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

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Abstract

Cerebrovascular disease (CVD) accounts for the major cause of morbidity and mortality in industrialized countries. However, effects of high-dose simvastatin therapy on patients with acute cerebral infarction still unclear. In this study, the clinical efficacy of high-dose simvastatin on patients with cerebral infarction was investigated. A total of 180 patients with acute cerebral infarction were randomized divided into control group (n=60), high-dose simvastatin (HDS) group (n=60) and low-dose simvastatin (LDS) group (n=60). Control group, HDS group and LDS group received conventional treatment, conventional treatment together with simvastatin 80 mg/d and conventional treatment as well as simvastatin 40 mg/d respectively for 3 months. Biochemical indices, neurological deficit and plaque thickness and volume were assessed and recorded after treatment. After simvastatin treatment, the plasma levels of Triglyceride, Total cholesterol, Low-density lipoprotein were significantly decreased in HDS group and LDS group, and HDS were significantly increased in HDS group and LDS group. Also, simvastatin decreased levels of IL-6 and TNF-α, two major inflammatory factors in plasma. Furthermore, improved neurological deficit were found in simvastatin treatment groups. In addition, simvastatin treatment also improved plaque states include plaque thickness and volume in HDS group and LDS group. Therefore, simvastatin could improve acute cerebral infarction and high-dose of simvastatin treatment was better than low-dose of simvastatin treatment.

Keywords: High-dose; Simvastatin; Acute cerebral infarction

Introduction

Cerebrovascular disease (CVD) is the third most common cause of death worldwide [1,2]. CVD accounts for the major cause of morbidity and mortality in industrialized countries and responsible for stroke and transient ischemic attack (TIA) [3,4]. There are about 500,000 new or recurrences stroke cases each year [5].

Simvastatin (epistatin), an HMG-CoA reductase inhibitor, acts by decreasing cholesterol synthesis and by increasing low density lipoprotein (LDL) catabolism via increased LDL receptor activity [6]. Simvastatin was beneficial in a lot of immunologic VCD [7]. Evidences indicated that simvastatin could stable plaque and improve the long-term prognosis of patients with CVD [8]. The common dose of simvastatin for CVD treatment was 10 mg/d to 40 mg/d [9]. No reports were reported on high-dose simvastatin therapy (e.g. 80 mg/d or 100 mg/d) for patients with acute cerebral infarction.

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

Methods

Study population

This prospective cohort study was performed from October 2015 to August 2016. A total of 180 patients with acute cerebral infarction were admitted to the neurology departments of the 88 Hospital of People’s Liberation Army during 72 hours of stroke (Table 1) were studied. This study was approved by the Institutional Review Board of the 88 Hospital of People’s Liberation Army (Number: HPLA2167529), and all participants gave written informed consent.

| Characteristic     | Control group (n=60) | HDS group (n=60) | LDS group (n=60) |
|--------------------|----------------------|------------------|------------------|
| Age, years         |                      |                  |                  |
| Male, n (%)        | 62.1 ± 11.9          | 61.6 ± 13.1      | 62.4 ± 10.8      |
| Hypertension n (%) | 42 (70.0)            | 39 (65.0)        | 40 (66.7)        |

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Demographic and baseline characteristics

The clinical characteristics of the patients were summarized in Table 1. This study involved 180 patients (121 males, 59 females) aged 48-74 years (mean 62.0 ± 11.9 years) with ~52 culprit lesions. Hypertension was found in 119 patients (66.1%) and type 2 diabetes mellitus in 26 patients (14.4%). There were 99 patients (55.0%) who were smokers and 26 patients (14.4%) who were alcoholics. The mean systolic pressure was 157.1 ± 21.9, and the mean diastolic pressure was 87.4 ± 15.4. All the patients involved in this study were divided randomly into control group, HDS ± 21.9, and the mean diastolic pressure was 87.4 ± 15.4. All the patients (14.4%) were alcoholics.

Results

Treatments

Control group received conventional treatments including dehydration of intracranial pressure, brain protection, circulation improvement, and symptomatic treatments. High-dose simvastatin (HDS) therapy group and low-dose simvastatin (LDS) therapy group received conventional treatment together with simvastatin 80 mg/d or 20 mg/d respectively. All the treatments were performed for 3 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 3,000 rpm for 15 min at 4°C and stored at -80. Levels of plasma total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), IL-6 and TNF-α were measured by automatic biochemistry analyzer.

Evaluation of neurological deficit

Neurological deficit were conducted in control group, HDS group and LDS group according to NIHSS criterion.

Statistical analysis

Data are presented as mean ± SD. Comparisons of patients' clinical parameters and overall survival times between groups were analyzed using the Mann-Whitney U test. A difference is considered significant if P<0.05. All statistical analyses were carried out using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA).

High-dose simvastatin regulated plasma lipids levels

Concentration of plasma TG, TC, LDL and HDL in control group, HDS group and LDS group were measured before and after treatment to determine the effect of high-dose of simvastatin on plasma lipids. Results indicated that both low-dose and high-dose simvastatin significantly decreased plasma lipid levels including cholesterol, triglycerides, and LDL (Table 2). Furthermore, levels of cholesterol and triglycerides were decreased notably in HDS group compared with LDS group. In addition, the plasma HDL concentration was significantly increased in HDS group and LDS group. The HDL level was higher in HDS group than LDS group.

High-dose simvastatin regulated levels of IL-6 and TNF-α

To assess the effect of high-dose simvastatin on the inflammation, levels of IL-6 and TNF-α were determined of each group. Results showed that simvastatin significantly decreased both levels of IL-6 and TNF-α (Table 3). Furthermore, high-dose simvastatin has a better ability in improving inflammation because of levels of IL-6 and TNF-α were lower in HDS group.

Table 1: Baseline features of the study patients.

|                      | Control group | HDS group | LDS group |
|----------------------|---------------|-----------|-----------|
| Diabetes n (%)       | 9 (15.0)      | 7 (11.7)  | 10 (16.7) |
| Smoking n (%)        | 33 (55.0)     | 35 (58.3) | 31 (51.7) |
| Drinking %           | 8 (13.3)      | 10 (16.7) | 8 (13.3)  |
| Systolic pressure    | 157.1 ± 20.5  | 156.4 ± 21.1 | 157.9 ± 24.2 |
| Diastolic pressure   | 87.3 ± 13.3   | 86.9 ± 16.4 | 88.1 ± 16.5 |

Table 2: Plasma lipids levels of different groups.

| Group | Control group | HDS group | LDS group |
|-------|---------------|-----------|-----------|
|       | Before (mmol/L) | After (mmol/L) | Before (mmol/L) | After (mmol/L) | Before (mmol/L) | After (mmol/L) |
| TG    | 1.5 ± 0.3     | 1.6 ± 0.5  | 0.8 ± 0.3*  | 1.8 ± 0.5     | 1.4 ± 0.3▲  |
| TC    | 5.5 ± 0.8     | 5.3 ± 0.8  | 5.0 ± 0.7   | 3.4 ± 0.3*    | 5.1 ± 0.5   | 4.4 ± 0.4▲  |
| LDL   | 2.9 ± 0.8     | 3.1 ± 1.1  | 3.0 ± 1.0   | 2.2 ± 0.5*    | 3.2 ± 0.7   | 2.6 ± 0.6▲  |
| HDL   | 1.1 ± 0.3     | 1.3 ± 0.3  | 1.0 ± 0.4   | 1.8 ± 0.4*    | 1.1 ± 0.2   | 1.5 ± 0.3▲  |

Table 3: Plasma levels of IL-6 and TNF-α.

| Group | Control group | HDS group | LDS group |
|-------|---------------|-----------|-----------|
|       | Before | After | Before | After | Before | After |
| IL-6  |        |       |        |       |        |       |
| TNF-α |        |       |        |       |        |       |

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Table 3: Levels of plasma IL-6 and TNF-α of different groups. Data are presented as mean ± SD. *P<0.05 after treatment versus before treatment in HDS group; ▲P<0.05 after treatment in HDS group versus after treatment in LDS group; ▲P<0.05 after treatment versus before treatment in LDS group.

| Group | Before | After |
|-------|-------|-------|
| IL-6  | 277.5 ± 16.3 | 288.4 ± 15.1 |
|       | 284.9 ± 18.7 | 217.8 ± 13.3 |
| TNF-α | 1.89 ± 0.24  | 1.91 ± 0.22  |
|       | 1.88 ± 0.21  | 0.92 ± 0.14* |

High-dose simvastatin improved neurological deficit

Neurological deficit was evaluated and scored in control group, HDS group and LDS group before and after the treatment. As shown in table 4, both HDS and LDS groups got lower scores than control group. In addition, the neurological deficit score was lower in HDS group than LDS group.

Table 4: Neurological deficit scores of different groups. Data are presented as mean ± SD. *P<0.05 after treatment versus before treatment in HDS group; ▲P<0.05 after treatment in HDS group versus after treatment in LDS group; ▲P<0.05 after treatment versus before treatment in LDS group.

| Group | Before | After |
|-------|-------|-------|
| Control group | 11.29 ± 2.98 | 8.97 ± 0.95 |
| HDS group | 11.44 ± 3.22 | 7.32 ± 0.64* |
| LDS group | 11.33 ± 3.70 | 7.81 ± 0.56▲ |

High-dose simvastatin improved plaque thickness and volume

The plaque thickness and volume of patients of each group were measured to further determine the influence of high-dose of simvastatin on plaque. Data showed that simvastatin significantly decreased plaque thickness and volume. Furthermore, the plaque thickness and volume were lower in HDS group, compared with LDS group (Figure 1).

Discussion

Simvastatin is a long-established hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, first introduced in 1988 [10]. Simvastatin would also inhibit the biosynthesis of isoprenoid intermediates such as geranyl and farnesyl pyrophosphate, and then affect the posttranslational prenylation of several important cell-signaling proteins during immune responses [11]. Therefore, simvastatin has been shown to have antitumor potential in many different cell lines [12-14].

Atherosclerosis is a systemic disease with high level of lipid and responsible for major clinical events, such as stroke and acute cerebral infarction [15]. Atherosclerosis is the principal cause of death in the USA, Europe, and parts of Asia [16]. Simvastatin was an effective lipid-lower drug that was used extensively in many medical practices [17]. Simvastatin been shown to reduce the progression of coronary atherosclerosis and clinical trials indicated that treatment with simvastatin could reduce the morbidity and mortality of CVD [18]. In this study, we find that low-dose and high-dose of simvastatin regulated plasma lipids levels including significantly decreased cholesterol, triglycerides, and LDL levels and dramatically increased HDL level. Moreover, high-dose of simvastatin could strengthen this effect compared with low-dose of simvastatin.

Clinical further studies demonstrated that simvastatin not only regulated plasma lipids concentrations, but also improved inflammation response, such as enhances anti-inflammation effect in CVD [19,20]. IL-6 and TNF-α, two major inflammation markers, were elevated significantly in simvastatin treated patients of this study. IL-6 and TNF-α levels were higher in HDS group than LDS group.

Additional studies shown that, besides the lipid-lower effect, simvastatin could also stabilized the atherosclerotic plaque and have beneficial effects on cerebral circulation and brain parenchyma during ischemic stroke and reperfusion [21]. We measured the plaque thickness and volume of patients in three groups and found that simvastatin could significantly decreased plaque thickness and volume.
Furthermore, the plaque thickness and volume were lower in HDS group, compared with LDS group.

The common dose of simvastatin for CVD treatments was 10 mg/d to 40 mg/d. However, very few reports were found on high-dose (e.g. 80 mg/d) simvastatin therapy for patients with acute cerebral infarction. In this study, 80 mg/d simvastatin was used to assess its effect on CVD. We found that high-dose of simvastatin could significantly improve plasma lipids levels, enhances anti-inflammation effect and decreased plaque thickness and volume than low-dose of simvastatin. In addition, the adverse effects in HDS group were mild and transient.

In conclusion, this prospective, randomized, placebo-controlled trial demonstrated that treatment with 80 mg of simvastatin per day has a better therapeutic effect on patients with acute cerebral infarction than 20 mg of simvastatin one day. These results support the initiation of simvastatin treatment after a stroke or TIA.

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Declaration of Interests

The authors have no conflict of interest to disclose.

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