Effects of emergency hyperbaric oxygen therapy on nerve injury, angiogenesis and cerebral blood perfusion in patients with acute cerebral infarction

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ABSTRACT

Objective: To explore the effects of emergency hyperbaric oxygen therapy on nerve injury, angiogenesis and cerebral blood perfusion in patients with acute cerebral infarction. Methods: A total of 118 patients with acute cerebral infarction who were treated in the hospital between April 2015 and October 2017 were selected as study subjects and divided into hyperbaric oxygen group (n=59) and control group (n=59) by random number table method. Control group received conventional therapy, hyperbaric oxygen group received conventional therapy combined with hyperbaric oxygen therapy, and both groups were treated for 2 weeks. The differences in nerve injury, angiogenesis and cerebral blood perfusion were compared between the two groups before and after treatment. Results: Differences in nerve injury, angiogenesis and cerebral blood perfusion were not significant between the two groups immediately after diagnosis. After 2 weeks of treatment, serum nerve injury indexes IGF-1, Copeptin, PAO, AQP4 and H-FABP contents of hyperbaric oxygen group were lower than those of control group; serum angiogenesis indexes PEDF, Ang-1 and VEGF contents were higher than those of control group whereas ES content was lower than that of control group; stenotic-side cerebral blood perfusion parameters CBF and CBV levels were higher than those of control group whereas TTP level was lower than that of control group. Conclusion: Emergency hyperbaric oxygen therapy can effectively reduce nerve injury, promote cerebral angiogenesis and increase cerebral blood perfusion in patients with acute cerebral infarction.

1. Introduction

Acute cerebral infarction is the most common cerebrovascular disease in the middle-aged and elderly people and also the main emergency causing death in patients, and how to early rescue patients and save their life to the greatest extent is the key of the clinical research[1,2]. Thrombolysis, neurotrophy, lipid lowering, blood pressure regulating and other conventional therapies have been widely used in the early treatment of acute cerebral infarction, but the specific therapeutic effect is uneven. Hyperbaric oxygen is a reliable way to relieve the hypoxic condition of the body, and many scholars believe that the early application of hyperbaric oxygen therapy can relieve the lesion hypoxia condition and optimize the treatment outcome of patients with cerebral infarction[3,4]. In this research, early hyperbaric oxygen was used for the treatment of patients with acute cerebral infarction in our hospital, and its clinical value was discussed from nerve injury, cerebral angiogenesis and cerebral blood perfusion in order to provide practical reference for subsequent establishment of therapies for similar patients.

2. Information and methods

2.1 Case information

A total of 118 patients with acute cerebral infarction who were treated in our hospital between April 2015 and October 2017 were chosen as the study subjects and divided into hyperbaric oxygen group (n=59) and control group (n=59) by random number table method. There were 31 males and 28 females in the hyperbaric oxygen group, and they were 41-79 years old; there were 32 males and 27 females in the control group, and they were 43-78 years old.
The difference in above data distribution was not significant between the two groups, and the research proposal was submitted to and approved by the ethics committee of the hospital.

Inclusion criteria: (1) diagnosed with acute cerebral infarction by head CT; (2) without history of cerebral infarction; (3) without history of hyperbaric oxygen therapy; (4) 18-80 years old; (5) with family’s informed consent.

Exclusion criteria: (1) combined with history of cerebrovascular malformation or cerebral hemorrhage; (2) combined with neurological disorders such as Alzheimer’s disease and Parkinson’s disease; (3) combined with malignant tumor diseases; (4) combined with systemic infectious diseases.

2.2 Therapy

Control group received clinical routine therapy for acute cerebral infarction, including thrombolysis, neurotrophy, regulating glucose lipid metabolism, regulating blood pressure, anticoagulation, etc.

Hyperbaric oxygen group were treated with hyperbaric oxygen on the basis of routine treatment, which was as follows: they were treated in hyperbaric oxygen chamber within 24 h after admission, the pressure was controlled at 0.2 MPa and the pressure time was 20 min. The patient inhaled oxygen for 1 h in the chamber under the stable pressure and then left the chamber after decompression, and the therapy was done once/d, and lasted for 2 weeks.

2.3 Observation indexes

Immediately after diagnosis and after 2 weeks of treatment, peripheral blood samples were collected from the two groups of patients at the same time and centrifuged to separate the upper serum, and then the obtained samples were cryopreserved for test. Multiskan microplate reader was used to test the levels of nerve injury indexes insulin-like growth factor-1 (IGF-1), copeptin, polyamine oxidase (PAO), aquaporin-4 (AQP4) and heart-type fatty acid-binding protein (H-FABP) in them; Ria kit was used to detect serum levels of angiogenesis indexes pigment epithelium-derived factor (PEDF), angiotensin I (Ang-1), endostatin (ES) and vascular endothelial growth factor (VEGF). Transcranial Doppler was adopted to measure the stenotic-side cerebral blood perfusion parameter cerebral blood flow (CBF), cerebral blood volume (CBV) and time to peak (TTP) levels.

2.4 Statistical methods

Nerve injury index and angiogenesis index contents as well as cerebral blood perfusion parameter levels were expressed as mean ± standard deviation and input in statistical software SPSS 23.0 to calculate the statistic P, and P<0.05 was the standard of statistical significance in differences in the study.

3. Results

3.1 Nerve injury indexes

Comparison of serum nerve injury indexes IGF-1 (ng/mL), Copeptin (nmol/mL), PAO (U/L), AQP4 (pg/mL) and H-FABP (pg/mL) contents between the two groups was as follows: serum IGF-1, Copeptin, PAO, AQP4 and H-FABP contents were not significantly different between the two groups immediately after diagnosis (P>0.05); after 2 weeks of treatment, serum IGF-1, Copeptin, PAO, AQP4 and H-FABP contents of both groups were lower than those immediately after diagnosis (P<0.05). After 2 weeks of treatment, serum IGF-1, Copeptin, PAO, AQP4 and H-FABP contents of hyperbaric oxygen group were lower than those of control group (P<0.05), shown in Table 1.

3.2 Angiogenesis indexes

Comparison of serum angiogenesis indexes PEDF (ng/mL), Ang-1 (ng/mL), ES (ng/mL) and VEGF (pg/mL) contents between the two groups was as follows: serum PEDF, Ang-1, ES and VEGF contents were not significantly different between the two groups immediately after diagnosis (P>0.05); after 2 weeks of treatment, serum PEDF, Ang-1 and VEGF contents of both groups were higher than those immediately after diagnosis whereas ES contents were lower than those immediately after diagnosis (P<0.05). After 2 weeks of treatment, serum PEDF, Ang-1 and VEGF contents of hyperbaric oxygen group were higher than those of control group whereas ES content was lower than that of control group (P < 0.05), shown in Table 2.

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IGF-1</th>
<th>Copeptin</th>
<th>PAO</th>
<th>AQP4</th>
<th>H-FABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>Immediately after admission</td>
<td>140.28±16.37</td>
<td>7.53±0.91</td>
<td>15.48±1.63</td>
<td>0.43±0.05</td>
<td>492.37±56.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 2 weeks of treatment</td>
<td>121.07±13.46</td>
<td>5.17±0.56</td>
<td>10.15±1.42</td>
<td>0.31±0.04</td>
<td>375.09±43.85</td>
</tr>
<tr>
<td>Hyperbaric oxygen group</td>
<td>59</td>
<td>Immediately after admission</td>
<td>140.31±15.99</td>
<td>7.49±0.86</td>
<td>15.39±1.72</td>
<td>0.44±0.06</td>
<td>490.88±54.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 2 weeks of treatment</td>
<td>98.26±10.17*</td>
<td>3.04±0.39*</td>
<td>6.09±0.75*</td>
<td>0.19±0.03*</td>
<td>219.57±24.66*</td>
</tr>
</tbody>
</table>

Note: compared with same group immediately after admission, *P<0.05; compared with control group after 2 weeks of treatment, #P<0.05.

Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>PEDF</th>
<th>Ang-1</th>
<th>ES</th>
<th>VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>Immediately after admission</td>
<td>15.49±2.07</td>
<td>8.11±0.86</td>
<td>170.37±19.81</td>
<td>105.48±11.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 2 weeks of treatment</td>
<td>28.06±3.41*</td>
<td>9.05±0.98*</td>
<td>131.28±14.96</td>
<td>126.29±14.35*</td>
</tr>
<tr>
<td>Hyperbaric oxygen group</td>
<td>59</td>
<td>Immediately after admission</td>
<td>15.72±2.11</td>
<td>8.09±0.83</td>
<td>171.28±18.54</td>
<td>104.79±12.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 2 weeks of treatment</td>
<td>41.78±4.59*</td>
<td>10.77±1.85*</td>
<td>102.75±13.19*</td>
<td>158.13±17.94*</td>
</tr>
</tbody>
</table>

Note: compared with same group immediately after admission, *P<0.05; compared with control group after 2 weeks of treatment, #P<0.05.
with the degree of nerve damage and neurotrophic factor release, so its content is positively correlated with the degree of nerve injury and determine the clinical effectiveness. IGF-1 has neuroprotective effect, and its reactive synthesis increases the degree of nerve injury and can effectively protect the neural function and reduce its damage degree in patients with acute cerebral infarction.

The main pathological change in patients with cerebral infarction is the decline of cerebral blood perfusion after target vessel infarction, and this is also one of the important internal mechanisms for it to optimize patients’ neural function. The study results indicated that the serum contents of above nerve injury-related indexes of hyperbaric oxygen group decreased after treatment, and combined with the physiological roles of these factors, it shows that emergency hyperbaric oxygen therapy can effectively protect the neural function and reduce its damage degree in patients with acute cerebral infarction.

There is blood supply disorder in lesion vessel after cerebral infarction, the degree of body's protective angiogenesis will largely determine the patients’ treatment outcome, and a variety of pro-angiogenesis factors are involved in the process. PEDF can be combined with receptor to activate the downstream signaling pathway and play a series of roles such as nourishing nerves and promoting angiogenesis, and its high expression is helpful for the recovery of neurological function[16]. Ang-1 can strengthen the junction between endothelial cells, reduce vascular permeability and induce the vascular endothelial function to become stable, and it can play a positive role in accelerating angiogenesis, increasing the blood supply to brain cells in lesion area and other aspects[17,18]. ES is one of the most effective angiogenesis inhibitors at present, and its high expression is a sign of poor prognosis in patients with cerebral infarction[19]. VEGF can specifically act on vascular endothelial cells and exert powerful pro-angiogenesis effect, and the clinical realization of neuroprotective effect of multiple drugs also depends on promoting VEGF content[20]. The study results showed that serum pro-angiogenesis factors PEDF, Ang-1 and VEGF contents of hyperbaric oxygen group were higher while anti-angiogenesis factor ES content was lower after treatment, it indicates that hyperbaric oxygen therapy helps to promote the cerebral angiogenesis in patients with acute cerebral infarction, and this is also one of the important internal mechanisms for it to optimize patients’ neural function.

The main pathological change in patients with cerebral infarction is the decline of cerebral blood perfusion after target vessel infarction, and the ultimate goal of thrombolysis and other therapies is also to recanalize infarcted vessels, increase cerebral blood flow perfusion and restore blood oxygen supply to neurons[21,22]. Trancranial

### 3.3 Cerebral perfusion parameters

Comparison of stenotic-side cerebral blood perfusion parameters CBF (mL/min 100 g), CBV (mL/100 g) and TTP (s) levels between the two groups was as follows: stenotic-side CBF, CBV and TTP levels were not significantly different between the two groups immediately after diagnosis (P>0.05); after 2 weeks of treatment, stenotic-side CBF and CBV levels of both groups were higher than those immediately after diagnosis whereas TTP levels were lower than those immediately after diagnosis (P<0.05). After 2 weeks of treatment, stenotic-side CBF and CBV levels of hyperbaric oxygen group were higher than those of control group whereas TTP level was lower than that of control group (P<0.05), shown in Table 3.

### 4. Discussion

Acute cerebral infarction causes the reduction of local oxygen and blood supply due to cerebral thrombosis, forms ischemic hypoxic injury and even leads to irreversible neuron apoptosis, permanent neurological damage and even death. Hyperbaric oxygen is a therapy to ease the body’s anoxic state, it has been confirmed in animal models with cerebral infarction that the early application of hyperbaric oxygen can improve the cerebral anoxia state, and the principle is to increase cerebral blood oxygen pressure, speed up the oxygen supply to the infarcts and improve cerebral metabolic rate[5–7]. In this study, emergency hyperbaric oxygen was used in the treatment of patients with acute cerebral infarction, and the optimizing effect of this treatment on the patient’s condition was discussed.

Local cerebral infarction can directly lead to ischemic hypoxic injury of neurons in the blood supply region, which will lead to nerve cell damage and nerve function[8,9]. Many factors specifically exist in neurons or are closely related to the nerve cell function, and early detection of their contents after cerebral infarction can reflect the degree of nerve injury and determine the clinical effectiveness. IGF-1 has neuroprotective effect, and its reactive synthesis increases after brain injury to inhibit central neuron apoptosis and induce neurotrophic factor release, so its content is positively correlated with the degree of nerve damage[10]. Copeptin content is highly correlated with the poor prognosis of cerebrovascular disease, and the reduction of serum Copeptin content after treatment is the symbol of improvement of disease[11]. PAO is a rate-limiting enzyme of polyamine interconversion pathway in the brain, PAO content rapidly increases after brain trauma and it participates in the formation of cerebral edema. AQP4 is a brain protein massively released after cerebral hemorrhage, and specific reduction of AQP4 content in circulating blood of patients with cerebral hemorrhage can effectively reduce cerebral edema[12,13]. H-FABP is mainly expressed in the brain, myocardium and skeletal muscle, and it is immediately released from the cells into the blood circulation after cell injury and death[14,15]. The study results indicated that the serum contents of above nerve injury-related indexes of hyperbaric oxygen group increased immediately after admission, and then decreased after treatment, and combined with the physiological roles of these factors, it shows that emergency hyperbaric oxygen therapy can effectively protect the neural function and reduce its damage degree in patients with acute cerebral infarction.

Table 3.

Comparison of stenotic-side cerebral blood perfusion parameter levels before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>CBF</th>
<th>CBV</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>59</td>
<td>Immediately after admission</td>
<td>39.48±4.51</td>
<td>2.37±0.28</td>
<td>5.49±0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 2 weeks of treatment</td>
<td>43.17±4.88</td>
<td>2.69±0.31</td>
<td>4.77±0.48</td>
</tr>
<tr>
<td>Hyperbaric oxygen group</td>
<td>59</td>
<td>Immediately after admission</td>
<td>39.61±4.37</td>
<td>2.34±0.29</td>
<td>5.46±0.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 2 weeks of treatment</td>
<td>49.63±5.82*</td>
<td>3.26±0.37*</td>
<td>4.18±0.43*</td>
</tr>
</tbody>
</table>

Note: compared with same group immediately after admission, *P<0.05; compared with control group after 2 weeks of treatment, *P<0.05.
Doppler can directly reflect the cerebral blood flow perfusion in patients, including CBF, CBV, TTP and other parameters. Cerebral CBF and CBV levels decrease while TTP level increases significantly after cerebral infarction[23]. In the study, CBF and CBV levels of hyperbaric oxygen group were higher while TTP level was lower after treatment, it indicates that the cerebral blood flow perfusion increases and cerebrovascular resistance decreases in patients with acute cerebral infarction after emergency hyperbaric oxygen treatment, and this macroscopically shows the relief of illness in patients with cerebral infarction.

In all, it is concluded that emergency hyperbaric oxygen therapy can effectively alleviate nerve injury degree, promote angiogenesis and increase cerebral blood flow perfusion in patients with acute cerebral infarction, it is an effective therapy and it is recommended in clinical practice in the future.

References


