Serum indicators and endothelial function of hyperbaric oxygen combined with memantine and Aricept treatment of senile vascular dementia

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ABSTRACT

Objective: To find the effect of hyperbaric oxygen combined with memantine and Aricept treatment of senile vascular dementia on serum indicators and endothelial function. Methods: A total of 126 cases of patients with senile vascular dementia treated in our hospital from March 2012 to December 2014 were selected as research subjects, treatment that patients received was retrospectively analyzed, and patients were divided into observation group 64 cases and control group 62 cases. Control group received memantine and Aricept therapy, observation group received hyperbaric oxygen combined with memantine and Aricept therapy, and then differences in levels of serum TGF-β, IGF-1 and ICAM-1, Hcy, MDA and SOD, NPY, sFas, sFasL and so on, ET and EPC between two groups were compared. Results: Serum TGF-β ad IGF-1 levels of observation group after treatment were higher than those of control group, and ICAM-1 levels were lower than those of control group; Hcy and MDA levels of observation group after treatment were lower than those of control group; Hcy and MDA levels of observation group after treatment were lower than those of control group; serum NPY, sFas, sFasL and Ca2+ values of observation group after treatment were lower than those of control group, and PON-1 value was higher than that of control group; ET values of observation group at various points in time after treatment were lower than those of control group, and EPC contents were higher than those of control group. Conclusion: Hyperbaric oxygen combined with memantine and Aricept treatment for patients with senile vascular dementia can effectively improve the disease and optimize endothelial function, and it has active clinical significance.

1. Introduction

Vascular dementia (VD) trends to occur in the elderly population, and cerebral hypoxic ischemic hypoperfusion caused by all kinds of cerebrovascular accident is the main cause of the disease. Small artery that is in hypoperfusion state for a long time causes local brain neuron necrosis and patients gradually develop cognitive dysfunction[1]. Current treatment of VD mainly relies on drugs such as memantine, Aricept and so on, they can inhibit VD progress but their role in reversing patients’ cognitive function is very small.

Hyperbaric oxygen is a new way that is currently recommended for treatment of patients with VD, and it mainly increases blood oxygen level to increases partial pressure of oxygen in brain tissue and promotes reversibly hypoxic brain tissue function recovery[2]. In the research, the effect of hyperbaric oxygen combined with memantine and Aricept treatment of senile vascular dementia on serum indicators and endothelial function was mainly analyzed, hereby reported as follows.

2. Information and methods

2.1. General information

A total of 126 cases of patients with senile vascular dementia treated in our hospital from March 2012 to December 2014 were
selected as research subjects, diagnosed by magnetic resonance imaging and in accordance with the diagnostic criteria for senile dementia developed by National Institute of Psycho and Stroke of US. Treatment that patients received was retrospectively analyzed, and patients were divided into observation group 64 cases and control group 62 cases. Control group included 32 male cases and 30 female cases, they were 64-75 years old and the average age was (68.76±4.91) years; differences in gender, age and other baseline information between two groups were without statistical significance, P>0.05 and they were comparable.

2.2. Treatment methods

Control group received memantine and Aricept therapy, and details were as follows: Aricept 5 mg/d, adjusting specific drug dose according to patients' conditions and maximum dose no more than 10 mg/d; memantine 10 mg/time, 2 times/d.

Observation group received hyperbaric oxygen combined with memantine and Aricept therapy, and details were as follows: hyperbaric oxygen therapy for 2 h every day and 60 d as a course of treatment. At the same time, memantine and Aricept were taken, and specific usage and dosage were same as those of control group.

2.3. Observation indicators

Before treatment, after 30 d of treatment, after 60 d of treatment and 30 d after the end of treatment, 2 mL of fasting peripheral blood was drawn from patients in the morning, enzyme-linked immunosorbent assay (ELISA) was used to detect transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1) and intercellular adhesion molecule-1 (ICAM-1) levels in blood. Homocysteine (Hcy) in blood was detected, xanthine oxidase method was used to detect superoxide dismutase (SOD) and thiobarbituric acid chemical colorimetric method was used to detect malondialdehyde (MDA) contents. Radioimmunoassay was used to detect neuropeptide Y (NPY) level; ELISA was used to detect serum soluble apoptotic molecules sFas, sFasL, and endothelin (ET) levels; indirect ion selective electrode was used to detect Ca²⁺ concentration; phenol acetate method was used to detect paraoxonase (PON-1) activity. Flow cytometry was used to detect endothelial progenitor cell (EPC) contents in peripheral blood.

3. Results

3.1. TGF-β, IGF-1 and ICAM-1 levels

Before and after patients with senile vascular dementia received treatment, blood was drawn to detect TGF-β, IGF-1 and ICAM-1 contents in it, and ELISA detection showed that before treatment, differences in TGF-β, IGF-1 and ICAM-1 levels between two groups were without statistical significance (P>0.05), after 30 d of treatment, after 60 d of treatment and 30 d after the end of treatment, TGF-β ad IGF-1 levels in blood of observation group were higher than those of control group, and ICAM-1 levels were lower than those of control group (P<0.05), shown in Figure 1.

3.2. Hcy, MDA and SOD levels

Hcy, MDA and SOD levels in blood of two groups were detected before and after treatment, and results showed that differences in Hcy, MDA and SOD levels in blood between two groups were without statistical significance before treatment (P>0.05), Hcy and MDA levels of both groups in various periods after treatment were lower than those before treatment and SOD levels were higher than those before treatment (P<0.05), Hcy and MDA levels of observation group after 30 d of treatment, after 60 d of treatment and 30 d after the end of treatment were lower than those of control group at corresponding points in time and SOD levels were higher than those of control group (P<0.05), shown in Figure 2.

3.3. Levels of NPY, sFas, sFasL and so on

Different methods were used to detect blood samples of patients after treatment, differences in NPY, sFas, sFasL, Ca²⁺ and PON-1 contents were specifically compared, and results showed that serum NPY, sFas, sFasL and Ca²⁺ values of observation group 30 d after treatment were lower than those of control group, and PON-1 value was higher than that of control group (P<0.05), shown in Table 1.

3.4. ET and EPC levels

Detection of endothelin and endothelial progenitor cell contents in blood showed that differences in ET and EPC contents between
Table 1
Comparison of levels of serum NPY, sFas, sFasL and so on between two groups after treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>NPY (ng/L)</th>
<th>sFas</th>
<th>sFasL</th>
<th>Ca2+</th>
<th>PON-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>120.73±10.96</td>
<td>83.92±7.11</td>
<td>138.63±9.74</td>
<td>8.98±0.75</td>
<td>161.29±11.58</td>
</tr>
<tr>
<td>Control group</td>
<td>141.72±13.69</td>
<td>138.26±11.05</td>
<td>205.22±15.31</td>
<td>11.45±1.13</td>
<td>137.25±12.05</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Two groups were without statistical significance before treatment (*P* >0.05), ET values of both groups after treatment were lower than those before treatment and EPC contents were higher than those before treatment (*P* <0.05), ET values of observation group at various points in time after treatment were lower than those of control group, and EPC contents were higher than those of control group (*P* <0.05), shown in Figure 3.

Figure 2. Comparison of Hcy, MDA and SOD levels in blood between two groups before and after treatment

Figure 3. Comparison of endothelin and endothelial progenitor cell contents in blood between two groups before and after treatment

4. Discussion

Vascular dementia (VD) is dementia syndrome caused by a variety of cerebrovascular diseases, the pathological and physiological basis of the disease includes cerebral hypoperfusion, low metabolism, excitatory amino acid toxicity oxidative stress and so on, which eventually result in disorder of material and energy metabolism in cerebral nerve cells, and end up with cerebral nerve cell necrosis and cognitive dysfunction[3]. The incidence of VD gradually increases along with the process of population aging, which brings heavy psychological and economic burdens to both patients and their families. VD trends to occur in elderly people, it is mainly manifested as cognitive and motor dysfunction and its treatment is centered on improving the hypoxia-ischemia state of nerve cells. Memantine and Aricept are commonly used drugs for treatment of VD, memantine belongs to excitatory amino acid receptor antagonist, and it can block neuron injury caused by pathologically increased glutamic acid concentration. Aricept belongs to cholinesterase inhibitor, and it can enhance cholinergic neuron function, reversibly inhibit acetylcholinesterase hydrolysis of acetylcholine, and eventually play the role of promoting brain cell metabolism and improving cerebral circulation. Drug treatment of VD has achieved certain progress, but long-term improvement on patients’ cognitive function is limited[4,5]. Application of hyperbaric oxygen in VD increases in recent years, and the possible mechanisms of it to improve patients’ cognitive function are as follows: 1) increasing partial pressure of oxygen in blood, quickening oxygen diffusion in tissue, relieving hypoxia in brain tissue and promoting ATP synthesis in brain; 2) reducing permeability of blood in brain and improving microcirculation; 3) reducing viscosity of red blood cells, decreasing thrombosis and accelerating absorption of thrombus; 4) reducing nitric oxide release and decreasing oxidative damage of brain tissue caused by ischemia reperfusion. In the research, hyperbaric oxygen, memantine and Aricept were all used for treatment of patients with VD, and the changes in levels of a series of factors in their peripheral blood were specifically observed.

Transforming growth factor-β (TGF-β) is anti-inflammatory agent that can stabilize intracellular concentration, antagonize neurotoxicity of excitatory amino acid and exert antioxidant and anti-apoptotic effect[6]. Insulin-like growth factor-1 (IGF-1) belongs to endogenous neurotrophic factor, has direct anti-apoptotic effect and can improve the survival rate of neurons. IGF-1 is degraded to terminal tripeptide in the body, and it can act on N-methyl-D-aspartic acid (NMDA) receptor, reduce cholinergic neuron deletion and protect neurons damaged by neurotoxic substances[7]. IGF-1 can also reduce the generation of oxygen free radicals in the body and alleviate neuron damage to some extent, and many studies have shown that decreased IGF-1 level may be one of the important...
reasons of aggravated cognitive impairment in patients with vascular dementia. Intercellular adhesion molecule-1 (ICAM-1) is involved in the interactions between cells and between cells and extracellular matrix, and study has shown that synaptic plasticity of hippocampal neuron plays an important role in pathological changes of dementia and ICAM-1 is the sign of synaptic plasticity. In the research, serum TGF-β, IGF-1 and ICAM-1 levels of two groups were compared at first, and results showed that TGF-β and IGF-1 levels of observation group after treatment were higher and ICAM-1 levels were lower, indicating that hyperbaric oxygen combined with memantine and Aricept therapy could improve nerve cell protection effect and inhibit nerve cell apoptosis.

Homocysteine (Hcy) is amino acid product after demethylation of methionine, and it cannot be synthesized in the body under normal conditions. Studies have shown that is HHcy is an independent risk factor of vascular diseases, and it has great correlation with cognitive dysfunction[8,9]. Study has shown that there is significant abnormality of superoxide dismutase (SOD) and malondialdehyde (MDA) optical density values in patients with dementia, indicating that oxidative stress response is involved in neuron damage in the process of dementia. MDA belongs to lipid peroxide, is an important oxygen free radical mediator, is positively correlated with oxidative stress response, and can reflect body’s antioxidant capacity. In central nervous system, ET can increase intracellular calcium ion concentration, cause vasoconstriction and regulate cerebral blood flow, and ET can stimulate vascular smooth muscle cell proliferation, induce cerebrovascular diseases and result in irreversible brain tissue damage[15]. Continuously high level of ET can aggravate damage from hypoxia and ischemia of brain tissue, form a vicious cycle and ultimately lead to the occurrence of vascular dementia. Endothelial progenitor cell (EPC) not only maintains the physiological function of normal vascular system, but is also involved in regeneration and repair of vessels in the pathological state. Study has confirmed that EPC in circulating blood is conducive to the restoration of blood supply in ischemic tissue and enhancement of nerve function repair. Mobilizing EPC in peripheral blood is an important part of promoting nerve repair in ischemic damage area of patients with vascular dementia, and its significance to hippocampus that controls learning and memory is more important. In the research, the changes in ET levels and EPC contents of patients from treatment were compared, and results showed that ET values of observation group after treatment decreased and EPC contents increased, indicating that combined therapy could effectively reduce the degree of oxidative stress and inhibit the occurrence of neuron damage.

Neuropeptide Y (NPY) relationship with learning and memory as well as cerebral vasomotion function has been receiving clinical attention, NPY is the neuropeptide with highest content in central nervous tissue, and its content in hippocampus was the highest. It is currently accepted that the main loop structure causing learning and memory impairment after cerebral ischemia is in hippocampus, so NPY level has direct correlation with the degree of dementia of patients[11]. Fas/FasL system includes Fas, FasL, sFas and sFasL, belongs to important membrane protein molecules mediating cell apoptosis, and has important function in normal immune response, hematopoietic regulation, abnormal cell clearance and other aspects. In cerebral ischemia rat models, it is found that there is neuron apoptosis in hippocampus and the quantity is associated with rats’ cognitive dysfunction. Foreign studies have shown that sFasL level in healthy elderly people is lower than that of young people, indicating that soluble apoptotic molecules sFas and sFasL are involved in cell apoptosis process. PON-1 is synthesized by liver, belongs to calcium ion-dependent arylesterase, can reduce oxidative stress state and lipid peroxidation injury in the body, and also has antiatherosclerotic effect[13,14]. Study has shown that in mouse models, PON-1 gene knockout can aggravate the probability of vascular endothelial oxidative stress damage and angiogenesis, indicating that weakened PON-1 activity may be involved in the onset process of vascular dementia. Schmitz[12] studies the correlation between vascular dementia and serum Ca²⁺ concentration and finds that both serum Ca²⁺ concentration and superoxide dismutase concentration decrease significantly and MDA level increases. In the research, levels of above factors in blood were detected, and results showed that serum NPY, sFas, sFasL and Ca²⁺ values of observation group after treatment decreased and PON-1 value increased, indicating that hyperbaric oxygen combined with memantine and Aricept therapy could effectively reduce the degree of oxidative stress and inhibit the apoptosis of neurons.

Plasma endothelium is currently known strongest vasconstriction factor, and when pathogenic factors cause vascular endothelium damage, endothelin (ET) level in plasma rapidly increases. In central nervous system, ET can increase intracellular calcium ion concentration, cause vasoconstriction and regulate cerebral blood flow, and ET can stimulate vascular smooth muscle cell proliferation, induce cerebrovascular diseases and result in irreversible brain tissue damage[15]. Continuously high level of ET can aggravate damage from hypoxia and ischemia of brain tissue, form a vicious cycle and ultimately lead to the occurrence of vascular dementia. Endothelial progenitor cell (EPC) not only maintains the physiological function of normal vascular system, but is also involved in regeneration and repair of vessels in the pathological state. Study has confirmed that EPC in circulating blood is conducive to the restoration of blood supply in ischemic tissue and enhancement of nerve function repair. Mobilizing EPC in peripheral blood is an important part of promoting nerve repair in ischemic damage area of patients with vascular dementia, and its significance to hippocampus that controls learning and memory is more important. In the research, the changes in ET levels and EPC contents of patients from treatment were compared, and results showed that ET values of observation group after treatment decreased and EPC contents increased, indicating that combined therapy could optimize patients’ cerebrovascular conditions and actively repair nerve injury caused by ischemia.

To sum up, it is concluded as follows: hyperbaric oxygen combined with memantine and Aricept treatment for patients with senile vascular dementia can effectively improve the disease and optimize endothelial function, and it’s worth popularization in clinical practice in the future.
References