Influence of mouse nerve growth factor combined with hyperbaric oxygen on serum cytokines and cognitive function in patients with delayed encephalopathy after carbon monoxide poisoning

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ABSTRACT

Objective: To study the influence of mouse nerve growth factor (mNGF) combined with hyperbaric oxygen on serum cytokines and cognitive function in patients with delayed encephalopathy after carbon monoxide poisoning (DEACMP). Methods: 218 patients with DEACMP who were treated in our hospital between June 2012 and September 2016 were chosen as research subjects and retrospectively divided into the control group (n=100) who underwent hyperbaric oxygen treatment and the observation group (n=118) who underwent mouse nerve growth factor combined with hyperbaric oxygen treatment. Serum contents of nerve injury indexes and inflammatory mediators were compared between two groups of patients and cognitive function was assessed. Results: Before treatment, differences in serum levels of nerve injury indexes and inflammatory mediators, total MMSE score and each dimension score were not statistically significant between two groups of patients. After treatment, serum contents of nerve injury indexes creatine kinase-BB (CK-BB), neuron-specific enolase (NSE), S-100 β protein (S-100 β ) and lactate (Lac) in observation group were lower than those in control group; serum contents of inflammatory mediators interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-18 (IL-18), hypersensitive C-reactive protein (hs-CRP) and tumor necrosis factor (TNF-α ) were lower than those in control group; total MMSE score and each dimension score were higher than those of control group. Conclusion: mNGF combined with hyperbaric oxygen treatment of DEACMP is helpful to reduce the nerve injury and systemic inflammatory response, and improve the cognitive function.

1. Introduction

Delayed encephalopathy of carbon monoxide poisoning (DEACMP) is the mental symptom similar to acute of dementia occurring in patients with carbon monoxide (CO) poisoning after a few days or weeks of “pseudo-recovery period” after rescue, and it mainly appears within two months after acute poisoning[1,2]. DEACMP is mainly characterized by slow in response, mental retardation, increased muscle tension, gatism, etc., and the higher the age of patients with CO poisoning, the higher the incidence of DEACMP. DEACMP can cause severe damage to the brain and heart, and early active interventions are needed to optimize the outcome of the treatment[3]. Hyperbaric oxygen is a common way of DEACMP treatment that increases the plasma oxygen solubility to increased brain tissue oxygen content, but a new study says that the effect of hyperbaric oxygen treatment of DEACMP alone has limitations, many patients still have a serious neurologic injury, and other targeted cerebral protection drugs are needed to expand curative effect[4]. The mouse nerve growth factor (mNGF) is a neurotrophic agent that has been successfully used in the treatment of brain hemorrhage, stroke and so on[5]. mNGF was used to treat patients with DEACMP in the study and the effects of combination therapy on patients’ neurological impairment and cognitive function were discussed.
2. Information and methods

2.1 Case information

A total of 218 patients with delayed encephalopathy after carbon monoxide poisoning who were treated in our hospital between June 2012 and September 2016 were chosen as research subjects and divided into control group (n=100) who underwent hyperbaric oxygen treatment and the observation group (n=118) who underwent mouse nerve growth factor combined with hyperbaric oxygen treatment after the therapies were reviewed. Control group included 52 male cases and 48 female cases that were 20-71 years old; observation group included 60 male cases and 58 female cases that were 18-73 years old. Two groups of patients were not statistically different in gender or age distribution (P>0.05), patients' families signed informed consent, and the research was discussed and approved by the hospital ethics committee.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) with clear CO poisoning history; (2) with the clinical manifestations of delayed encephalopathy such as mental and intellectual disorder, changes in muscular tone and gatism after lucid interval; (3) head CT/MRI showed extensive white matter injury; (4) without history of cerebral infarction, cerebral hemorrhage or traumatic brain injury. Exclusion criteria: (1) associated with cognitive disorders such as Parkinson's and Alzheimer's disease; (2) associated with disorders that may affect normal cognition, such as depression and anxiety; (3) associated with severe heart, liver and kidney dysfunction; (4) associated with nerve growth factor allergy; (5) associated with serious tuberculosis, pneumothorax and high pressure oxygen contraindication.

2.3 Therapy

Control group of patients received hyperbaric oxygen therapy, which was as follows: the treatment pressure 0.2 MPa, pressurized for 20 min, oxygen uptake for 80 min at stable pressure, rest for 5 min in the middle of oxygen uptake, decompressed for 20 min, the above treatment for 1 time a day, 10 times as a course of treatment, for 3 consecutive courses of treatment. Observation group of patients, on the basis of hyperbaric oxygen, received the mouse nerve growth factor treatment, specifically as follows: mouse nerve growth factor (Xiamen Beidazhilu Biological Engineering Co., LTD., approved by S20060052) 20 μg, by intramuscular injection, 1 time/d, for consecutive treatment of 4 weeks.

2.4 Serum cytokines

Before and after treatment, 3.0 mL of cubital venous blood was extracted from two groups of patients respectively at same point in time, anti-coagulated and then centrifuged at 4 °C (3 000 r/min, 10 min) to take the upper serum and set it aside. RIA method was used to detect serum levels of nerve injury indexes, including creatine kinase-BB (CK-BB), neuron-specific enolase (NSE), S-100 β protein (S-100 β) and lactate (Lac), RIA kits were bought from Roche Company in the United States, and the article number was MDH-298, LAKS-762, DGA-462 and ASGD-361 respectively. Enzyme-linked immunosorbent assay method was used for determining serum levels of inflammatory mediators, including interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-18 (IL-18), hypersensitive C-reactive protein (hs-CRP) and tumor necrosis factor (TNF- α), ELISA kits were purchased from Sigma Company in the United States, and the article number was MD829, AL165, DI283, SG162 and HD3772 respectively.

2.5 Cognitive function

Before and after treatment, mini-mental state examination (MMSE) was used to assess the cognitive function of the two groups of patients. MMSE included five dimensions of directive force (0-10 points), memory (0-3 points), attention and calculation (0-5 points), recall capacity (0-3 points) and language competence (0-9 points), total score was 0-30 points, and the higher the score, the better the cognitive ability.

2.6 Statistical methods

Statistical software was SPSS 20.0 and the statisticians received professional statistical training and passed the exam. Nerve injury indexes, inflammatory mediators, cognitive function and other measurement data were in terms of mean ± standard deviation and the comparison was by t test. P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Nerve injury indexes

Before treatment, differences in serum contents of nerve injury indexes CK-BB (U/L), NSE (μg/L), S-100 β (μg/L) and Lac (mmol/L) were not statistically significant between two groups of patients (P>0.05). After treatment, serum contents of nerve injury indexes...
Comparison of serum nerve injury index contents between two groups of patients before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>CK-BB</th>
<th>NSE</th>
<th>S-100β</th>
<th>Lac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>100</td>
<td>Before treatment</td>
<td>74.39±9.15</td>
<td>20.38±2.75</td>
<td>0.45±0.06</td>
<td>7.38±0.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>33.21±5.49</td>
<td>11.17±1.64</td>
<td>0.17±0.02</td>
<td>4.11±0.53</td>
</tr>
<tr>
<td>Observation group</td>
<td>118</td>
<td>Before treatment</td>
<td>73.85±8.97</td>
<td>20.27±2.91</td>
<td>0.44±0.05</td>
<td>7.35±0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>16.18±2.05</td>
<td>4.89±0.56</td>
<td>0.09±0.01</td>
<td>1.76±0.25</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, \( P<0.05 \); compared with control group after treatment, \( P<0.05 \).

Comparison of serum inflammatory mediator contents between two groups of patients before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IL-6</th>
<th>IL-10</th>
<th>IL-18</th>
<th>hs-CRP</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>100</td>
<td>Before treatment</td>
<td>102.37±13.85</td>
<td>154.38±17.19</td>
<td>32.18±4.52</td>
<td>23.37±3.11</td>
<td>54.38±6.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>61.23±7.94</td>
<td>83.25±9.17</td>
<td>15.47±2.15</td>
<td>11.21±1.94</td>
<td>29.45±3.63</td>
</tr>
<tr>
<td>Observation group</td>
<td>118</td>
<td>Before treatment</td>
<td>103.28±12.66</td>
<td>153.26±16.84</td>
<td>31.79±4.37</td>
<td>23.48±3.09</td>
<td>54.75±6.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>25.49±4.21*</td>
<td>34.22±5.09*</td>
<td>7.09±0.85*</td>
<td>3.38±0.45*</td>
<td>12.17±2.04*</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, \( P<0.05 \); compared with control group after treatment, \( P<0.05 \).

Comparison of cognitive function between two groups of patients before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Directive force</th>
<th>Memory</th>
<th>Attention and calculation</th>
<th>Recall capacity</th>
<th>Language competence</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>100</td>
<td>Before treatment</td>
<td>2.18±0.34</td>
<td>0.53±0.08</td>
<td>1.17±0.18</td>
<td>0.92±0.14</td>
<td>2.13±0.34</td>
<td>8.23±0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>6.32±0.72</td>
<td>1.53±0.21</td>
<td>3.18±0.43</td>
<td>1.74±0.23</td>
<td>5.21±0.57</td>
<td>19.32±2.54</td>
</tr>
<tr>
<td>Observation group</td>
<td>118</td>
<td>Before treatment</td>
<td>2.21±0.32</td>
<td>0.55±0.07</td>
<td>1.15±0.19</td>
<td>0.95±0.11</td>
<td>2.09±0.32</td>
<td>8.19±0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>9.03±0.89</td>
<td>2.24±0.28</td>
<td>4.03±0.47</td>
<td>2.25±0.67</td>
<td>7.94±0.89</td>
<td>25.38±3.42</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, \( P<0.05 \); compared with control group after treatment, \( P<0.05 \).

CK-BB, NSE, S-100β and Lac in both groups were lower than those before treatment, serum contents of nerve injury indexes CK-BB, NSE, S-100β and Lac in observation group were lower than those in control group, and differences were statistically significant (\( P<0.05 \)), shown in Table 1.

3.2 Inflammatory mediators

Before treatment, differences in serum contents of inflammatory mediators IL-6 (pg/mL), IL-10 (pg/mL), IL-18 (ng/L), hs-CRP (mg/L) and TNF-α (pg/mL) were not statistically significant between two groups of patients (\( P>0.05 \)). After treatment, serum contents of inflammatory mediators IL-6, IL-10, IL-18, hs-CRP and TNF-α in both groups were lower than those before treatment, serum contents of inflammatory mediators IL-6, IL-10, IL-18, hs-CRP and TNF-α in observation group were lower than those in control group, and differences were statistically significant (\( P<0.05 \)), shown in Table 2.

3.3 Cognitive function

Before treatment, differences in total MMSE score and each dimension score were not statistically significant between two groups of patients (\( P>0.05 \)). After treatment, total MMSE score and each dimension score of both groups were higher than those before treatment, the total MMSE score and each dimension score of observation group were higher than those of control group, and differences were statistically significant (\( P<0.05 \)), shown in Table 3. (0-10 points), memory (0-3 points), attention and calculation (0-5 points), recall capacity (0-3 points) and language competence

4. Discussion

DEACMP is an idiopathic encephalopathy in patients with CO poisoning, the main pathological change is extensive brain white matter myelin depigmentation, it is the most significant in the frontal and parietal lobe, and brain atrophy can appear with the extension of the course. DEACMP pathogenesis is not clear and speculated to be directly related to CO effect on potently combining hemoglobin and making it lose its ability to carry oxygen, and brain tissue tolerance to hypoxia is the worst, so brain tissue damage and a series of clinical manifestations appear the earliest[6]. Hyperbaric oxygen is one of the most common methods in the clinical treatment of DEACMP, which increases the blood oxygen content and improves blood oxygen diffusion radius so as to increase the oxygen content in brain tissue, accelerate the aerobic metabolism of brain tissue and be conducive to blocking the sustained central nervous system demyelination progress[7,8]. mNGF is extracted from mouse submandibular gland, and animal experiments have confirmed that it can improve the toxic peripheral neuropathy-induced limb movement dysfunction, reduce the incidence of myelin swelling and reduce the degenerated nerve number[9,10]. In the study, mNGF was added on the basis of hyperbaric oxygen therapy, and the clinical value of combination therapy was expatiated from the aspects of
At the same time of brain injury, patients can present macroprotective effect, which is the important mechanism for it to achieve the cerebral therapy can significantly reduce systemic inflammatory response, confirming that adding mNGF on the basis of hyperbaric oxygen indexes in observation group were lower than those in control group, were lower than those before treatment, and serum contents of above parameters were compared between two groups of patients, and it was found that after treatment, serum CK-BB, NSE, S-100 β contents in both groups were lower than those in control group, explaining that mNGF treatment can effectively optimize the cognitive function of DEACMP patients, and this is the macro performance for the therapy to realize cerebral protective effect.

mNGF combined with hyperbaric oxygen therapy helps to relieve neurologic injury, inhibit systemic inflammatory response and finally improve cognitive function in patients with DEACMP, and it is worth popularization and application in clinical practice in the future.

References

with delayed neuropsychiatric encephalopathy induced by carbon monoxide poisoning, who recovered from severe neurocognitive impairment by repetitive hyperbaric oxygen therapy. *Seishin Shinkeigaku Zasshi* 2014; **116**(8): 659-669.


