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Effect of early rehabilitation training on oxygen free radical generation and nerve injury in patients with cerebral hemorrhage

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ABSTRACT

Objective: To study the effect of early rehabilitation training combined with edaravone on oxygen free radical generation and nerve injury in patients with cerebral hemorrhage. **Methods:** A total of 56 patients with acute cerebral hemorrhage who were treated in Zigong Third People′s Hospital between July 2014 and March 2017 were selected and randomly divided into early rehabilitation group and routine rehabilitation group, the early rehabilitation group began the rehabilitation training 2 d after cerebral hemorrhage condition was stabilized, and routine rehabilitation group began the rehabilitation training 14 d after cerebral hemorrhage. Serum contents of oxygen free radicals, nerve injury markers and neurotrophic molecules were detected 28 d and 56 d after cerebral hemorrhage. **Results:** 28 d and 56 d after cerebral hemorrhage, serum MDA, AOPP, 8-OHdG, GFAP, NSE, Tf, Ft and S100B levels of early rehabilitation group were significantly lower than those of routine rehabilitation group while BDNF, NGF, NTF-α and IGF-I levels were significantly higher than those of routine rehabilitation group. **Conclusion:** Early rehabilitation training combined with edaravone for cerebral hemorrhage can inhibit the oxygen free radical generation, reduce the degree of nerve injury and improve the neurotrophic state.

1. Introduction

Cerebral hemorrhage is a common clinical cerebrovascular disease with high fatality rate and disability rate. Although the diagnosis and treatment of cerebral hemorrhage has been improved and the mortality of the disease has decreased in recent years, the high morbidity will still affect patients' daily life and also increase the burden on the family and society[1,2]. Edaravone is the drug that has scavenging effect on oxygen free radicals, can remove the continuously generated oxygen free radicals in hematoma lesions and alleviate neuronal oxidative stress damage, and is beneficial to the recovery of neural function[3]. Rehabilitation training has been an important means of improving neurological function, and routine rehabilitation training begins 14 d after haemorrhage[4,5]. In recent years, the concept of early rehabilitation training advocates that the rehabilitation training begins from the 2nd day after the stabilization of the neurological symptoms, which could help the recovery and reconstruction of nerve functions. In the following studies, we analyzed the effect of early rehabilitation training on oxygen free radical generation and nerve injury in patients with cerebral hemorrhage.

2. Case information and research methods

2.1 General case information

A total of 56 patients with acute cerebral hemorrhage who were treated in Zigong Third People's Hospital between July 2014 and March 2017 were selected as research subjects, all patients were with cerebral hemorrhage lesions confirmed by skull CT and with bleeding < 30 mL, and they were with limb dysfunction on admission, without serious disturbance of consciousness, and with Glasgow coma scale > eight points; patients with history of cerebral hemorrhage and cerebral infarction, and patients complicated with severe heart, liver and kidney injury were excluded. Random number table was used to divide the enrolled 56 patients with cerebral hemorrhage into two groups, each with 28 cases. Early

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rehabilitation group included 16 men and 12 women that were 49-76 years old; the routine rehabilitation group included 18 men and 10 women that were 47-77 years old. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Clinical therapy

The two groups of patients received conventional symptomatic therapy such as controlling blood pressure, maintaining water electrolyte balance, dehydration and brain cell activator, and surgical hematoma suction and drainage were performed if necessary. Control group, on the basis of conventional symptomatic treatment, received edaravone anti-free radical treatment, and the method was as follows: edaravone 30 mg in 100 mL of saline, by intravenous drip, 2 times/d, for 14 consecutive days of treatment; regular rehabilitation training began 14 d later. On the basis of routine symptomatic treatment, the observation group received edaravone anti-free radical treatment, and the method was the same as that of control group. When the nervous system was no longer progressing, rehabilitation training began 2 d later. The training contents of the two groups included the correct placement of body position, passive activity of limb joints, arms lifting and swinging training, turning over and sitting, standing and walking, language, swallowing, etc.

2.3 Serum index detection

28 d and 56 d after cerebral hemorrhage, 5 mL of cubital venous blood was collected respectively and centrifuged to separate serum, radioimmunoprecipitation kit was used to detect malondialdehyde (MDA), advanced oxidation protein products (AOPP) and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels, and enzyme-linked immunosorbent assay kit was used to determine the contents of glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), transferrin (Tf), ferritin (Ft), S100 β protein, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophic factor-α (NTF-α) and insulin-like growth factor-I (IGF-I).

2.4 Statistical methods

SPSS 19.0 software was used to input data, differences in measurement data between two groups were by t test, and P<0.05 indicated statistical significance in differences in test results.

3. Results

3.1 Serum oxygen free radical levels

28 d and 56 d after cerebral hemorrhage, analysis of serum oxygen free radicals-related indexes MDA (μmol/L), AOPP (μmol/L) and 8-OHdG (μg/L) between two groups of patients was as follows: serum MDA, AOPP and 8-OHdG levels of early rehabilitation group 28 d and 56 d after cerebral hemorrhage were significantly lower than those of routine rehabilitation group. Differences in serum MDA, AOPP and 8-OHdG levels were statistically significant between two groups of patients 28 d and 56 d after cerebral hemorrhage (P<0.05).

3.2 Serum nerve injury marker levels

28 d and 56 d after cerebral hemorrhage, analysis of serum nerve injury markers GFAP (pg/mL), NSE (ng/mL), Tf (μg/mL), Ft (ng/mL) and S100B (ng/mL) between two groups of patients was as follows: serum GFAP, NSE, Tf, Ft and S100B levels of early rehabilitation group 28 d and 56 d after cerebral hemorrhage were significantly lower than those of routine rehabilitation group. Differences in serum GFAP, NSE, Tf, Ft and S100B levels were statistically significant between two groups of patients 28 d and 56 d after cerebral hemorrhage (P<0.05).

Table 1.
Serum oxygen free radical levels after treatment.

Groups	n	Time	MDA	AOPP	8-OHdG
Early rehabilitation group	28	28 d after cerebral hemorrhage	11.39±1.74*	79.65±8.94*	5.63±0.68*
		56 d after cerebral hemorrhage	8.21±1.04*	62.14±7.81*	8.94±1.05*
Routine rehabilitation group	28	28 d after cerebral hemorrhage	18.53±2.23	113.25±14.59	7.63±0.93
		56 d after cerebral hemorrhage	13.49±1.87	101.32±13.26	10.93±1.25

*: index comparison between early rehabilitation group and routine rehabilitation group, P<0.05.

Table 2.
Serum nerve injury marker levels after treatment.

Groups	n	Time	GFAP	NSE	Tf	Ft	S100B
Early rehabilitation group	28	28 d after cerebral hemorrhage	2.03±0.28*	38.72±5.52*	2.95±0.36*	221.3±33.2*	1.37±0.19*
		56 d after cerebral hemorrhage	1.52±0.18*	30.21±3.58*	2.41±0.33*	183.1±22.6*	1.13±0.15*
Routine rehabilitation group	28	28 d after cerebral hemorrhage	3.11±0.45	58.11±7.92	4.03±0.56	303.5±37.2	2.09±0.29
		56 d after cerebral hemorrhage	2.42±0.29	42.36±5.96	3.25±0.41	252.1±33.2	1.78±0.22

*: index comparison between early rehabilitation group and routine rehabilitation group, P<0.05.

Table 3.
Serum neurotrophic molecule levels after treatment.

Groups	*n*	Time	BNDF	NGF	NTF-α	IGF-I
Early rehabilitation group	28	28 d after cerebral hemorrhage	5.87±0.72*	0.83±0.10*	2.39±0.34*	42.31±4.52*
		56 d after cerebral hemorrhage	7.03±0.89*	0.98±0.12*	3.71±0.46*	54.22±7.04*
Routine rehabilitation group	28	28 d after cerebral hemorrhage	4.64±0.59	0.64±0.08	1.70±0.22	33.47±4.07
		56 d after cerebral hemorrhage	5.71±0.75	0.72±0.09	1.98±0.24	41.28±5.13

*: index comparison between early rehabilitation group and routine rehabilitation group, $P<0.05$.

3.3 Serum neurotrophic molecule levels

28 d and 56 d after cerebral hemorrhage, analysis of serum neurotrophic molecules BDNF (ng/mL), NGF (ng/mL), NTF-α (ng/mL) and IGF-I (nmol/L) between two groups of patients was as follows: serum BDNF, NGF, NTF- and IGF-I levels of early rehabilitation group 28 d and 56 d after cerebral hemorrhage were significantly higher than those of routine rehabilitation group. Differences in serum BDNF, NGF, NTF-α and IGF-I levels were statistically significant between two groups of patients 28d and 56d after cerebral hemorrhage ($P<0.05$).

4. Discussion

Intracerebral hemorrhage has high morbidity, bleeding lesion damage to neural function can cause damage to limb function, language function, swallowing function, cognitive function and so on, and the nerve injury left in the recovery process will affect patients' daily life, and also add burden to family and society. Cerebral hemorrhage can cause nerve function damage by direct damage factors and indirect damage factors, bleeding lesion compression on brain tissue is a direct cause of nerve damage, and continuous production of adverse metabolites in the lesion is the indirect cause of nerve damage. Oxygen free radicals are important toxic by-products that cause damage to nerve function. In the process of oxidative stress reaction activation, oxygen free radicals are massively produced and cause oxidative damage to brain tissue. Edaravone is a drug that scavenges free radicals and is used for treatment of brain hemorrhage. Rehabilitation training is the important way to promote neural functional recovery in patients with cerebral hemorrhage, previous study believed that 14 d after hemorrhage is the right time to begin rehabilitation training, and new research shows that early rehabilitation training 2 d after neurological symptoms are stable can more effectively promote neural functional recovery[6].

In recent years, the value of early rehabilitation training to promote the recovery of nerve function after cerebral hemorrhage has received more and more attention[7], but the specific mechanism for early rehabilitation to promote neuronal function recovery is still unclear. Excessive oxygen free radical generation is the most critical factor in neural functional secondary injury after intracerebral hemorrhage, and continuously generated oxygen free radicals can cause damage to the structures of neurons, glial cells and endothelial cells, and then lead to oxidative stress damage[8]. The lipid, protein and nucleic acid in cellular structure are vulnerable to oxygen free radicals, which can cause cell membrane, mitochondria, nucleus and other structure damage after they are oxidized, and also generate the corresponding oxidation products of MDA, AOPP and 8-OHdG[9,10]. In order to define the effect of early rehabilitation training on oxygen free radical generation in patients with cerebral hemorrhage, the changes in serum levels of above oxidation products were analyzed after treatment in the study, and the results showed that serum MDA, AOPP and 8-OHdG levels of early rehabilitation group 28 d and 56 d after cerebral hemorrhage were significantly lower than those of routine rehabilitation group. This indicates that early rehabilitation training can be more effective than conventional rehabilitation training in inhibiting the generation of oxygen free radicals and reducing the oxidative stress injury of nerve function.

The damage of neurons and glial cells in pathogenesis of cerebral hemorrhage can directly cause the release of multiple molecules from cells into cerebrospinal fluid, which enter into the blood circulation through the damaged blood-brain barrier. GFAP, NSE and S100B are the important molecules in nerve cells, GFAP is mainly expressed in glial cells and participates in the regulation of cytoskeleton form [11], and the NSE and S100B are mainly expressed in neurons and participate in the regulation of glycolysis process, calcium homeostasis[12,13]. Tf and Ft are the main forms of iron ions in the body. Cerebral hemorrhage causes massive hemoglobin decomposition and increases iron ion generation, which is characterized by the increase of Tf and Ft levels[14]; the over-generated iron ion will further increase the generation of oxygen free radicals and promote the activation of oxidative stress response[15]. In order to define the effect of early rehabilitation training on nerve damage in patients with cerebral hemorrhage, the changes in serum levels of above nerve injury molecules were analyzed after treatment in the study, and the result showed that serum GFAP, NSE, Tf, Ft and S100B levels of early rehabilitation group 28 d and 56 d after cerebral hemorrhage were significantly lower than those of routine rehabilitation group. This indicates that early rehabilitation training can be more effective than conventional rehabilitation training in reducing the release of nerve injury molecules and reducing the degree of nerve injury.

The recovery and reconstruction of nerve function in the recovery of cerebral hemorrhage depend on various cytokines with neurotrophic function, such as BDNF, NGF, NTF-α and IGF-I. BDNF and NGF are cytokines that promote growth, which can promote neuron

regeneration, axon growth and synaptic structure formation, and is conducive to the reconstruction of neurologic functions[16,17]; NTF-α is a kind of cytokine that can improve the neurotrophic state, and it can avoid the excessive damage and apoptosis of neurons and thus promote the reconstruction of neurologic function[18,19]; IGF-I is a cytokine with extensive proliferation-promoting effect, which can promote the proliferation of neurons and endothelial cells, and can improve nerve function and increase collateral circulation[20]. In order to further clarify the effect of early rehabilitation training on the degree of nerve injury in patients with cerebral hemorrhage, the changes in serum levels of neurotrophic molecules were analyzed after treatment in the study, and the results showed that serum BDNF, NGF, NTF-α and IGF-I levels of early rehabilitation group 28 d and 56 d after cerebral hemorrhage were significantly higher than those of routine rehabilitation group. This means that the early rehabilitation training is more effective than conventional rehabilitation training in promoting the secretion of neurotrophic molecules, thus improving the neurotrophic status, promoting nerve function reconstruction and alleviating nerve damage.

Early rehabilitation training combined with edaravone for cerebral hemorrhage can be more effective than conventional rehabilitation training combined with edaravone in inhibiting oxygen free radical generation, relieving nerve injury and improving neurotrophic status.

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