Mechanism of treating ischemic stroke by atorvastatin combined with Huoxuetongmai capsules

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Objective: To investigate the mechanism of treating ischemic stroke by atorvastatin combined with Huoxuetongmai capsules, for helping clinical treatment of ischemic stroke.

Methods: A total of 160 cases of patients with ischemic stroke were selected, and randomly divided into observation group and control group, each group was 80 cases, control group was given conventional treatment, and observation group was given atorvastatin combined with Huoxuetongmai capsules based on the above conventional treatment, the changes of hemodynamic indexes, inflammation factors and coagulation function related indexes in patients with ischemic stroke were detected before and after treatment.

Results: The comparison of hemodynamic indexes, inflammation factors and coagulation function related indexes in the two groups before treatment was not statistically significant. Compared with before treatment, hemodynamic indexes (whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, maximum red blood cell aggregation index and hematocrit) and inflammation factors (IL-6, IL-8, CRP and TNF-α) in observation group after treatment by atorvastatin combined with Huoxuetongmai capsules significantly decreased, while coagulation function related indexes (FIB, DDI, TXB2 and PAI-1) significantly increased, and were considered to be statistically significant. Compared with control group after treatment, hemodynamic indexes, coagulation function related indexes (FIB, DDI, TXB2 and PAI-1) and inflammation factor in observation group after combined treatment significantly decreased, while PT significantly increased, there were statistically significant difference between the groups.

Conclusion: The treatment of ischemic stroke by atorvastatin combined with Huoxuetongmai capsules could improve hemodynamic indexes, inflammation factors and coagulation function related indexes in patients with ischemic stroke, and provide help for clinical treatment of ischemic stroke.

1. Introduction

The lifestyle and living standards are constantly improved with the rapid development of society, and the number of patients with stroke enhances unceasingly, its mortality and morbidity are rising[1]. Thrombosis and atherosclerosis block the blood supply of brain, and cause cerebral ischemic anoxia and serious damage of nerve function, cause losing life ability and serious damage of body and mind for patients, and bring a heavy burden to the family[2,3]. Therefore, positive and effective treatments of ischemic stroke have become the priority of the broad masses of medical workers[4]. This study aims to investigate the mechanism of treating ischemic stroke by atorvastatin combined with Huoxuetongmai capsules, and provide help for clinical treatment of ischemic stroke.

2. Clinical data and methods

2.1. General data

This study was conducted after patients or patient’s family sign the informed consent. A total of 160 cases of patients with ischemic stroke from January 2010 to January 2016 were selected, all
patients' conditions were consistent with the diagnosis standard of patients with ischemic stroke from "All kinds of cerebrovascular disease diagnosis", and the patients were confirmed by MRI and CT. 160 cases of patients were randomly divided into observation group and control group, each group was 80 cases. In the observation group, there were 46 males and 34 females, 18 cases of patients with multiple brain infarction, 30 cases of patients with basal nucleus infarction and 32 cases of patients with lacunar infarction, the ages were 50-79 years and the average were (64.9±5.5) years. In the control group, there were 44 males and 36 females, 19 cases of patients with multiple brain infarction, 31 cases of patients with basal nucleus infarction and 30 cases of patients with lacunar infarction, the ages were 50-79 years and the average were (65.3±5.6) years. The illness severity, weight and size etc in the two groups were not statistically different (P>0.05), each patient has no kidney disease, heart disease, liver disease, immune system disease, endocrine disease and other diseases, and has received no previous treatment and has detailed information before treatment.

2.2 Methods

The control group was received conventional therapy including control of intracranial pressure, oxygen, control of platelet aggregation, protection of the brain and nerve functions, activating brain and blood circulation. The observation group was given atorvastatin (approved by H20051408, Pfizer Pharmaceuticals Ltd) based on the above conventional treatment before bed with a dose of 20 mg/d, in the same time, the patients were given Huoxuetongmai capsules (approved by Z10880004, Shanxi Yooga Pharmaceuticals Ltd) with a dose of 3 capsules once (3 times a day). The treatment time of the two groups were 30 d.

2.3. Detecting indexes

4 mL of peripheral blood in patients with ischemic stroke before and after treatment were collected, the supernatant was collected after centrifugal and placed in -80 °C for subsequent testing. The indexes of tumor necrosis factor alpha (TNF alpha), C-reactive protein (CRP), interleukin 6 (IL-6) and interleukin 8 (IL-8) were detected by enzyme linked immunosorbent assay kit (Shanghai Enzyme-linked biological technology co., LTD, Shanghai Crystal biological engineering co., LTD, Jiangsu Jingmei biotechnology co., LTD). Platelet thrombus alkanes B2 (TXB2), D-dimer (DDI), fibrinolytic enzyme activators inhibitor (PAI-1), prothrombin time (PT) and fibrinogen (FIB) were detected by Sysmex automatic coagulometer (Japan), the experimental operations were conducted in strict accordance with the instructions.

Whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, maximum red blood cell aggregation index and hematocrit in patients were detected by fully automatic hemorheology detector (Type: ZL6000i), the experimental operations were conducted in strict accordance with the instructions.

2.4. Statistical analysis

SPSS 19.0 statistical package was conducted for statistical analysis of indexes in patients with ischemic stroke. Measurement data were described as mean ± standard deviation with variance analysis, pair wise comparison was conducted by t test, values of P<0.05 were considered to be statistically significant.

3. Results

3.1. Comparison of hemodynamic indexes in the two groups before and after treatment

The analysis and comparison of hemodynamic indexes in patients with ischemic stroke by hemorheology detector have found that: the comparison of hemodynamic indexes in the two groups before treatment was not statistically significant (P>0.05). Compared with before treatment, hemodynamic indexes (whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, maximum red blood cell aggregation index and hematocrit) in observation group after treatment by atorvastatin combined with Huoxuetongmai capsules significantly decreased, which were (4.32±0.43) mPa•s, (8.48±2.15) mPa•s, (1.71±0.09) mPa•s, (5.35±0.25) and (35.04±3.01)% respectively, and were considered to be statistically significant (P<0.05). Whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, maximum red blood cell aggregation index and hematocrit in control group after treatment significantly decreased, the comparison of hemodynamic indexes was statistically significant (P<0.05). Compared with control group after treatment, hemodynamic indexes in observation group after combined treatment significantly decreased, there were statistically significant difference between the groups (P<0.05). See Table 1.

3.2 Comparison of coagulation functions in the two groups before and after treatment

The analysis and comparison of coagulation functions in patients with ischemic stroke have found that: the comparison of coagulation function related indexes in the two groups before treatment was not statistically significant (P>0.05). Compared with before treatment, coagulation function related indexes (FIB, DDI, TXB2 and PAI-1) in observation group after treatment by atorvastatin combined with Huoxuetongmai capsules significantly decreased, while PT significantly increased, which were (3.16±0.25) g/L, (0.52±0.24) μg/mL, (63.55±5.75) pg/mL, (8.32±2.15) ng/mL and (14.31±0.51) s, respectively, and were considered to be statistically significant (P<0.05). FIB, DDI, TXB2 and PAI-1 in control group

Table 1.

Comparison of hemodynamic indexes in the two groups before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Whole blood high shear viscosity (mPa•s)</th>
<th>Whole blood low shear viscosity (mPa•s)</th>
<th>Plasma viscosity (mPa•s)</th>
<th>Maximum red blood cell aggregation index</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>before treatment</td>
<td>7.16±0.45</td>
<td>17.52±2.03</td>
<td>1.92±0.14</td>
<td>7.77±0.30</td>
<td>43.47±3.34</td>
</tr>
<tr>
<td></td>
<td>after treatment</td>
<td>4.32±0.43*</td>
<td>8.48±2.15*</td>
<td>1.71±0.09*</td>
<td>5.35±0.25*</td>
<td>35.04±3.01*</td>
</tr>
<tr>
<td>Control</td>
<td>before treatment</td>
<td>7.18±0.46</td>
<td>17.63±2.22</td>
<td>1.94±0.12</td>
<td>7.79±0.24</td>
<td>43.66±3.12</td>
</tr>
<tr>
<td></td>
<td>after treatment</td>
<td>5.39±0.51*</td>
<td>13.02±2.06*</td>
<td>1.80±0.14*</td>
<td>6.12±0.22*</td>
<td>39.22±3.25*</td>
</tr>
</tbody>
</table>

Note: compared with self before treatment, *P<0.05; compared with control group after treatment, †P<0.05.
after treatment significantly decreased, while PT significantly increased, the comparison of coagulation function related indexes was statistically significant ($P<0.05$). Compared with control group after treatment, coagulation function related indexes (FIB, DDI, TXB2 and PAI-1) in observation group after combined treatment significantly decreased, while PT significantly increased, there were statistically significant difference between the groups ($t=15.52$, 9.91 and 9.13, $P<0.05$). See Table 2.

3.3. Comparison of inflammation factors in the two groups before and after treatment

The analysis and comparison of inflammation factors in patients with ischemic stroke by ELISA have found that: the comparison of inflammation factors in the two groups before treatment was not statistically significant ($P>0.05$). Compared with before treatment, inflammation factors (IL-6, IL-8, CRP and TNF-$\alpha$ ) in observation group after treatment by atorvastatin combined with Huoxuetongmai capsules significantly decreased, which were (27.73±5.34) ng/mL, (146.71±15.42) pg/mL, (8.12±2.54) mg/L and (1.76±0.31) mg/L, respectively, and were considered to be statistically significant ($P<0.05$). IL-6, IL-8, CRP and TNF-$\alpha$ in control group after treatment significantly decreased, the comparison of inflammation factors was statistically significant ($P<0.05$). Compared with control group after treatment, inflammation factors (IL-6, IL-8, CRP and TNF-$\alpha$ ) in observation group after combined treatment significantly decreased, there were statistically significant difference between the groups ($P<0.05$). See Table 3.

4. Discussion

The lifestyle and living standards are constantly improved with the rapid development of society, and the number of patients with stroke enhances unceasingly, its mortality and morbidity are rising, and its incidence reached 120/100 thousand[5,6]. Stroke, heart disease and malignant tumor have become the diseases with the highest death rates in the current world[7]. Stroke could be divided into two kinds: ischemic stroke and hemorrhagic stroke. Atherosclerosis is one of the primary causes of induced ischemic stroke[8], atherosclerosis could cause vascular rupture or thrombosis, blood rheology change and increased blood cohesion[9], which make patients suffering blood vessel blockage, supply shortage of local brain blood, serious damage of ischemia, anoxia and necrosis[10]. Brain injury could cause troubles of movement and language with a serious impact on survival and quality of life for patients, which could severely weaken the patients' ability to return society and receive information. At present, the clinical treatment for ischemic stroke is given priority to thrombolysis, patients have obtained certain curative effects but still cannot meet the needs, fast and effective cures of ischemic stroke have become the priority of the medical and scientific research workers[11,12].

Statins are common preventive drugs for cardiovascular and cerebrovascular diseases, which have a good therapeutic effect on reducing blood fat, and could promote the increases of lower LDL cholesterol and high density lipoprotein cholesterol, suppressing inflammation in the body, stable plaques, and promote the recovery of damaged brain[13,14]. Aorvastatin is a common statin drug, which can not only be applied in lipid-lowering diminish inflammation and protecting brain, but also can restrain the proliferation of smooth muscle cells and improve brain blood flow loop[15,16], and ensure adequate blood, brain oxygen and nutrition supply, and plays an important role in the recovery of ischemic stroke. There are some adverse reactions for aorvastatin, too much or a long time treated with atorvastatin could cause myopathy of rhabdomyolysis, abnormal liver enzymes, diarrhea, nausea and etc[17], therefore, overcoming the adverse reaction is the key to ensure the treatment of ischemic stroke by atorvastatin. TCM holds that the occurrence of ischemic stroke is mainly caused by Qi deficiency and blood stasis, loss of blood oxygen, stasis resistance of choroid blood and etc, which could lead to language loss, disturbance of consciousness and hemiplegia for patients. Thus promoting blood circulation and removing blood stasis have become the treatment goals of ischemic stroke. The main active ingredient of Huoxuetongmai capsules is hirudin, which plays an important role in the inhibition of thrombosis. A large study showed that Huoxuetongmai capsules have good therapeutic effects on promoting blood circulation to remove blood stasis, improving microcirculation, adjusting blood coagulation function, expansion of the capillaries and reducing infarction[18], it is easy to use and has small side effects, which could be able to make up for the inadequacy of atorvastatin. The combination of these two drugs plays an important role in treatment of ischemic stroke and improvement of the patients' life.

This study showed that the treatment of ischemic stroke by atorvastatin combined with Huoxuetongmai capsules has improved hemodynamic indexes, inflammation factors and coagulation

### Table 2
Comparison of coagulation functions in the two groups before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>PT (s)</th>
<th>FIB (g/L)</th>
<th>DDI (µg/mL)</th>
<th>TXB2 (µg/mL)</th>
<th>PAI-1 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>before treatment</td>
<td>9.35±0.42</td>
<td>4.44±0.27</td>
<td>1.12±0.25</td>
<td>135.94±7.88</td>
<td>13.71±2.31</td>
</tr>
<tr>
<td></td>
<td>after treatment*</td>
<td>14.31±0.51*</td>
<td>3.16±0.25*</td>
<td>0.52±0.24*</td>
<td>63.55±5.75*</td>
<td>8.32±2.15*</td>
</tr>
<tr>
<td>Control</td>
<td>before treatment</td>
<td>9.40±0.39</td>
<td>4.48±0.26</td>
<td>1.14±0.24</td>
<td>132.78±5.82</td>
<td>13.67±2.37</td>
</tr>
<tr>
<td></td>
<td>after treatment*</td>
<td>11.51±0.48*</td>
<td>3.72±0.27*</td>
<td>0.85±0.26*</td>
<td>82.32±5.61*</td>
<td>11.45±2.29*</td>
</tr>
</tbody>
</table>

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

### Table 3
Comparison of inflammation factors in the two groups before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>IL-6 (ng/mL)</th>
<th>IL-8 (pg/mL)</th>
<th>CRP (µg/mL)</th>
<th>TNF-$\alpha$ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>before treatment</td>
<td>64.55±5.67</td>
<td>458.63±14.33</td>
<td>31.62±2.21</td>
<td>3.06±0.37</td>
</tr>
<tr>
<td></td>
<td>after treatment*</td>
<td>27.73±5.34*</td>
<td>146.71±15.42*</td>
<td>8.12±2.54*</td>
<td>1.76±0.31*</td>
</tr>
<tr>
<td>Control</td>
<td>before treatment</td>
<td>64.87±5.88</td>
<td>460.48±14.78</td>
<td>32.01±2.47</td>
<td>3.04±0.29</td>
</tr>
<tr>
<td></td>
<td>after treatment*</td>
<td>41.61±5.69*</td>
<td>190.73±15.69*</td>
<td>15.74±2.43*</td>
<td>2.04±0.26*</td>
</tr>
</tbody>
</table>

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

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function related indexes in patients with ischemic stroke. Hirudin in Huoxuetongmai capsules is a kind of effective thrombin inhibitors, which could prevent platelet aggregation, inhibit thrombin and platelet activating factor, and improve the patient's blood coagulation function[19]. Hirudin could decrease plasma viscosity, maximum red blood cell aggregation index and hematocrit, improve the patient's blood rheology and prevent the formation of thrombus[20]. What's more, hirudin could inhibit the increase of endothelial cell permeability and protect the endothelial cells at the same time[21]. The application of atorvastatin not only improves the patient's blood coagulation function, blood rheology and brain nerve, but also has significant inhibitory effects on inflammatory markers[22,23]. Inflammation factors (IL-6 and TNF) could promote the expression of tissue factors in monocyte and endothelial cells, and start the related blood coagulation system. Thrombin compounds, anticoagulant material and activated protein C would promote inflammation and eventually contribute to the dysfunction of organs[24]. Atorvastatin inhibits various cytotoxicity protease in patients' body, and further inhibits the synthesis of IL-6, IL-8, CRP and TNF- α [25]. Reduced inflammation factors have improved the patient's blood coagulation function and blood rheology.

In conclusion, the treatment of ischemic stroke by atorvastatin combined with Huoxuetongmai capsules could improve hemodynamic indexes, inflammation factors and coagulation function related indexes in patients with ischemic stroke, and provide help for clinical treatment of ischemic stroke.

References