Effect of rehabilitation training combined with neurotrophic therapy on the nerve cytokine secretion and oxidative stress in rehabilitation period of patients with traumatic brain injury

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ABSTRACT

Objective: To study the effect of rehabilitation training combined with neurotrophic therapy on the nerve cytokine secretion and oxidative stress in rehabilitation period of patients with traumatic brain injury. Methods: A total of 98 patients in rehabilitation period of traumatic brain injury who were treated in our hospital between July 2013 and September 2016 were collected and divided into control group and observation group according to the random number table method, and 49 cases in each group. Control group received regular neurotrophic therapy, and observation group received rehabilitation training combined with neurotrophic therapy. The differences in the contents of nerve cytokines and oxidative stress indexes were compared between the two groups before and after intervention. Results: Before intervention, differences in serum levels of nerve injury indexes, neurotrophy indexes, amino acid neurotransmitters and oxidative stress indexes were not statistically significant between the two groups of patients. After intervention, serum nerve injury indexes MBP, NGB, NSE and S-100B levels as well as excitatory amino acids Glu and Asp levels of observation group were lower than those of control group; neurotrophy indexes BDNF and GDNF levels as well as inhibitory amino acids GABA and Gly levels were higher than those of control group; serum oxidative stress indexes SOD and CAT levels were higher than those of control group; MDA level was lower than that of control group. Conclusions: Rehabilitation training combined with neurotrophic therapy can effectively optimize the nerve function and reduce the systemic oxidative stress state of patients in rehabilitation period of traumatic brain injury.

1. Introduction

Traumatic brain injury can lead to different degree of neurologic injury, patients are in rehabilitation period after emergency operation, and the reasonableness of intervention method in this stage will directly determine the prognosis and quality of life of patients[1,2]. Adding exogenous neurotrophic drug treatment in rehabilitation period is the method to treat patients with traumatic brain injury, which helps the recovery of damaged neuron function and the improvement of language and limb function, but its curative effect has limitations, and some patients are still have serious physical dysfunction. Rehabilitation training is the language and limb function training under the help of specialists, which can effectively enhance the tissue muscle strength in damaged parts and help restore the nerve - muscle reflex, and its effect on nerve cell function in patients with brain injury has received extensive attention[3,4]. In the study, rehabilitation training was added on the exogenous neurotrophic drug therapy, and its roles were discussed from the nerve cell secretion function, oxidative stress state and other aspects in order to clarify the advantages of combination therapy.

2. Materials and methods

2.1 Case information

A total of 98 patients in rehabilitation period of traumatic brain injury who were treated in our hospital between July 2013 and September 2016 were collected, and the families of the patients signed the informed consent. According to the random number table...
method, the enrolled patients were divided into control group and observation group. 49 cases in each group. Control group included 26 males and 23 females who were 32-78 years old; observation group included 27 males and 22 females who were 34-75 years old. There was no significant difference in gender and age distribution between the two groups (P>0.05), and the hospital ethics committee approved the study.

Inclusion criteria: (1) made clear the history of brain injury and successfully completed the operation; (2) had different degree of residual mental and limb dysfunction; (3) had normal functions before brain injury; (4) coordinated the rehabilitation therapy. Exclusion criteria: (1) had abnormal combined basic cognitive function and unable to cooperate with the implementation of rehabilitation exercise; (2) had systemic infectious diseases; (3) had risk factors for brain injury unrelated to brain injury, such as cerebrovascular malformation and brain tumors.

2.2 Therapy

Control group of patients received routine neurotrophic treatment for patients in rehabilitation period of brain injury, specifically as follows: added 250 mL of saline in 40 mg of ganglioside injection (Qilu Pharmaceutical Co., Ltd., approved by H20056782), adopted the method of intravenous drip, 1 time/d, and 4 weeks as a course of treatment.

On the basis of neurotrophic treatment, observation group of patients received the rehabilitation training, including physical rehabilitation training: (1) early mild physical activity: intervention staff helped the patients with passive muscle strength training, including the upper limb shoulder abduction and extorsion, knuckle flexion, lower limb hip extorsion, knee joint flexion, ankle dorsiflexion, toe flexion and so on, each joint was exercised for 5-10 times each time, 10 min/time, 3-4 times a day. (2) Active training: intervention staff helped the patients with Bobath handshake, bridge-style movement, getting up and sitting down as well as upper and lower limb coordination training. The patients were instructed to conduct balance training, stand and walk, and their ability to dress, wash their face, rinse mouth and other daily activities were exercised after further rehabilitation of the limb function. Language rehabilitation training: (1) preliminary language skill training: the auditory stimuli were strengthened, the tongue, lips, soft palate and other exercise training were conducted at first, and the pronunciation transformation, listening comprehension, picture description and other specific training contents were selected. (2) Practical communication skill training: with the improvement of patients’ language competence, patients were communicated with, 1 time/d, 30min for each time, for continuous 4 weeks of treatment.

2.3 Observation indexes

Before and after intervention, 3-5 mL of fasting cubital venous blood was obtained from two groups of patients, added anticoagulant and centrifuged at low speed (3 500 r/min, 10-15 min) to get the upper serum. Radioimmunoassay was used to detect serum levels of nerve injury indexes myelin basic protein (MBP), neuroglobin (NGB), neuron-specific enolase (NSE) and S-100B protein (S-100B); enzyme-linked immunosorbent assay method was used to detect the levels of neurotrophy indexes brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF); electrochemiluminescence was used to detect the levels of amino acid neurotransmitter glutamic acid (Glu), aspartate (Asp), y-aminobutyric acid (GABA) and glycine (Gly); enzyme-linked immunosorbent assay method was used to detect the serum levels of oxidative stress indexes superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA).

2.4 Statistical methods

The statisticians used software SPSS 24.0 to record and calculate the data in the study. Nerve injury indexes, neurotrophy indexes, amino acid neurotransmitters, oxidative stress indexes and other measurement data were in terms of mean ± standard deviation, comparison within group before and after intervention was done by paired t test and comparison between groups was done by grouping t test. P<0.05 indicated statistical significance in differences.

3. Results

3.1 Nerve injury indexes

Before intervention and after 4-week intervention, comparison of serum nerve injury indexes MBP (ng/L), NGB (pg/mL), NSE (ng/mL) and S-100B (pg/mL) levels between two groups of patients was as follows: before intervention, serum MBP, NGB, NSE and S-100B levels were not significantly different between the two groups of patients (P>0.05); after 4-week intervention, serum MBP, NGB, NSE and S-100B levels of both groups were lower than those before intervention (P<0.05), and serum MBP, NGB, NSE and S-100B levels of observation group after 4-week intervention were lower than those of control group (P<0.05), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>MBP (ng/L)</th>
<th>NGB (pg/mL)</th>
<th>NSE (ng/mL)</th>
<th>S-100B (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>49</td>
<td>Before intervention</td>
<td>0.93±0.15</td>
<td>314.38±39.75</td>
<td>30.47±4.51</td>
<td>1.64±0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After intervention</td>
<td>0.61±0.07</td>
<td>130.27±16.58</td>
<td>17.62±2.14</td>
<td>0.87±0.09</td>
</tr>
<tr>
<td>Observation group</td>
<td>49</td>
<td>Before intervention</td>
<td>0.92±0.17</td>
<td>315.67±36.88</td>
<td>30.42±4.37</td>
<td>1.63±0.21</td>
</tr>
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<td></td>
<td></td>
<td>After intervention</td>
<td>0.35±0.05</td>
<td>59.86±15.75</td>
<td>9.08±1.16</td>
<td>0.52±0.07</td>
</tr>
</tbody>
</table>

*: before intervention vs. after intervention within group, P<0.05; #: observation group vs. control group after intervention, P<0.05.

3.2 Neurotrophy indexes

Before intervention and after 4-week intervention, comparison of serum nerve neurotroph index levels BDNF (pg/mL) and GDNF (ng/mL) between two groups of patients was as follows: before intervention, serum BDNF and GDNF levels were not significantly different between the two groups of patients (P>0.05); after 4-week intervention, serum BDNF and GDNF levels of both groups were lower than those before intervention (P<0.05), and serum BDNF and GDNF levels of observation group after 4-week intervention were lower than those of control group (P<0.05), shown in Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>BDNF (pg/mL)</th>
<th>GDNF (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>49</td>
<td>Before intervention</td>
<td>4.38±0.57</td>
<td>2.11±0.25</td>
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<tr>
<td></td>
<td></td>
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<td>7.17±0.85</td>
<td>3.42±0.28</td>
</tr>
<tr>
<td>Observation group</td>
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<td>Before intervention</td>
<td>4.31±0.54</td>
<td>2.09±0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After intervention</td>
<td>9.64±1.09</td>
<td>4.87±0.57</td>
</tr>
</tbody>
</table>

*: before intervention vs. after intervention within group, P<0.05; #: observation group vs. control group after intervention, P<0.05.

Table 1. Changes in serum nerve injury index levels before and after intervention.

<table>
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<tr>
<th>Groups</th>
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<th>Time</th>
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*: before intervention vs. after intervention within group, P<0.05; #: observation group vs. control group after intervention, P<0.05.

Table 2. Changes in serum neurotrophy indexes before and after intervention.
3.2 Neurotrophy indexes

Before intervention and after 4-week intervention, comparison of serum neurotrophy indexes BDNF (pg/mL) and GDNF (ng/mL) levels between two groups of patients was as follows: before intervention, serum neurotrophy indexes were not significantly different between observation group and control group ($P > 0.05$); serum BDNF and GDNF levels of both groups after 4-week intervention were significantly higher than those before intervention ($P < 0.05$), serum BDNF and GDNF levels of observation group after 4-week intervention were significantly lower than those before intervention, and serum BDNF and GDNF levels of control group after 4-week intervention were significantly higher than those before intervention, as shown in Table 2.

3.3 amino acid neurotransmitters

Before intervention and after 4-week intervention, comparison of serum amino acid neurotransmitters Glu (ng/mL), Asp (ng/mL), GABA (pg/mL) and Gly (pg/mL) levels between two groups of patients was as follows: before intervention, serum levels of amino acid neurotransmitters were not significantly different between observation group and control group ($P > 0.05$); serum excitatory amino acids Glu and Asp levels of both groups after 4-week intervention were significantly lower than those before intervention, while inhibitory amino acids GABA and Gly levels were significantly higher than those before intervention, and serum excitatory amino acids Glu and Asp levels of observation group after 4-week intervention were significantly lower than those of control group while inhibitory amino acids GABA and Gly levels were significantly higher than those of control group.

3.4 Oxidative stress indexes

Before intervention and after 4-week intervention, comparison of serum oxidative stress indexes SOD (U/mL), CAT (U/mL) and MDA (ng/mL) levels was as follows: before intervention, serum levels of oxidative stress indexes were not significantly different between observation group and control group; serum SOD and CAT levels of both groups after 4-week intervention were significantly higher than those before intervention, while MDA levels were significantly lower than those before intervention, and serum SOD and CAT levels of observation group after 4-week intervention were significantly higher than those of control group while MDA level was significantly lower than that of control group.

4. Discussion

There is obvious nerve injury in patients with brain injury, characterized by the dysfunction of intelligence, language, swallowing, limb and other aspects, the patients will still have different levels of dysfunction after emergency operation and positive neurotrophic intervention, it will severely influence the patient’s normal life, even lead to mood disorders and extreme behavior in severe cases. Rehabilitation training is the common method for convalescent functional exercise of patients with nerve injury, but most of the patients have poor compliance and cannot complete the training content, or some families fail to pay enough attention to rehabilitation training and do not conduct regular training after surgery, and a number of scholars speculate that this is an important cause of poor outcome of final treatment in patients with brain injury patients[5-7]. The effect of rehabilitation training on the patients with brain injury mainly focused on the subjective physical activity, muscle strength and other aspects before, there are few studies on the level of serology. In the study, based on conventional neurotrophic therapy, regular rehabilitation training was introduced to patients in rehabilitation period of brain injury, and its roles were discussed from nerve damage, neurotrophy, neurotransmitters, oxidative stress, etc.

There is obvious nerve injury in patients with brain injury, many specific factors leak from inside of the neurons and glial cells into the outside, and enter into the peripheral blood through the damaged blood brain barrier, so their serum levels rise and are mostly closely related to the degree of nerve damage and neurological rehabilitation. MBP, NGB, NSE and S-100B are the typical nerve damage markers that specifically exist in nerve cells under physiological condition, their levels are little in circulating blood, and their high expression mostly indicates the presence of nerve injury and poor clinical treatment effect[8-10]. In the study, serum levels of nerve damage indexes were compared between two groups of patients before and after the intervention, found that serum nerve injury indexes MBP, NGB, NSE and S-100B levels of both groups were lower after intervention compared with those before intervention; further compared with control group, serum MBP, NGB, NSE and S-100B levels of the observation group were lower, regular rehabilitation training on the basis of neurotrophic treatment can effectively reduce the degree of nerve injury was confirmed, it is also the internal reason for the macro recovery of limb function.

Neurotrophy/nerve injury are a pair of balancing factors, the combination therapy can reduce nerve damage has been made clear in the above, the neurotroph marker levels were further compared between two groups of patients in the study. BDNF is a protein with neurotrophic function, which is widely expressed in the human
nervous system in physiological state, and promotes the survival of nerve cells by increasing the gene expression of anti-apoptotic proteins. GDNF is derived from glial cells, and its high expression contributes to the nutrition and survival of glial cells[11,12]. It was found in this study that compared with those before intervention, the serum BDNF and GDNF levels of both groups were higher after intervention; further compared with the control group, serum BDNF and GDNF levels of the observation group were higher after the intervention, the rehabilitation training combined with neurotrophic treatment can increase the levels of neurotrophic factors was confirmed, this further encourages neurotrophy/nerve damage balance to shift in the direction of nerve cell rehabilitation. A variety of neurotransmitters are involved in the process of nerve injury and nerve repair, among which the excitatory amino acids Glu and Asp expression immediately increase dramatically early after nerve damage, which have strong neurotoxicity and can further nerve damage[13,14]; GABA and Gly belong to the inhibitory amino acids, their expression is in dynamic equilibrium with that of excitatory amino acids in physiological condition, and the decrease of their expression could reduce the inhibitory effect on excitatory amino acids and the protective effect on neurons[15,16]. In the study, differences between two groups of patients in serum excitatory/ inhibitory amino acid expression were compared, and it was found that compared with those before intervention, serum excitatory amino acids Glu and Asp levels were lower while inhibitory amino acids GABA and Gly levels were higher; further compared with control group, serum excitatory amino acids Glu and Asp levels of the observation group were lower after the intervention, levles of inhibitory amino acids GABA and Gly were higher, confirming that the rehabilitation training combined with neurotrophic therapy can effectively balance the amino acid neurotransmitter expression, and reduce the nerve injury.

Both brain injury and ischemia-reperfusion injury after operation involve the oxidative stress, in other words, local cerebral and systemic oxidative stress reaction in patients are closely related to the disease severity and treatment prognosis[17]. SOD and CAT are factors that have antioxidant effect, can neutralize the excessive oxygen free radicals and lipid oxidation products so as to avoid tissue damage; MDA is a typical oxidative metabolite, its content is consistent with the oxidative damage of the body[18,19]. In the study, serum levels of oxidative stress indexes were compared between two groups of patients before and after the intervention, and it was found that compared with those before intervention, serum SOD and CAT levels of both groups were higher while MDA levels were lower after intervention; further compared with the control group, levels of serum SOD and CAT of the observation group were higher, and level of MDA after the intervention were lower, confirming that the rehabilitation training combined with neurotrophic therapy can effectively reduce the oxidative stress reaction, and this is also one of the important mechanisms for it to reduce nerve injury and promote physical functional recovery.

Rehabilitation training combined with neurotrophic therapy for patients in convalescence of traumatic brain injury can effectively reduce the nerve injury, enhance neuroprotective effect and reduce systemic oxidative stress reaction, it is a more efficient and reasonable rehabilitation therapy combined with using neurotrophic therapy alone, and it is worthy of popularization and application in clinical practice in the future.

References:


