Effect of intensive lipid-lowering therapy on inflammatory factors and fibrinolytic system in patients with acute cerebral infarction

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ARTICLE INFO

Objective: To investigate the effects of atorvastatin calcium on the inflammatory factors and fibrinolytic system in patients with acute cerebral infarction. Methods: A total of 170 inpatients with acute cerebral infarction in Neurological department of our hospital between December 2014 and December 2015 were selected as Subjects in the study, and randomly divided into intensive lipid-lowering therapy group (85 cases) and control group (85 cases). before the treatment, FPG, HbA1c (%), TG, TCH and LDL-C, HDL-C in patients were detected. hs-CRP, IL-6, IL-8, IL-10, TNF- in serum, and PAI-1, t-PA, FIB in plasma were detected and compared between before treatment and 8 weeks after the treatment. Results: patients with acute cerebral infarction in intensive lipid-lowering therapy group and control group showed no significant difference in inflammatory factors (hs-CRP, IL-6, IL-8, IL-10, TNF- ) and fibrinolytic system (PAI-1, t-PA, FIB) before treatment. After eight weeks of treatment, hs-CRP, IL-6, IL-8, TNF-, PAI-1 and FIB in patients in both groups were lower than that before treatment, and had statistical difference. IL-10, t-PA was increased than that before treatment and also had significant difference. In intensive lipid-lowering therapy group, the variation ranges of hs-CRP, IL-6, IL-8, IL-10, TNF-, PAI-1, t-PA and FIB were greater than that of the control group, and were statistically different. Conclusion: Atorvastatin calcium, the intensive lipid-lowering therapy, can reduce hs-CRP, IL-6, IL-8, TNF-, PAI-1, t-PA and FIB levels significantly in the acute cerebral infarction patients, and elevate levels of IL-10 and t-PA in serum. It has the effect on inhibiting inflammation and regulating the fibrinolytic activity.

1. Introduction

Acute cerebral infarction is a common disease in the middle-aged and old[1]. In particular, with the development of population aging, the morbidity of acute cerebral infarction is more and more higher[2]. As the disability rate and recurrence rate of acute cerebral infarction is high[3], it can bring a heavy burden to the family and society. So the prevention and treatment of acute cerebral infarction is extremely important. This study investigates the effects of atorvastatin calcium on the inflammatory factors and fibrinolytic system in patients with acute cerebral infarction, in order to provide a theoretical basis for clinical treatment.

2. Materials and methods

2.1. Clinical data

A total of 170 patients with acute cerebral infarction in Neurological department of our hospital between December 2014 and December 2015 were selected as subjects in the study, among whom there were 94 males and 76 females. Their mean age was (64.89 ± 11.94) years old. Inclusion criteria: (1) They were in line with the 2010 edition of acute cerebral infarction diagnosis standard set by the neurology branch of Chinese Medical Association[4]; (2) They were examined and verified acute cerebral infarction patients by head CT or MRI; (3) The onset time was less than 24 hours; (4) They were all willing to participate in this study, and their
compliance is good. Exclusion criteria: (1) Those aged more than 80 years; (2) Patients suffered from infectious diseases, rheumatism, rheumatoid immune diseases, endocrine disorders, coronary heart disease, acute myocardial infarction, malignant tumor diseases, etc.; (3) Patients with the history of cerebral infarction, cerebral hemorrhage or transient cerebral ischemia disease; (4) During pregnancy and lactation women; (5) Patients had used statin drugs, anti-inflammatory drugs within 8 weeks before the treatment; (6) Those did not want to participate in this study, or had terrible compliance. In accordance with the principle of randomization, 170 cases of acute cerebral infarction included in the study were divided into intensive lipid-lowering treatment group and control group, 85 patients in each group. All subjects signed informed consent. The study compared the general situations of all acute cerebral infarction patients in the intensive lipid-lowering therapy group and the control group, and found that patients in both groups had no statistical differences in gender, age, BMI, systolic blood pressure, diastolic pressure, FPG, HbA1c (%), TG, TCH and LDL-C, HDL-C, time of onset, and were comparable ($P>0.05$).

### 2.2. Treatment method

All patients in intensive lipid-lowering therapy group and control group were treated with basic symptomatic treatments of regulation of blood pressure, anti-platelet aggregation, neuroprotection etc. On the basis of symptomatic treatments, patients in the control group were given oral atorvastatin calcium 20 mg/d (Dalian Pfizer pharmaceuticals) for continuous 8 weeks; While the intensive lipid-lowering therapy group were given oral atorvastatin calcium 40 mg/d (Dalian Pfizer pharmaceuticals) for continuous 8 weeks on the basis of symptomatic treatments. Myocardial enzyme examination of kidney function was conducted in a medication week. If liver function enzymes were higher than 3 times the normal value, then stop the use of atorvastatin calcium. If patients suffered muscle soreness, rhabdomyolysis, and other adverse reactions, they should exit the treatment immediately.

### 2.3. Physical examination

Examination before treatment was performed on all patients, and systolic blood pressure, diastolic blood pressure and BMI data were collected.

### 2.4. Laboratory examination

5 mL Morning fasting venous blood was extracted for all patients on admission. The fasting plasma glucose (FPG), glycosylated hemoglobin [HbA1c, cholesterol (TG), triglyceride (TCH), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were detected by the Beckman automatic biochemistry analyzer. Fasting venous blood 5ml of all the patients were respectively taken before treatment and 8 weeks after treatment, from which serum was separate. And the concentration of high sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin 8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-a (TNF-a) was tested. Hs CRP, IL-6, IL-8, IL-10 and TNF-a was detected by enzyme linked immunoassay with the detection kit produced by Shanghai ailex company, and the detection was strictly according to the instructions. At the same time, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), plasma fibrinogen (FIB) was tested from 5 mL fasting venous blood of all the patients taken before treatment and 8 weeks after treatment. The PAI-1 and t-PA was detected by enzyme linked immunoassay with the detection kit produced by Shanghai ailex company and the detection was strictly according to the instructions. While Detection of FIB was conducted by FM-16 computer plasma fibrin original determination instrument (Siemens).

### 2.5. Data input and analysis

Data Epi 3 software was used for entry of the survey data, and SPSS 20 statistical software package was used for statistical analysis when data had been checked. Measurement data was indicated by mean ± standard deviation. Comparison in group adopted Z test with the paired data, and comparison between groups adopted Z test with independent samples. $P<0.05$ indicated that the difference has statistical significance.

### 3. Results

#### 3.1 Comparison of inflammatory factors in patients with acute cerebral infarction in 2 groups, the intensive lipid-lowering therapy group and the control group

In this study, through the comparison of inflammatory factors in

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>hs-CRP (ng/mL)</th>
<th>IL-6 (pg/mL)</th>
<th>IL-8 (pg/mL)</th>
<th>IL-10 (pg/mL)</th>
<th>TNF-α (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive lipid lowering treatment group ($n=85$)</td>
<td>Before treatment</td>
<td>7.69±3.58</td>
<td>15.53±8.65</td>
<td>109.68±6.32</td>
<td>17.42±5.26</td>
<td>9.05±2.18</td>
</tr>
<tr>
<td></td>
<td>After the treatment</td>
<td>1.72±0.36*</td>
<td>6.41±2.15**</td>
<td>42.09±11.36*</td>
<td>30.54±5.69*</td>
<td>3.22±1.05*</td>
</tr>
<tr>
<td>Control group ($n=85$)</td>
<td>Before treatment</td>
<td>7.65±3.69</td>
<td>15.82±8.73</td>
<td>108.53±7.11</td>
<td>16.38±6.20</td>
<td>8.92±2.34</td>
</tr>
<tr>
<td></td>
<td>After the treatment</td>
<td>4.08±0.94*</td>
<td>10.11±3.80*</td>
<td>65.46±11.29*</td>
<td>23.53±6.47*</td>
<td>5.27±1.94*</td>
</tr>
</tbody>
</table>

Note: Compared with the same group before treatment, *$P<0.05$; Compared with the control group after treatment, **$P<0.05$.
patients with acute cerebral infarction in the treatment group and the control group, it was found that the levels of serum hs-CRP, IL-6, IL-8, IL-10 and TNF-a before treatment in patients in two groups had no significant difference (P>0.05). After eight weeks of treatment, serum hs-CRP, IL-6, IL-8, TNF-a in patients in two groups reduced compared with those before treatment, and it had significant difference (P<0.05). Serum IL-10 was increased than that before treatment and also had significant difference (P<0.05). In intensive lipid-lowering treatment group, the variation ranges of hs-CRP, IL-6, IL-8, IL-10, and TNF-a were greater than that of the control group, and were statistically different (P<0.05). See table 1.

3.2. Comparison of fibrinolytic system in patients with acute cerebral infarction in 2 groups, the intensive lipid-lowering therapy group and the control group

In this study, through the comparison of fibrinolytic system in patients with acute cerebral infarction in the treatment group and the control group, it was found that the plasma PAI-1, t-PA, FIB before treatment in patients in two groups had no significant difference (P>0.05). After eight weeks of treatment, plasma PAI-1, FIB in patients in two groups reduced compared with those before treatment, and it had significant difference (P<0.05). Plasma t-PA was increased than that before treatment and also had significant difference (P<0.05). In intensive lipid-lowering treatment group, the variation ranges of the plasma PAI-1, t-PA and FIB were greater than that of the control group, and were statistically different (P<0.05). See table 2.

4. Discussions

In 2009, scholars in European and American countries put out the concept of intensive lipid-lowering therapy for acute cerebral infarction patients[5]. There are not many studies on this subject in our country[6]. In this study, atorvastatin calcium was used in the intensive lipid-lowering therapy on patients with acute cerebral infarction. And it explored the effect of atorvastatin calcium on inflammatory factors and fibrinolytic system in patients with acute cerebral infarction, providing an important theoretical basis for the clinical treatment.

Acute cerebral infarction occurs on the basis of atherosclerosis, of which the inflammation is an important cause[7]. The main function of Serum hs-CRP, the acute inflammatory reaction protein, is to promote secretion of neutrophils, basophils and other inflammatory cells[8,9]. At the same time, it activates complement and monocyte macrophage system, and thereby it involves the inflammatory reaction of atherosclerosis. IL-6 can interacts with hs-CRP, promoting each other to release, thus participates in the inflammatory reaction[10]; The main role of IL-8 is to promote the release of neutrophils, inhibit its apoptosis, and promote the transference of neutrophils to cerebral ischemic areas, which clogs up blood vessels and induces generation of inflammatory cells to produce brain injury[11]; IL-10 is an important anti-inflammatory factor, which can inhibit the production of inflammatory factors IL-6, TNF-a, etc. And it protects cerebral cells in cerebral ischemia[12]. TNF-a is an important inflammatory factor. It can induce synthesis and release of potent vasoactive substances, increase capillary permeability, and plays an important role in the inflammatory reaction of acute cerebral infarction[13]. Currently, researches[14-17] has found that statins can decrease the level of inflammatory factors and exert anti-inflammatory effects, but the effect of regular doses of statins in the treatment of acute cerebral infarction is poor. In recent years, the high dose of statins used in intensive lipid-lowering therapy on acute cerebral infarction has better effect. In this study, through the comparison of inflammatory factors in patients with acute cerebral infarction in the treatment group and the control group, it was found that the levels of serum hs-CRP, IL-6, IL-8, IL-10 and TNF-a before treatment in patients in two groups had no significant difference (P>0.05). After eight weeks of treatment, serum hs-CRP, IL-6, IL-8, IL-10, TNF-a in patients in two groups reduced compared with those before treatment, and it had significant difference (P<0.05). Serum IL-10 was increased than that before treatment and also had significant difference (P<0.05). In intensive lipid-lowering treatment group, the variation ranges of hs-CRP, IL-6, IL-8, IL-10, and TNF-a were greater than that of the control group, and were statistically different (P<0.05). See table 2.

### Table 2
Comparison of fibrinolysis system in patients with acute cerebral infarction in 2 groups, the intensive lipid-lowering therapy group and the control group.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>PAI-1 (ng/mL)</th>
<th>t-PA (IU/L)</th>
<th>FIB (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive lipid lowering treatment group</td>
<td>85</td>
<td>Before treatment</td>
<td>15.67±3.28</td>
<td>1.50±0.34</td>
<td>5.36±1.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After the treatment</td>
<td>8.22±3.21 *</td>
<td>2.93±0.42 *</td>
<td>3.14±0.56 *</td>
</tr>
<tr>
<td>Control group</td>
<td>85</td>
<td>Before treatment</td>
<td>15.89±3.47</td>
<td>1.41±0.38</td>
<td>5.27±1.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After the treatment</td>
<td>12.40±2.50 *</td>
<td>1.96±0.39</td>
<td>4.02±0.61</td>
</tr>
</tbody>
</table>

Note: Compared with the same group before treatment, *P<0.05; Compared with the control group after treatment, *P<0.05.
in patients with acute cerebral infarction in the treatment group and the control group, it was found that the plasma PAI-1, t-PA, FIB before treatment in patients in two groups had no significant difference (P>0.05). After eight weeks of treatment, plasma PAI-1, FIB in patients in two groups reduced compared with those before treatment, and it had significant difference (P<0.05). Plasma t-PA was increased than that before treatment and also had significant difference (P<0.05). In intensive lipid-lowering treatment group, the variation ranges of the plasma PAI-1, t-PA and FIB were greater than that of the control group, and were statistically different (P<0.05). Therefore, a larger dose of atorvastatin calcium in intensive lipid lowering treatment can reduce plasma PAI-1, FIB levels, increase t-PA level, and enhance the fibrinolytic activity, so as to achieve therapeutic effect.

In summary, atorvastatin calcium adopted in intensive lipid-lowering therapy can reduce levels of hs-CRP, IL-6, IL-8, TNF-a, PAI-1, FIB, elevate levels of serum interleukin-10 (IL-10) and t-PA significantly in patients with acute cerebral infarction. It is effective in inhibiting inflammation, and regulating of fibrinolytic activity.

References