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Clinical study of the improvement of butylphthalide combined with edaravone therapy on neural functional recovery in acute cerebral infarction after interventional therapy

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ABSTRACT

Objective: To study the improvement value of butylphthalide combined with edaravone therapy on neural functional recovery in acute cerebral infarction after interventional therapy. **Methods:** Patients with acute cerebral infarction who received interventional therapy in our hospital from May 2012 to May 2015 were randomly divided into antioxidant group and control group, control group received conventional anti-platelet and lipid-lowering therapy, antioxidant group received butylphthalide and edaravone on the basis of conventional treatment, and the levels of serum oxygen free radicals, oxidation products, antioxidants and S100 β were determined. **Results:** 3 d after treatment, serum •OH, •O_2, NO• and •ONOO- content of both antioxidant group and control group were lower than those instantly after interventional therapy, and serum •OH, •O_2, NO• and •ONOO- content of antioxidant group 3 d after treatment were lower than those of control group; 3 d after treatment, serum MDA and AOPP content of antioxidant group were significantly lower than those of control group while SOD and GSH content were significantly higher than those of control group; 3 d, 5 d and 7 d after treatment, serum S100 β levels of both antioxidant group and control group were lower than those instantly after interventional therapy, and serum S100 β levels of antioxidant group 3 d, 5 d and 7 d after treatment were lower than those of control group. **Conclusion:** Butylphthalide combined with edaravone therapy for acute cerebral infarction after interventional therapy can improve neural functional recovery, and the functioning molecular target of the treatment is to remove oxygen free radicals.

1. Introduction

Acute cerebral infarction is a common neurological emergency with abrupt onset and rapid development, both morbidity and mortality rates are high, and it has caused great harm to both life safety and quality of life of patients. With the development of cerebrovascular interventional therapy technology in recent years, early intervention after the occurrence of cerebral infarction can effectively recanalize the infracted cerebral vessels, restore blood perfusion of brain tissue and block nerve function injury caused by ischemia hypoxia. Nevertheless, brain tissue can produce a variety of adverse metabolic products during ischemia hypoxia process and continue to produce neurotoxicity. The oxygen free radicals are the important metabolic products of nerve damage, and removal of oxygen free radicals can improve the recovery of neural function[1,2]. Butylphthalide and edaravone are two drugs with free radical scavenging effect, the existing studies have confirmed the above two drugs can improve the neural function in patients with cerebral infarction[3,4], but there is no clear research on the specific functioning molecular targets. In the following study, the improvement value of butylphthalide combined with edaravone therapy on neural functional recovery in acute cerebral infarction after interventional therapy as well as the scavenging effect on

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oxygen free radicals was analyzed, and the specific results were as follows.

2. Subjects and methods

2.1. Subjects

A total of 68 cases of patients with acute cerebral infarction who received interventional therapy in our hospital from May 2012 to May 2015 were selected as research subjects, all patients were diagnosed with cerebral infarction through head CT or MRI, they were treated in Emergency of the hospital within 6h after onset, and they received emergency interventional therapy. Patients with previous history of cerebral infarction and interventional therapy and those with cerebral hemorrhage were ruled out. After signing informed consent, the included patients were randomly divided into antioxidant group and control group: (1) antioxidant group: 34 cases of patients included 22 male cases and 12 female cases who were (54.9±7.3) years old; (2) control group: 34 cases of patients included 20 male cases and 14 female cases who were (55.2±7.8) years old. The comparison of general information between two groups showed no significant difference.

2.2. Treatment methods

Both groups received emergency interventional therapy and routine anti-platelet and lipid-lowering therapy after intervention, and the methods were as follows: Bayaspirin Enteric-coated Tablets 100 mg, oral administration, 1/day, Clopidogrel Hydrogen Sulphate Tablets 75 mg, oral administration, 1/day and Atorvastatin 20 mg, oral administration, 1/day, for consecutive half a year. Observation group received butylphthalide combined with edaravone therapy on the basis of routine therapy, and the methods were as follows: Butylphthalide Soft Capsules 0.2 g, oral administration, 3/day and edaravone (specification 30 mg) in 100 mL saline, intravenous drip, 2/day, for consecutive 14 d.

2.3. Neural functional recovery assessment methods

Serum specimens instantly after interventional therapy and 3 d after treatment were collected, and free radical kit was used to determine hydroxyl free radical (•OH), superoxide anion free radical ($•O_2$), nitric oxide free radical (NO•) and nitro free radical (•ONOO-) content; serum specimens 3 days after treatment were collected, and enzyme-linked immunosorbent kit was used to determine malondialdehyde (MDA), advanced oxidation protein product (AOPP), superoxide dismutase (SOD) and glutathione (GSH) content; serum specimens instantly after interventional therapy as well as and 3 d, 5 d and 7 d after treatment were collected, and enzyme-linked immunosorbent kit was used to determine S100 β protein content.

2.4. Statistical methods

SPSS 21.0 software was used to input data, measurement data between two groups was analyzed by t test, data within group at different points in time was by repeated measures analysis of variance and $P<0.05$ indicated statistical significance in differences.

3. Results

3.1. Imaging characteristics of infarction lesions

Before interventional therapy, head CT images of typical cases in both antioxidant group and control group showed obvious infarction lesions; 1 week after interventional therapy, head CT images of typical cases in antioxidant group and control group still showed visible infarction lesions, the area of infarction lesions of antioxidant group was less and the absorption was more ideal.

3.2. Oxygen free radical content

Instantly after interventional therapy, serum •OH, $•O_2$, NO• and •ONOO- content of antioxidant group and control group were not statistically different ($P>0.05$); 3 days after treatment, serum •OH, $•O_2$, NO• and •ONOO- content of both antioxidant group and control group were lower than those instantly after interventional therapy, and differences within the same group at different points in time were significant ($^aP<0.05$); serum •OH, $•O_2$, NO• and •ONOO- content of antioxidant group 3 days after treatment were lower than

Table 1.
Comparison of oxygen free radical content before and after treatment.

Group	Treatment conditions	•OH(nmol/L)	$•O_2$(nmol/L)	NO•(nmol/L)	•ONOO-(nmol/L)
Antioxidant	Instantly after intervention	103.4±15.1	55.2±7.8	43.8±6.3	77.5±10.4
	3 d after treatment	32.3±6.5^{ab}	9.3±1.1^{ab}	11.4±1.7^{ab}	23.3±4.1^{ab}
Control	Instantly after intervention	105.1±14.7	56.4±8.1	41.9±7.2	78.1±9.3
	3 d after treatment	70.5±9.2^{a}	23.1±4.8^{a}	23.1±4.9^{a}	50.2±8.9^{a}

Comparison within the same group at different points in time showed differences, $^aP<0.05$; differences between two groups at the same point in time were significant, $^bP<0.05$.

those of control group, and differences between two groups 3 days after treatment were significant ($^bP<0.05$).

3.3. Content of oxidation products and antioxidants

(1) analysis of serum oxidation product content of two groups 3 d after treatment was as follows: serum MDA and AOPP content of antioxidant group were significantly lower than those of control group; (2) analysis of serum antioxidant content of two groups 3 d after treatment was as follows: serum SOD and GSH content of antioxidant group were significantly higher than those of control group; differences in the content of oxidation products and antioxidants were significant between two groups 3 days after treatment ($P<0.05$).

3.3. Nerve injury marker molecule

Instantly after interventional therapy, serum S100 β levels of antioxidant group and control group were not statistically different ($P>0.05$); 3 d, 5 d and 7 d after treatment, serum S100 β levels of both antioxidant group and control group were lower than those instantly after interventional therapy, and differences within the same group at different points in time were significant ($^aP<0.05$); serum S100 β levels of antioxidant group 3 d, 5 d and 7 d after treatment were lower than those of control group, and differences between two groups at different points in time after treatment were significant ($^bP<0.05$).

4. Discussion

Interventional therapy is the preferred method for emergency treatment of acute cerebral infarction, and can effectively recanalize the infracted cerebral vessels, restore blood perfusion of brain tissue and block the damaging effect of ischemia hypoxia on nerves. After the occurrence of cerebral infarction, early interventional treatment to restore blood perfusion of brain tissue can maximum reduce nerve function damage and improve patients′ prognosis. However, brain tissue has gone through a period of ischemia hypoxia and had irreversible function damage before interventional therapy, and metabolites under ischemia hypoxia condition will continue to damage neural function after interventional therapy and impact reconstruction and recovery of neurological function. In hypoxia phase and hypoxia-reoxygenation phase, massively produced oxygen free radicals in local tissue are the important materials to cause nerve tissue damage, regular neurotrophic treatment after interventional therapy can't effectively remove local oxygen free radicals, thus oxygen free radicals can continue to cause damage to nerve tissue after interventional therapy[5,6].

In recent years, the nerve injury effect of oxygen free radicals in the process of cerebral infarction has received more and more attention from neurologists, and removal of oxygen free radicals has become the important molecular target to improve neural function after cerebral infarction[7]. Edaravone is a kind of antioxidant, is strongly fat-soluble and can reach brain tissue through the blood-brain barrier, eliminate oxygen free radicals in local cerebral infarction lesions, reduce oxidative stress response mediated by oxygen free radicals and protect neurons and endothelial cells[8,9]. Butylphthalide is a kind of synthetic L-butylphthalide that can increase blood flow in ischemic brain tissue, improve microvascular perfusion, enhance the activity of antioxidant enzymes and inhibit the production of oxygen free radicals[10,11]. Study has shown that edaravone combined with butylphthalide can improve neural function in patients with acute cerebral infarction[12], but it is not yet clear whether the above two drugs can directly remove oxygen free radicals in patients with acute cerebral infarction.

In this study, edaravone combined with butylphthalide was adopted after interventional treatment of acute cerebral infarction, aiming

Table 2.
Comparison of the content of oxidation products and antioxidants after treatment.

Group	Oxidation products		Antioxidants	
	MDA (μmol/L)	AOPP (μmol/L)	SOD (U/mL)	GSH (U/mL)
Antioxidant	5.36±0.82	64.4±10.3	145.2±17.9	94.7±11.6
Control	8.94±1.19	89.6±12.7	93.4±11.6	40.3±6.8
T	8.182	8.893	7.182	12.591
P	<0.05	<0.05	<0.05	<0.05

Table 3.
Comparison of serum S100 β levels after treatment (ng/L).

Group	Instantly after intervention	3 d after treatment	5 d after treatment	7 d after treatment
Antioxidant	2.58±0.33	1.55±0.19^{ab}	1.12±0.14^{ab}	0.78±0.09^{ab}
Control	2.62±0.29	2.14±0.32^{a}	1.77±0.21^{a}	1.40±0.22^{a}
T	0.392	6.023	7.8963	9.222
P	>0.05	<0.05	<0.05	<0.05

Comparison within the same group at different points in time showed differences, $^aP<0.05$; differences between two groups at the same point in time were significant, $^bP<0.05$.

at exerting the scavenging effect of these two drugs on oxygen free radicals. In order to define the application value of edaravone combined with butylphthalide after interventional therapy, the imaging data was compared to directly reflect the absorption of cerebral infarction lesions, and head CT showed that the absorption of infarction lesions of antioxidant group was better than that of control group, which confirmed the positive value of edaravone combined with butylphthalide for the treatment of acute cerebral infarction. Both edaravone and butylphthalide can remove oxygen free radicals, common oxygen free radicals in the body include hydroxyl free radical (•OH), superoxide anion free radical ($•O_2$), nitric oxide free radical (NO•) and nitro free radical (•ONOO-), and the analysis of the content of oxygen free radicals in serum showed that serum •OH, $•O_2$, NO• and •ONOO- content of antioxidant group after treatment were lower than those of control group. Thus it confirms that the application of edaravone combined with butylphthalide therapy after interventional treatment of acute cerebral infarction can more effectively remove oxygen free radicals. Massively produced oxygen free radicals within cerebral infarction lesions can cause peroxidation of a variety of components in cellular structure. Peroxidation product of lipid component in biomembrane structures of cell membrane and organelle is MDA, peroxidation product of protein component is AOPP, and determining the content of MDA and AOPP can indirectly reflect the oxygen free radical generation. The body itself has natural antioxidants, among which GSH and SOD are the two main antioxidant enzymes that will be massively consumed in the continuous generation process of oxygen free radicals[13]. In the study, the analysis of the content of serum oxidation products and antioxidants after treatment proved that serum MDA and AOPP content of antioxidant group were significantly lower than those of control group while SOD and GSH were significantly higher than those of control group. This means that edaravone combined with butylphthalide therapy can reduce the generation of peroxidation products and the consumption of antioxidant enzymes, and then confirms that the oxygen free radicals are effectively removed. In addition, the nerve injury marker molecule S100 β levels in serum were followed up within 1 week after treatment[14,15] in order to reflect the protective effect of edaravone combined with butylphthalide therapy on neural function, and serum S100 β levels of antioxidant group 3 d, 5 d and 7 d after treatment were significantly lower than those of control group.

To sum up, butylphthalide combined with edaravone therapy for acute cerebral infarction after interventional therapy can improve neural functional recovery, and the functioning molecular target of the treatment is to remove oxygen free radicals.

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