Effect of High-Dose Atorvastatin Therapy on Patients with Acute Cerebral Infarction

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Abstract

Background: This study was to investigate the clinical effect of high-dose atorvastatin on patients with acute cerebral infarction.

Materials and Methods: 234 patients with acute cerebral infarction were randomized divided into control group (n=78), high-dose atorvastatin (HDA) group (n=78) and low-dose atorvastatin (LDA) group (n=78). 80L group and 20L group were received lovastatin 80 mg/d or 20 mg/d respectively for three months, and all of subjects received the same conventional treatments. Biochemical indices, plaque thickness and volume and neurological deficit were assessed and recorded before and after treatment.

Results: After atorvastatin treatment, the plasma levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) were significantly decreased in HDA group and LDA group, and high-density lipoprotein (HDL) were significantly increased in HDA group and LDA group (P<0.05). Moreover, atorvastatin could also decreased MMP-9 and hs-CRP levels (P<0.05), two major inflammatory factors in plasma. In addition, atorvastatin treatment also improved plaque status include plaque thickness and volume in HDA group and LDA group (P<0.05). Furthermore, improved neurological deficit were found in atorvastatin treatment groups.

Conclusion: This study demonstrated that high-dose of atorvastatin has a good therapeutically effect on patients with acute cerebral infarction which could significantly improve plasma lipids levels, enhances anti-inflammation effect and decreased plaque thickness and volume than low-dose of atorvastatin.

Keywords: High-dose; low-dose; atorvastatin; acute cerebral infarction

Introduction

Cerebro Vascular Disease (CVD) accounts for the one of major causes of morbidity and mortality in developed countries, and it is the third most common cause of death worldwide and responsible for stroke and Transient Ischemic Attack (TIA) [1-5]. There are about 500,000 new or recurrences stroke cases each year [6].

Atorvastatin, a kind of statins, is one of the most widely prescribed drugs in the world. Evidences demonstrated that atorvastatin could stable plaque and improve the long-term prognosis of patients with CVD [7,8]. The common dose of atorvastatin for CVD treatment was 10 mg/d, 20 mg/d or 40 mg/d [9-11]. Very few reports on high-dose (e.g. 80 mg/d or 100 mg/d) atorvastatin therapy for patients with acute cerebral infarction [12].

In this study, 80 mg/d atorvastatin therapy was performed for CVD treatment. Biochemical indices, neurological deficit and adverse reactions were assessed and recorded after treatment to evaluate the outcome of high-dose atorvastatin therapy on patients with acute cerebral infarction.

Materials and Methods

Ethical Statements

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Guangzhou overseas Chinese hospitals and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Patient Population

This prospective cohort study was performed from February 2015 to March 2016. A total of 234 patients with acute cerebral infarction were admitted to the neurology departments of Guangzhou overseas Chinese hospitals within 72 of stroke (Table 1) were studied. This study was approved by the Institutional Review Board of Guangzhou overseas Chinese hospitals, and all participants gave written informed consent.

All the patients with acute cerebral infarction were confirmed by computerized tomography or magnetic resonance imaging, and all of the chose subjects were acute ischemic/embolic stroke. They received no any other lipid, hormones, anti-inflammatory or anti-oxidant drugs during atorvastatin treatment. Patients with malignant, anaemia, hyperpyrexia, autoimmune disease, malnutrition were excluded from this study. The pregnant and lactating women were also removed from this study.
### Table 1: Baseline features of 234 patients with acute cerebral infarction.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n=78)</th>
<th>High-dose atorvastatin group (n=78)</th>
<th>Low-dose atorvastatin group (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.3 ± 11.4</td>
<td>61.4 ± 11.5</td>
<td>61.7 ± 11.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>45 (55.1)</td>
<td>47 (60.3)</td>
<td>50 (64.1)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>43 (62.4)</td>
<td>49 (62.8)</td>
<td>46 (59.0)</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>13 (16.7)</td>
<td>13 (16.7)</td>
<td>16 (20.5)</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td>44 (56.4)</td>
<td>40 (51.3)</td>
<td>42 (53.8)</td>
</tr>
<tr>
<td>Drinking (%)</td>
<td>8 (10.3)</td>
<td>13 (16.7)</td>
<td>11 (14.1)</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>155.9 ± 21.9</td>
<td>156.9 ± 23.1</td>
<td>158.7 ± 25.4</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>87.6 ± 12.9</td>
<td>86.6 ± 14.2</td>
<td>89.3 ± 16.2</td>
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</table>

**Treatments**

Control group received the conventional treatments including dehydration of intracranial pressure, brain protection, circulation improvement, and symptomatic treatments. HDA group and LDA group received conventional treatment together with atorvastatin 80 mg/d and 10 mg/d respectively. All the treatments were performed for three months.

**Plasma lipid and inflammatory factors analysis**

Blood for lipid and inflammatory factors analysis were collected from each group before and after treatments. Plasma was separated by centrifugation at 4,000 rpm for 20 min at 4 and stored at -80. Plasma total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), MMP-9 and hs-CRP levels were measured by automatic biochemistry analyzer (Xiangtan, DHF84, Xiangtan, China).

**Measurement of plaque thickness and volume**

We measured the anterior cerebral artery and middle cerebral artery plaque thickness and volume of patients using color Doppler ultrasound (Mind ray, DC-N6, Shenzhen, China) in three groups to determine the effect of high-dose/low-dose lovastatin on plaque.

**Evaluation of neurological deficit**

Neurological deficit were conducted in control group, 80L group and 20L group according to the National Institute of Health Stroke Scale (NIHSS) criterion. NIHSS is a 15-item impairment scale used to measure stroke severity. The NIHSS includes the following domains: level of consciousness, eye movements, integrity of visual fields, facial movements, arm and leg muscle strength, language, sensation, coordination, neglect and speech. Item scores are summed to a total score ranging from 0 to 42 [13].

**Statistical analysis**

Data are presented as mean ± SD. Comparisons of patients’ clinical parameters and the patients’ outcome between groups were analyzed using the Mann-Whitney U test. A difference is considered significant if P<0.05 or P<0.01. All statistical analyses were carried out using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA).

**Results**

### Demographic and baseline characteristics

The clinical characteristics of the patients were summarized in Table 1. This study involved 234 patients (142 male, 92 female) aged 49-74 years (mean 61.8 ± 11.3 years). Hypertension was found in 138 patients (59%) and type 2 diabetes mellitus in 42 patients (17.9%). There were 126 patients (53.8%) were smokers and 32 patients (13.7%) were alcoholics. The mean systolic pressure of the patients was 157.2 ± 23.5, and the mean diastolic pressure of the patients was 87.8 ± 14.4. All the patients involved in this study were divided randomly into control group, HDA group and LDA group. There were no differences found about baseline characteristics among three groups (P < 0.05). Finally, 5 patients in HDA group and 4 patients in LDA group were excluded.

**High-dose atorvastatin can better improve plasma Lipids levels**

We measured concentration of plasma TC, TG, LDL and HDL in control group, HDA group and LDA group before and after treatment to determine the effect of high-dose atorvastatin on plasma lipids. Results established that both low-dose and high-dose atorvastatin decreased significantly plasma lipid levels including TG, TC and LDL (Figure 1a, b, c). Moreover, TG, TC and LDL levels were decreased notably in HDA group compared with LDA group (P<0.05). In addition, the plasma HDL concentration was increased significantly in HDA group and LDA group (Figure 1d), and the HDL level was higher in HDA group than LDA group (P < 0.05).

**High-dose atorvastatin can better improve inflammation**

To assess the effect of high-dose atorvastatin on the inflammation, levels of hs-CRP and MMP-9 were determined in control group, HDA group and LDA group. These results showed that High-dose or low-dose atorvastatin significantly decreased both MMP-9 and hs-CRP expression levels (Figure 2a, b). Furthermore, the high-dose atorvastatin has a better ability in improving inflammation compared with LDA group.

**High-dose atorvastatin can better reduce plaque thickness and volume**

In order to know the changes of plaque after treated with atorvastatin, plaque thickness and volume were detected. The results indicated that atorvastatin could significantly decrease plaque thickness and volume at the dose of 80 mg/d or 10 mg/d. Furthermore, the plaque thickness and volume were lower in HDA group, compared with LDA group (Figure 3, P<0.05).
Figure 1: Plasma lipids levels of different groups were measured. TC (a), TG (b) and LDL (c) were significantly decreased after treated with atorvastatin, while HDL (d) was significantly increased. Data are presented as mean ± SD. *P< 0.05 and **P< 0.01 after treatment vs. before treatment in HDA group; *P< 0.05 after treatment in HDA group vs. after treatment in LDA group; #P<0.05 after treatment vs. before treatment in LDA group.

Figure 2: Inflammatory factors content in plasma. The content of hs-CRP (a) and MMP-9 (b) were measured. Data are presented as mean ± SD. *P< 0.05 and **P< 0.01 after treatment vs. before treatment in HDA group; *P< 0.05 after treatment vs. before treatment in LDA group.

High-dose atorvastatin can better improve patients’ outcome

Neurological deficit was evaluated and scored in control group, HDA group and LDA group before and after the treatment. NIHSS scores can reflect the patients’ outcome, the higher the score, the more severe the stroke. As shown in Table 2, both HDA and LDA groups got lower scores than control group. In addition, the NIHSS score was lower in HDA group than LDA group (P<0.05).

Discussion

Demographic and baseline characteristics

Atherosclerosis is a systemic disease with high level of lipid and responsible for major clinical events, such as stroke and acute cerebral infarction [14-16]. Atherosclerosis is the principal cause of death in the USA, Europe, and parts of Asia [17, 18]. Atorvastatin was an effective lipid-lower drug that was used extensively in many medical practices [19-21]. Atorvastatin has been shown to
reduce the progression of coronary atherosclerosis and clinical trials indicated that treatment with atorvastatin could reduce the morbidity and mortality of CVD [22]. In this study, we find that low-dose and high-dose of atorvastatin regulated plasma lipids levels including significantly decreased cholesterol, triglycerides, and LDL levels and dramatically increased HDL level. Moreover, high-dose of atorvastatin could strengthen this effect compared with low-dose of atorvastatin.

Clinical further studies demonstrated that atorvastatin not only regulated plasma lipids concentrations, but also improved inflammation response, such as enhances anti-inflammation effect in CVD [23-25]. Hs-CRP and MMP-9, two major inflammation markers, were elevated significantly in atorvastatin treated patients of this study. In addition, the plasma hs-CRP and MMP-9 levels were higher in HDA group than LDA group. Additional studies shown that, besides the lipid-lower effect, atorvastatin could also stabilized the atherosclerotic plaque and have beneficial effects on cerebral circulation and brain parenchyma during ischemic stroke and reperfusion [26]. We measured the plaque thickness and volume of patients in three groups and found that atorvastatin could significantly decreased plaque thickness and volume. Furthermore, the plaque thickness and volume were lower in HDA group, compared with LDA group.

The common dose of atorvastatin for CVD treatments were 10 mg/d, 20 mg/d or 40 mg/d. However, few reports were found on high-dose (e.g. 80 mg/d or 100 mg/d ) atorvastatin therapy for patients with acute cerebral infarction. In this study, 80 mg/d atorvastatin was used to assess its effect on CVD. We found that high-dose of atorvastatin could significantly improve plasma lipids levels, enhances anti-inflammation effect and decreased plaque thickness and volume than low-dose of atorvastatin. In addition, no adverse effect was found in HDA group.

**Figure 3:** Measure the thickness and volume of plaque. The thickness (A) and volume (B) of plaque before treatment and after treatment were measured using color Doppler ultrasound. Data are presented as mean ± SD. *P< 0.05 and **P< 0.01 after treatment vs. before treatment in HDA group; *P< 0.05 after treatment.

Table 2: Neurological deficit were conducted according to the National Institute of Health Stoke Scale (NIHSS) criterion.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>Control group</td>
<td>11.25±1.94</td>
<td>8.29±0.59</td>
</tr>
<tr>
<td>HDA group</td>
<td>11.17±1.74</td>
<td>7.08±0.41*</td>
</tr>
<tr>
<td>LDA group</td>
<td>11.45±1.84</td>
<td>7.62±0.55*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *P< 0.05 after treatment versus before treatment in HDA group; *P< 0.05 after treatment in HDA group versus after treatment in LDA group; *P<0.05 after treatment versus before treatment in LDA group.

**References**


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