyl Starch Injection can obviously improve the hemorheology of ACWI patients. Modern pharmacological studies have shown that Danshensu can promote the dissolution of fibrin, thereby reducing blood viscosity and improving blood rheology; Ligustrazine can inhibit the adhesion, aggregation and release of platelets, protect the deformability of erythrocytes, decrease blood viscosity and improve blood rheology, therefore, Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection has better effect on improving Hemorheology[17]. Hydroxyethyl Starch Injection is a blood volume expansion agent that can dilute the blood and reduce the aggregation of red blood cells, thereby reducing the high viscosity of the blood[18–20].

In summary, Salviae Miltiorrhizae and Ligustrazine Hydrochloride Injection combined with Hydroxyethyl Starch Injection can significantly improve the nerve function and hemorheology of ACWI patients, and reduce the inflammatory response, so it is worthy of clinical application.

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