Effect of Huanglian Jiedu Decoction on pitavastatin treatment of Alzheimer´s disease

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ABSTRACT

Objective: To explore the effect of Huanglian Jiedu Decoction on pitavastatin treatment of Alzheimer’s disease. Methods: A total of 200 cases of Alzheimer’s disease of our department and department of geriatrics medicine of Harbin fifth hospital were selected, patients were divided into observation group and control group according to the random number table method by half. The control group was treated with pitavastatin, and the observation group was given the Huanglian Jiedu Decoction based on the control group. Before and after treatment, levels of cerebrospinal fluid Aβ -1-42 protein, phosphorylated tau protein, inflammation related factors IL-1β, IL-6, TNF-α, liver and renal function indexes of the two group patients with Alzheimer’s disease were detected. Results: Compared with before treatment, levels of cerebrospinal fluid Aβ -1-42 protein and phosphorylated tau protein of the two groups were significantly decreased after treatment (P<0.05); after treatment, levels of cerebrospinal fluid Aβ -1-42 protein and phosphorylated tau protein of the observation group were significantly lower than those of the control group, (P<0.05); compared with before treatment, levels of inflammation related factors IL-1β, IL-6 and TNF-α of the two groups were significantly decreased after treatment (P<0.05); compared with the control group after treatment, after medication, levels of inflammation related factors IL-1β, IL-6 and TNF-α of the observation group were significantly decreased (P<0.05); compared with the control group after treatment, after combined treatment, levels of liver and renal function indexes of the observation group were significantly decreased (P<0.05). Conclusions: Huanglian Jiedu Decoction can decrease the level of inflammatory factors in patients with Alzheimer’s disease, while reduce toxic side-effects of pitavastatin, and improve treatment efficiency of pitavastatin on Alzheimer’s disease, which is of important clinical significance to improve rehabilitation and quality of life in patients of Alzheimer’s disease.

1. Introduction

Alzheimer’s disease is also known as presenile dementia, as a neurodegenerative disease, it often causes cognitive impairment and memory injury in the elderly, the pathogenesis is unknown presently[1,2], seriously impacts on the health and living quality of the elderly[3]. Huanglian Jiedu Decoction has a good effect of heat-clearing, detoxifying, and purging intense heat[4], and can improve people’s intelligence and life ability, effectively promote the treatment of Alzheimer’s disease with western medicine , but the mechanism is not yet clear[5]. The study was to explore the mechanism of Huanglian Jiedu Decoction improved pitavastatin treatment of Alzheimer’s disease, and provide help for future clinical treatment of Alzheimer's disease.

2. Materials and methods
2.1. General data

This study was permitted by ethics committee of our hospital and the fifth hospital of Harbin, and implemented after informed consents from all patients and their relatives. From January 2012 to December 2015, 200 patients with Alzheimer's disease of our department and geriatric medicine department of the fifth hospital of Harbin were selected, which were all consistent with the standards for diagnosis of Alzheimer's disease in the third edition of "Chinese classification of mental disorders", and the pathological behavior score of Alzheimer's patients were more than 8 points. According to the random number table method, 200 cases were divided into two groups, in the observation group (100 cases), there were 57 males and 43 females, aged from 57 to 79 years old, with an average of (67.3±9.5) years old; in the control group (100 cases), there were 52 males and 48 females, aged from 55 to 78 years old, with an average of (66.5±7.1) years old. The gender, age, course and intelligence degree between the two groups showed no significant difference (P>0.05), Each Alzheimer's patient had relative examinations, there were no other brain, kidney, liver, lung, endocrine and mental diseases, etc, and all did not receive any treatment before and had detailed information before treatment.

2.2. Methods

Patients in the control group were treated with 2 mg pitavastatin orally after meals, 1 times a day. The observation group was given Huanglian Jiedu Decoction (Coptis 9 g, gardenia 9 g, scutellaria 9 g and phellodendron 9 g) continuously based on oral pitavastatin, 1 dose per day, 3 times a day. Alzheimer's patients of the two groups had continuous medication for 12 weeks.

2.3. Index detection

Before and after treatment, 3 mL fasting venous blood of the elbow were extracted at 7:00-8:30 in the morning, at the same time, lumbar puncture was performed and 2 mL of cerebrospinal fluid were extracted. Enzyme linked immunosorbent assay was used for the determination of amyloid β-protein 1-42 (Aβ-1-42 protein), phosphorylated tau protein, interleukin-1β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). The kits were provided by Wuhan Hua Mei Biological Engineering Co., Ltd, Shanghai Tong Wei Reagent Co., Ltd, and Shanghai Enzyme-linked Biotechnology Co., Ltd, operations were carried out according to the instruction strictly. OD value of 450 nm was detected by metaplate (model: Infinite 200, company: TECAN, Switzerland), and the corresponding concentration was calculated by the standard curve.

Liver function about alanine aminotransferase (ALT) with aspartate aminotransferase (AST) and renal function about urea nitrogen (UN) with creatinine (Cr) were detected by Hitachi automatic biochemical analyzer (model: 7180, Japan), experimental operations were in strictly accordance with the instruction.

2.4. Statistical methods

SPSS 17.0 statistical software was adopted for data analysis, Measurement data were described as mean±standard deviation, using t test for comparison between the two groups. Values of P<0.05 were considered to be statistically significant difference.

3. Results

3.1. Cerebrospinal fluid Aβ-1-42 protein and phosphorylated tau protein before and after treatment

Before treatment, there was no significant difference in cerebrospinal fluid A β -1-42 protein and phosphorylated tau protein between the observation group and the control group (P>0.05); compared with before treatment, levels of A β -1-42 protein and phosphorylated tau protein in the observation group after the treatment were significantly decreased (P<0.05); In the control group, levels of A β -1-42 protein and phosphorylated tau protein were significantly decreased after the treatment with pitavastatin (P<0.05); after treatment, levels of A β -1-42 protein and phosphorylated tau protein in the observation group were significantly lower than those in the control group (P<0.05) (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Aβ-1-42 protein (pg/mL)</th>
<th>Phosphorylated tau protein (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation Group</td>
<td>Before treatment</td>
<td>463.91±24.19</td>
<td>524.12±27.48</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>306.78±31.51*</td>
<td>385.23±23.38*</td>
</tr>
<tr>
<td>Control Group</td>
<td>Before treatment</td>
<td>455.72±29.10</td>
<td>533.06±26.91</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>393.17±26.66*</td>
<td>421.67±25.90*</td>
</tr>
</tbody>
</table>

Note: compared with intra-group before treatment, *P<0.05; compared with the control group after treatment, *P<0.05.

3.2. Comparison of levels of inflammatory factors before and after treatment between two groups

Before treatment, there was no significant difference in inflammation factors IL-1 β, IL-6 and TNF-α between the

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>IL-1β (ng/L)</th>
<th>IL-6 (ng/L)</th>
<th>TNF-α (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>35.05±2.37</td>
<td>11.11±1.79</td>
<td>138.06±3.11</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>24.21±3.12*</td>
<td>5.28±1.96*</td>
<td>106.45±4.12*</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>35.39±2.54</td>
<td>11.53±1.25</td>
<td>137.88±3.13</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>28.81±2.90*</td>
<td>7.71±1.55*</td>
<td>121.99±3.85*</td>
</tr>
</tbody>
</table>

Note: compared with intra-group before treatment, *P<0.05; compared with the control group after treatment, *P<0.05.
observation group and control group ($P>0.05$); compared with before treatment, levels of inflammation factors IL-1β, IL-6 and TNF- in both groups were significantly decreased ($P<0.05$); after treatment, levels of inflammation factors IL-1β, IL-6 and TNF- in the observation group were significantly lower than those in the control group ($P<0.05$) (Table 2).

### 3.3. Comparison of liver function and renal function before and after treatment between two groups

Before treatment, there was no significant difference in ALT, AST, UN and Cr between the observation group and control group ($P>0.05$); compared with before treatment, levels of ALT, AST, UN, Cr in both groups were significantly increased ($P<0.05$); after treatment, levels of liver and renal function related factors ALT, AST, UN and Cr in the observation group were significantly lower than those in the control group ($P<0.05$) (Table 3).

### 4. Discussion

Alzheimer's disease is also known as presenile dementia[6], as a neurodegenerative disease, patients' intelligence of the cerebral hemisphere such as language function, memory function and reasoning function appear damaged condition, patients in the cerebral hemisphere were impaired. Alzheimer's patients appear neurofibrillary tangle, senile plaque, vacuole degeneration in neuron granule, amyloid deposit and neuron loss[7]. With the continuous increase of China's population aging, Alzheimer's has been one of the highest incidence of disease in the elderly, seriously affects the physical condition and the quality of life of the elderly, Alzheimer's disease has become a serious social problem nowadays[8]. To find appropriate drugs for Alzheimer's has become an urgent affair for medical workers.

Statins have similar structure with hydroxy methylglutaryl coenzyme A, thus can inhibit β-hydroxy-β-methylglutaryl coenzyme A reductase, pitavastatin shows stronger pharmacological activity than other statins because of the isopropy side chain[10,11]. Pitavastatin can not only reduce phosphorylation level of tau protein but also Aβ oligomer[12], meanwhile, pitavastatin has unique pharmacokinetic properties, that is, good oral absorption effect, stronger tolerance, longer half-life, higher bioavailability, and weak drug interactions[13,14], thus pitavastatin can effectively play a role in the treatment of Alzheimer's. A large number of clinical studies show that, pitavastatin has good therapeutic effect on Alzheimer's, which can relieve the illness in patients with Alzheimer's[15,16]. The study found that after the patients with Alzheimer's were treated with pitavastatin, levels of Aβ-1-42 protein and phosphorylated tau protein were decreased, which were consistent with previous studies, but still need to be further explored.

Traditional Chinese medicine holds that the brain is the main position of Alzheimer's, and also has a relationship with multiple organs. The main cause of Alzheimer's is toxin injuringcollaterals of the brain. Therefore, Chinese medicine detoxification treatment can alleviate Alzheimer's by eliminating toxin[17]. As the classic prescription of antipyretic detoxification, Huanglian Jiedu Decoction is composed of coptis, scutellaria, phellodendron and gardenia, which are both bitter and cold products, play the role of diarrhea firelight and triple burner fire, and can heat evil, relieving fever, cure various diseases. Huanglian Jiedu Decoction can increase cerebral blood flow, reduce the generation of free radicals in the body, eliminate inflammation and improve the memory[18]. In recent years, a large number of research results show that Huanglian Jiedu Decoction has a good therapeutic effect on Alzheimer's, can effectively reduce the inflammatory response in patients, dredge meridians and eliminate toxin[19].

The results of this study showed that Huanglian Jiedu decoction combined with pitavastatin can effectively reduce the content of Aβ-1-42 protein and phosphorylated tau protein in Alzheimer's patients. Phosphorylation and dephosphorylation of tau protein is in equilibrium under normal physiological conditions, however, there is tau protein hyperphosphorylation in Alzheimer's patients, which lead to a large number of neurofibrillary tangles in nerve cells, cause nerve damage and degeneration[20]. The decrease of phosphorylated Tau protein helps to alleviate nerve injury, and relieve the condition of Alzheimer's. The formation of Aβ-1-42 protein deposition leads to neuritic plaques is one of the characteristic pathological changes of brain in Alzheimer's patients[21]; Aβ-1-42 protein can form free radicals to damage neurons and cause neurocyte apoptosis; Aβ-1-42 protein can also interact with cholinergic neurons and inhibit acetylcholine release from hippocampal and cortical slices[22,23]. The combination of Huanglian Jiedu Decoction and pitavastatin reduced Aβ-1-42 protein content, and inhibited neurotoxicity induced by Aβ-1-42 protein. The decrease of Aβ-1-42 protein and phosphorylated Tau protein played an important role in curing Alzheimer's. Further detected inflammation related factors IL-1β, IL-6 and TNF-, founded that Huanglian Jiedu Decoction combined with pitavastatin can reduce levels of inflammation factors IL-1β, IL-6 and TNF- in the body, the decrease of inflammatory factor IL-1β, IL-6 and TNF- alleviated brain damage and stabilized the immune system in patients. Western medicine often causes liver function damage and renal function damage, through detection of liver function and renal function, the author founded that compared with the simple use of pitavastatin, Huanglian Jiedu Decoction

### Table 3

**Comparison of liver function and renal function before and after treatment between two groups.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>UN (mmol/L)</th>
<th>Cr (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>26.34±9.56</td>
<td>22.17±9.81</td>
<td>3.72±1.15</td>
<td>49.35±8.30</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>40.07±9.58*</td>
<td>40.25±9.87*</td>
<td>4.96±1.32*</td>
<td>53.41±7.96*</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>26.25±8.78</td>
<td>22.15±9.02</td>
<td>3.67±1.14</td>
<td>49.58±8.31</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>89.14±8.65*</td>
<td>95.23±4.90*</td>
<td>7.57±1.19*</td>
<td>58.45±7.96*</td>
</tr>
</tbody>
</table>

Note: compared with intra-group before treatment, *$P<0.05$; compared with the control group after treatment, *$P<0.05$.  

* indicates statistical significance.
combined with pitavastatin can significantly reduce levels of ALT, AST, UN and Cr, which alleviated liver and kidney injury induced by pitavastatin. The detoxification function of coptis, scutellaria, phellodendron and gardenia played an important role in relieving two damage to the body of drugs.

In conclusion, Huanglian Jiedu Decoction can improve the efficacy of pitavastatin, Huanglian Jiedu Decoction combined with pitavastatin can reduce the content of Aβ -1-42 protein and phosphorylated tau protein in Alzheimer's patients, at the same time, reduce the level of inflammatory factors and toxic side effects of pitavastatin. To provide a basis for combined Chinese with Western Medicine in Alzheimer's disease in the future.

References


