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Effect of butylphthalide combined with ozagrel sodium on cerebral perfusion and oxidative stress indexes in patients with transient ischemic attack

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This study has been undertaken to evaluate the effect of butylphthalide combined with ozagrel sodium on cerebral perfusion and oxidative stress indexes in patients with transient ischemic attack. In this study, a total of 116 patients diagnosed as transient ischemic attack in our hospital (February 2018-February 2020) have been selected and divided into two groups according to the treatment methods.58 cases in the control group have been treated with ozagrel sodium, 58 cases in the observation group have been treated with butylphthalide combined with ozagrelsodium. The CT perfusion imaging parameters, oxidative stress indexes, plaque area, and the levels of platelet activating factor (PAF), α-granule membrane protein-140 (GMP-140), fibrinogen (FIB), platelet aggregation rate (PAgT), neuron-specific enolase (NSE), oxygen-inducible factor-1α (HIF-1α), and matrix metalloproteinases-9 (MMP-9) in the two groups have been recorded, and the total effective rate and adverse reaction rate have been counted. The results shown that the total effective rate of the observation group is higher than that of the control group, and the difference is statistically significant (χ^2 = 4.640, P = 0.031). The average time (MTT) required for the two groups of contrast agents to pass through the local brain tissue and the time (TTP) required starting the injection of contrast agents to reach the peak concentration decreased compared to that with before treatment. After treatment, the MTT and TTP of the observation group are shorter than those of the control group (P < 0.05). Compared with before treatment, superoxide dismutase (SOD) in the two groups has higher than that in the control group, PAF, GMP-140, FIB, PAgT, NSE, HIF-1α, MMP-9, malondialdehyde (MDA) and plaque area has decreased. After treatment, the levels of related factors in the observation group are better than those in the control group, and the plaque area is less than that in the control group (P < 0.05).There has been no significant difference in the adverse reaction rate between the observation group and the control group (χ^2 = 0.438, P = 0.508).

Keywords: Butylphthalide, Sodium ozagrel, Transient ischemic attack, Oxidative stress, Plaque

Transient ischemic attack is a special kind of acute cerebrovascular disease, which indicates that acute cerebral infarction may occur. The clinical manifestations are transient aphasia, reversible limb hemiplegia, and sensory disturbance. The symptoms generally return to normal after several to tens of minutes. Its pathogenesis is complicated, which is related to cerebral vascular microthrombosis and local hypoperfusion[1,2]. It is currently recognized that improving local blood perfusion is the key to clinical treatment of transient ischemic attack. Sodium ozagrel is a thromboxane synthase inhibitor, which can expand blood vessels and inhibit thrombosis. It is widely used in the treatment of ischemic cerebrovascular diseases[3]. However, bleeding adverse reactions may occur during the medication. Butylphthalide is a component extracted from celery volatile oil, which has good anticonvulsant, increasing blood flow and other pharmacological effects. At present, butylphthalide is often used as an adjuvant drug for mild and moderate stroke in clinic, and satisfactory curative effect is obtained[4]. In recent years, butylphthalide has also been applied in the treatment of transient ischemic attack, but the reported studies have mostly focused on improving the symptoms of patients. This study observed the effects of butylphthalide combined with ozagrel sodium on cerebral perfusion and oxidative stress indexes in patients with transient ischemic attack. The results are as follows.

Experimental Section

A total of 116 patients diagnosed as transient ischemic attack in our Medical Laboratory Center, Second Hospital of Shandong University (February 2018-February 2020) were selected and divided into two groups according to the treatment methods. The control group of 58 cases, including 30 cases, 28 cases of women. The age was 48–70 years old, with average of (60.69 ± 5.87) years old. The course of

disease ranged from 2 h to 24 h, with an average of (10.02 ± 2.11)h. BMI (23.29 ± 2.05) kg/m^2. Complications: hypertension 12 cases, hyperlipidemia 7 cases, diabetes 9 cases and 19 cases of smoking history. The observation group had 58 cases, including 32 cases and 26 cases of women. The age was 45–70 years old, with average of (61.05 ± 6.14) years old. The course of disease ranged from 2 h to 24 h, with an average of (9.89 ± 2.27) h.BMI (23.23 ± 2.21) kg/m2. Complications: 11 cases of hypertension, 8 cases of hyperlipidemia, 10 cases of diabetes and 22 cases of smoking history. The general data of the two groups were not statistically significant (P >0.05).

Inclusion and exclusion criteria

Inclusion criteria: (i) meeting the criteria of "Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2010and confirmed by head CT or MRI; (ii) Age ≥ 40 years and (iii) Complete clinical data.

Exclusion criteria: (i) Patients with previous history of acute cerebrovascular diseases, new infarcts, cerebrovascular malformations and hemorrhagic diseases; (ii) Author of Meniere's disease or epilepsy; (iii) Allergic constitution;(iv) Patients with liver and kidney dysfunction, cardiac insufficiency, hematopoietic system diseases and immune system diseases; (v) Patients with mental disorders and malignant tumors and (vi) Cerebral hemorrhage due to cerebral aneurysms, brain tumors and other brain tumors[5].

Treatment methods

The control group was treated with intravenous infusion of ozagrel sodium injection (Shanxi Huawei Pharmaceutical Co., Ltd., specification: 2 mL: 40 mg, Chinese medicine standard H20067342), and 40 mg of ozagrel sodium was added to 250 mL of 0.9 % sodium chloride injection solution for intravenous infusion, 2 times/d[6]. The observation group was treated with butylphthalide soft capsules (Enbipu Pharmaceutical Co., Ltd., Shiyao Group, specification: 0.1 g, H20050299) combined with intravenous drip of ozagrelsodium. The usage and dosage of ozagrel sodium were the same as those of the control group. Fasting oral butylphthalide 0.2 g/time, three times daily[7]. The efficacy was evaluated after 4 weeks of continuous treatment in both groups.

Observation indicators and detection methods

The CT perfusion imaging parameters, oxidative stress indexes, plaque area and the levels of platelet activating factor (PAF), α-granule membrane protein-140 (GMP-140), fibrinogen (FIB), 7(HIF-1α) and matrix metalloproteinases-9 (MMP-9) were recorded before and after treatment in the two groups, and the total effective rate and adverse reaction rate of the two groups were counted.

CT perfusion imaging (CTPI) was used to obtain cerebral blood perfusion information before treatment and 4 weeks after treatment, respectively. MTT and TTP parameters were obtained after the original image was processed by software. MTT refers to the time required for the contrast agent to pass through the local brain tissue. TTP is the time from the beginning of injection to peak concentration.

The carotid plaque area was detected by ultrasound before treatment and 4 weeks after treatment, respectively. The plaque area refers to the size of atherosclerotic plaque with a thickness of more than 1.1 mm, which is thickened in the intima-media region of the carotid artery and protruding into the lumen. Detection instrument: Philips IE33 color Doppler ultrasound diagnostic apparatus, probe frequency 3.5Hz.

The oxidative stress index SOD was detected by MisraHp photochemical amplification method before treatment and 4 weeks after treatment. MDA was detected by thiobarbituric acid (TBA) colorimetric method, and the levels of serum PAF, GMP-140, NSE, HIF-1α and MMP-9 were detected by enzyme-linked immunosorbent assay (ELISA). The fasting venous blood of patients was collected in the morning, and the serum was centrifuged at a rotational speed of 3000 r/min at 4 °C. The above indexes were detected by ELX800 multi-functional microplate reader of Bertten Company, USA. The kit manufacturer was Shanghai Yaji Biotechnology Co., Ltd. Another blood sample was taken to detect FIB and PAgT by Prone 2048 A automatic coagulation analyzer.

Efficacy criteria

After the end of treatment evaluation, (i) Markedly effective: symptoms, signs disappeared, and maintain > 4weeks without recurrence; (ii) Effective: The frequency and duration of seizures decreased by > 50 % and (iii) Invalid: did not meet the above standards.

Total effective rate = significant efficiency + effective rate.

Statistical method

SPSS19.0 was used to process the data. The measurement index was described as ($\bar{\chi}\pm s$). The t-

test was used for comparison. The χ^2 test was used for comparison of the rates. $P < 0.05$ was statistically significant.

Results and Discussion

Comparison of curative effect between two groups

The total effective rate of the observation group was higher than that of the control group, and the difference was statistically significant ($\chi^2 = 4.640$, $P = 0.031$) as given in Table 1.

Comparison of CT perfusion imaging parameters between two groups

Compared with pretreatment, MTT、TTP decreased compared with pretreatment, and MTT、TTP was shorter than in the control group (P< 0.05) as given in Table 2.

Comparison of PAF, GMP-140, FIB and PAgT between two groups

Compared to pretreatment, PAF、GMP-140 FIB PAgT decreased compared with pretreatment, and the observed group was lower than the control group (P< 0.05) as given in Table 3.

Comparison of oxidative stress indexes between two groups

Compared with pretreatment, SOD increased than pretreatment, MDA decreased than pretreatment, SOD was higher than the control, and MDA was lower than the control (P< 0.05) as given in Table 4.

Note: Comparison with Pre treatment $^{*}P<0.05$; Comparison with control group, $^{\#}P<0.05$

Comparison of NSE, HIF-1α and MMP-9 between two groups

Compared to pretreatment, NSE、HIF-1α、MMP-9 decreased compared with pretreatment, and the observed group was lower than the control group (P< 0.05) as given in Table 5.

Comparison of plaque area between two groups

Compared to pre - treatment, the plaque area decreased compared with pre - treatment, and the observed group was smaller than the control group (P< 0.05) as given in Table 6.

Table 1 — Comparison of curative effect between two groups[n(%)].

Group	Number of cases	Remarkable effect	Effective	Invalid	Total effective rate
Control group	58	22（37.93）	24（41.38）	12（20.69）	46（79.31）
Observation group	58	31（53.44）	23（39.66）	4（6.90）	54（93.10）$^{\#}$

Note: Comparison with control group, $^{\#}P<0.05$。

Table 2 — Comparison of CT perfusion imaging parameters between two groups（ $\bar{\chi}$±s）.

Group	Number of cases	MTT（s）		TTP（s）	
		Before treatment	After treatment	Before treatment	After treatment
Control group	58	7.25±1.87	6.25±1.45*	13.25±2.85	10.35±2.12*
Observation group	58	7.29±1.82	3.12±1.05$^{*\#}$	13.17±2.79	6.75±1.89$^{*\#}$

Note : Comparison with Pre treatment, $^{*}P<0.05$; Comparison with control group, $^{\#}P<0.05$。

Table 3 — Comparison of PAF, GMP-140, FIB and PAgT between the two groups（ $\bar{\chi}$±s）.

Group	Number of cases	PAF（%）		GMP-140（g/L）		FIB（g/L）		PAgT（%）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	58	124.36±38.96	105.75±23.24*	46.21±9.22	40.12±4.87*	2.78±0.61	2.42±0.53*	85.63±15.45	61.02±12.36*
Observation group	58	120.84±42.05	90.36±16.47$^{*\#}$	46.14±8.63	34.56±3.66$^{*\#}$	2.75±0.68	2.01±0.37$^{*\#}$	82.66±16.79	47.63±11.69$^{*\#}$

Note : Comparison with Pre treatment, $^{*}P<0.05$; Comparison with control group, $^{\#}P<0.05$。

Table 4 — Comparison of oxidative stress indexes between the two groups（ $\bar{\chi}$±s）.

Group	Number of cases	SOD（U/mL）		MDA（nmol/L）	
		Before treatment	After treatment	Before treatment	After treatment
Control group	58	78.52±13.36	89.25±14.75*	8.44±2.03	7.02±1.54*
Observation group	58	75.92±12.77	97.26±16.33$^{*\#}$	8.47±1.95	5.94±1.36$^{*\#}$

Note : Comparison with Pre treatment, $^{*}P<0.05$; Comparison with control group, $^{\#}P<0.05$

Table 5 — NSE and HIF-1 in 2 groups and comparison of MMP-9（ $\bar{\chi}$±s）.

Group	Number of cases	NSE（μg/L）		HIF-1α（pg/mL）		MMP-9（ng/L）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	58	14.23±2.56	11.05±2.03*	351.25±85.66	284.02±41.03*	215.36±57.22	132.63±35.85*
Observation group	58	14.21±2.61	9.25±1.47*#	346.27±96.14	248.66±32.14*#	204.63±61.47	85.22±21.05*#

Note : Comparison with Pre treatment, *P<0.05; Comparison with control group, #P<0.05。

Table 6 — Comparison of plaque area between two groups（ $\bar{\chi}$±s，mm^2）.

Group	Number of cases	Plaque area	
		Before treatment	Post-treatment
Control group	58	26.78±5.25	20.93±3.36*
Observation group	58	26.54±6.37	19.11±3.05*#

Note : Comparison with Pre treatment, *P<0.05; Comparison with control group, #P<0.05。

Table 7 — Comparison of adverse reactions between the two groups[n(%)].

Group	Number of cases	Rash	Elevated transaminase	Gastrointestinal reaction	Total
Control group	58	1（1.72）	2（3.45）	1（1.72）	4（6.90）
Observation group	58	2（3.45）	3（5.17）	1（1.72）	6（10.34）

Comparison of adverse reactions between two groups

In the difference were compared with the control group (χ^2= 0.438, Pχ^2= 0.508) as given in Table 7.

Ozagrel sodium is a thromboxane synthase inhibitor that can directly act on the α chain of cellulose protein, inhibit thrombosis, expand cerebral vessels and improve local cerebral ischemia symptoms. However, its hemorrhagic complications limit its clinical application to a certain extent, and it is necessary to closely observe hemorrhagic adverse reactions in application. The active component of butylphthalide is racemic-3-n-butylphthalide, which can inhibit platelet aggregation, improve micro-circulation in cerebral ischemia area, reduce cerebral infarction area, and inhibit thromboxane A2 synthesis to alleviate cerebral vasospasm8,9. A large number of studies have found that butylphthalide has a satisfactory effect in improving the prognosis of patients with acute cerebral infarction10. Wang Mingyu et al. used butylphthalide sequential therapy combined with sodium ozagrel in the treatment of transient ischemic attack, found that it can better improve brain energy metabolism and ischemic microcirculation, control the ischemic area of brain tissue.

This study found that the total effective rate of butylphthalide combined with ozagrel sodium was higher than that of ozagrel sodium alone, and the plaque area of patients after treatment was smaller than that of ozagrel sodium alone. The adverse reaction rates of the two groups were similar. This result is basically consistent with the reported clinical research[11]. CTPI technology can detect abnormal cerebral hemodynamics in the early stage, and indirectly reflect the insufficient blood supply of brain tissue through MTT and TTP extension. This study found that MTT and TTP of patients treated with butylphthalide combined with sodium ozagrel were shorter than those treated with sodium ozagrel alone[12]. The results suggest that butylphthalide combined with sodium ozagrel in the treatment of transient ischemic attack can improve cerebral perfusion and have a good correction effect on cerebral insufficiency. This is because butylphthalide can relax blood vessels by promoting the release of NO and PGI2 from vascular endothelial cells, inhibiting the release of glutamate, reducing intracellular calcium concentration, improving local cerebral blood perfusion and increasing the number of capillaries in ischemic areas to improve microcirculation[12].

When transient cerebral insufficiency occurs, the energy metabolism of brain cells is dominated by hypoxic metabolism. Under hypoxic conditions, reactive oxygen species are generated in large quantities, resulting in lipid peroxidation damage of biofilm and formation of MDA in large quantities.SOD is an important antioxidant enzyme in the human body[13-18]. After the occurrence of peroxidation, SOD is depleted in large quantities, resulting in a decrease.NSE is an acidic protease with very small serum content, but it is released into the blood after neuronal injury, resulting in elevated serum NSE levels, so its serum level can reflect the

degree of nerve injury.HIF-1α is a hypoxia-induced factor, which is highly expressed under hypoxia and initiates the transcription of downstream element genes[14,15]. MMP-9 can cause plaque shedding and thrombosis by degrading extracellular matrix, increasing the risk of ischemic cerebrovascular disease[16]. This study found that the SOD level of patients treated with butylphthalide combined with sodium ozagrel was higher than that of patients treated with sodium ozagrel alone, and the levels of MDA, NSE, HIF-1α and MMP-9 were lower than those of patients treated with sodium ozagrel alone[17].The results suggest that butylphthalide combined with sodium ozagrel in the treatment of transient ischemic attack can protect neurons by reducing oxidative stress injury and inhibiting platelet activation.

Transient ischemic attack is a special type of ischemic cerebrovascular disease, which can progress into acute cerebral infarction if not treated in time. Active antithrombotic and antiplatelet therapy is the main treatment[18]. The therapeutic effect of sodium ozagrel alone is not ideal, and it is easy to cause hemorrhagic complications. In this study, on the basis of sodium ozagrel combined with butylphthalide treatment, found that it can improve the curative effect, and does not increase adverse reactions. In this study, the oxidative stress indexes and nerve injury indexes were preliminarily determined. Reducing oxidative stress injury, inhibiting platelet activation and protecting neurons were the important mechanisms of butylphthalide combined with sodium ozagrel in the treatment of this disease.

Conclusion

In summary, butylphthalide combined with ozagrelsodium in the treatment of transient is chemic attack can effectively control symptoms, improve cerebral perfusion, reduce oxidative stress injury, reduce plaque, and do not increase adverse reactions.

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