Clinical Effects of Chuanxiongsu in the Treatment of Prehypertension Patients with Hyperlipemia

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Abstract: Objective to observe the clinical effects of Chuanxiongsu in treatment of prehypertensive patients with hyperlipemia, and to investigate the possible mechanism of action. Methods A total of 200 cases of prehypertension with hyperlipemia were selected as our subjects, who were in out-patients clinic of Hubei Provincial Women’s & Children’s Hospital and Xinzhou District General Hospital in Wuhan, and were randomly divided into treatment group (A) and control group (B), 100 in each group. Patients in group B received Simvastatin, and patients in group A received Chuanxiongsu for 8-week treatment. The levels of blood pressure and blood lipid were measured before and after treatment for two groups of patients. And 100 healthy volunteers served as healthy control group (C). Results Compared with pretherapy, the level of blood lipid was significantly different after 8 weeks treatment in both groups (P<0.01), while no significant discrepancy was observed (P>0.05) between the two groups. Blood pressure decreased more in group A than group B, with statistic significance (P<0.01), after treatment. Meanwhile, group A experienced less side-effect than group B. Conclusion Chuanxiongsu, as an alternative to Simvastatin, can markedly improve blood lipid metabolism, effectively reduce the level of blood pressure to some extent that alleviates development of prehypertension, and is safer than Simvastatin. Totally, curative effect of Chuanxiongsu is better than that of Simvastatin, thus Chuanxiongsu is suggested to be applied in treatment of prehypertension patients with hyperlipemia.

Keywords: Chuanxiongsu Tablets, Simvastatin Capsule, Lipid, Blood Pressure, Prehypertension, Hyperlipemia, Comparative Effectiveness Research

1. Introduction
The incidence of prehypertension is higher and higher, which may progress to hypertension if not to intervene [1]. Therefore, both hypertension and blood lipid metabolic abnormalities are as major risk factors for cardio-cerebrovascular diseases. Lipid-regulating effect with Western medicine treatment such as Statins is beyond doubt, but drug adverse effects with myopathy, liver damage, etc. may hinder appropriate treatment. While traditional Chinese medicine such as Chuanxiongsu has fewer side effects than Western medicine. It has clinically been confirmed that Chuanxiongsu retains the natural activity of Chuanxiong and has the effect of Chinese traditional Huoxue Huayu, making definite efficiency to the cardiovascular diseases, but, so far, any clinical reports of Chuanxiongsu tablet administering prehypertension patients with hyperlipidemia haven’t been seen yet. This study collected 200 cases of the disease in order to compare the clinical effect in treating prehypertension with hyperlipemia between Simvastatin capsule and Chuanxiongsu tablet, meanwhile investigating the possible mechanism of action. The results were as follows.

2. Methods
2.1. Patient Selection
From October 2013 to October 2017 in the Department of Internal Medicine, Hubei Provincial Women’s and Children’s Hospital and General Hospital of Xinzhou District, Wuhan, a
total of 200 prehypertensive patients with hyperlipemia were selected. According to standards issued by 2010 Chinese guidelines for the management of hypertension [2], prehypertension was diagnosed when 120 mmHg (1 mmHg = 0.133 kPa) ≤ systolic blood pressure, (SBP) ≤ 139 mmHg and / or 80 mmHg ≤ diastolic blood pressure (DBP) ≤ 89 mmHg on at least two occasions on different days [2]. And the mean of three independent measurements was reported. The definition of hyperlipemia was consistent with The 4th academic conference on cerebrovascular diseases [3]. This study was in line with the medical ethics, getting medical ethics committee approval.

Blood pressure was determined under resting conditions with a calibrated mercury sphygmomanometer [4]. The exclusion criteria included essential hypertension, secondary hypertensive disorder, heart disease, peripheral vascular disease, neurologic disease, hematologic disease (including abnormal bleeding and blood coagulation), diabetes, obesity, respiratory disease, peptic ulcer, endocrine disease, immunologic disease, mental disease, malignant tumor, emergency conditions, trauma and operation for recent three months, inflammation and infection, severe liver and renal dysfunction, allergic constitution (including drug allergy) and drinking to excess.

### 2.2. Grouping of Patients and Research Methods

A total of 200 prehypertensive patients with hyperlipemia were randomly assigned to the treatment group (A) and control group (B), 100 in each group. Patients in group A took Chuanxiongsu tablet (50 mg/1 tablet, 100 mg each time, thrice per day), which was obtained from Chengdu Han Pharm. Company Limited, while those in group B took Simvastatin capsule (20 mg/capsule, 20 mg q. n.), which was obtained from Hangzhou MSD Pharmaceutical Company Limited. And all patients continuously treated for 8 weeks. The incidence of drug adverse reactions in two groups was observed. In addition, 100 healthy volunteers for physical examination served as healthy control group (C), who did not receive any treatment. Therapeutic effects in lowering blood pressure and regulating blood lipid metabolism were observed. SBP, DBP and serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol, (HDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB) were detected before and after 8-week treatment (ApoB) were detected before and after 8-week treatment.

### 2.3. Characteristics of Subjects

Patients preliminarily diagnosed as prehypertension with hyperlipemia (124 males and 76 females) were examined and had an average age of (51.75±9.48) Y, body mass of (68.93±7.92) Kg. There were no significant difference with general conditions, including age, sex, height, body mass, salt-intake, smoking, alcohol consumption, positive family history, between group A, B and C (P>0.05).

### 2.4. Collection and Analysis of Blood Samples

Fasting blood samples were collected and analyzed at the Biochemistry Department of the Hubei Provincial Women’s and Children’s Hospital and General Hospital of Xinzhou District respectively to determine blood lipid levels according to manufacturer’s instruction, measures of TC and TG using oxidase method, measures of LDL-C and HDL-C using direct cover method, ApoA1 and ApoB using immune turbidimetric method.

According to China’s blood pressure monitoring guide-2011 edition, the fifth (disappearance) Korotkoff sound is used to determine DBP. The blood pressure should be taken in the sitting position after 10 minutes of quiet rest, the average of three independent measurements must be taken and reported. If the first two readings differ by more than 5 mmHg, additional readings should be obtained.

### 2.5. Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD). Statistical analysis for the data of two-sets and three-sets comparisons were performed using the Student’s t-test, Chi-square test respectively. Statistical analysis was conducted with SPSS13.0 software with P<0.05 considered significant, and the highly significance of differences was set at P<0.01.

### 3. Results

1) Comparison of blood pressure and blood lipids index between the three groups before treatment. Detailed data were shown in Table 1.

2) Comparison of blood pressure and blood lipids index between the two groups (group A, B) before and after treatment. Detailed data were shown in Table 2.

#### Table 1. Comparison of blood pressure and blood lipids index between the three groups before treatment (X ± s, n = 100).

<table>
<thead>
<tr>
<th>group</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>TG (mmol/L)</th>
<th>TC (mmol/L)</th>
<th>LDL-C (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
<th>ApoA1 (g/L)</th>
<th>ApoB (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>139±9</td>
<td>84±8</td>
<td>2.5±0.5</td>
<td>5.5±0.8</td>
<td>4.3±0.6</td>
<td>0.9±0.4</td>
<td>1.0±0.1</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>B</td>
<td>142±10</td>
<td>83±7</td>
<td>2.4±0.4</td>
<td>5.3±0.7</td>
<td>4.6±0.7</td>
<td>0.8±0.3</td>
<td>1.2±0.2</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>C</td>
<td>113±9</td>
<td>73±7</td>
<td>1.4±0.7</td>
<td>3.8±0.8</td>
<td>2.2±0.5</td>
<td>1.3±0.4</td>
<td>1.4±0.2</td>
<td>0.7±0.3</td>
</tr>
</tbody>
</table>

Compared with healthy control group (HCP); P<0.01.
Table 2. Comparison of blood pressure and blood lipids index between the two groups before and after treatment (\( \bar{x} \pm s, n = 100 \)).

<table>
<thead>
<tr>
<th>group</th>
<th>n</th>
<th>LDL-C (mmol/L)</th>
<th>t</th>
<th>P</th>
<th>HDL-C (mmol/L)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>100</td>
<td>4.6±0.7</td>
<td>3.62</td>
<td>&lt;0.01</td>
<td>0.8±0.3</td>
<td>0.62</td>
<td>0.61</td>
</tr>
<tr>
<td>A</td>
<td>100</td>
<td>4.3±0.6</td>
<td>3.60</td>
<td>&lt;0.01</td>
<td>0.9±0.4</td>
<td>0.62</td>
<td>0.61</td>
</tr>
<tr>
<td>t</td>
<td>1.06</td>
<td>1.01</td>
<td></td>
<td></td>
<td>0.62±0.4</td>
<td>0.62</td>
<td>0.61</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>2.4±0.4</td>
<td>3.70</td>
<td>&lt;0.01</td>
<td>5.4±0.7</td>
<td>3.64±0.85</td>
<td>3.88</td>
</tr>
<tr>
<td>A</td>
<td>100</td>
<td>2.5±0.5</td>
<td>3.81</td>
<td>&lt;0.01</td>
<td>5.5±0.8</td>
<td>3.64±0.85</td>
<td>3.88</td>
</tr>
<tr>
<td>t</td>
<td>0.61</td>
<td>0.65</td>
<td></td>
<td></td>
<td>0.68±0.23</td>
<td>0.68</td>
<td>0.80</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>1.2±0.2</td>
<td>3.66</td>
<td>&lt;0.01</td>
<td>1.4±0.4</td>
<td>1.73±0.23</td>
<td>3.58</td>
</tr>
<tr>
<td>A</td>
<td>100</td>
<td>1.0±0.1</td>
<td>3.59</td>
<td>&lt;0.01</td>
<td>1.2±0.4</td>
<td>0.80±0.20</td>
<td>3.62</td>
</tr>
<tr>
<td>t</td>
<td>0.78</td>
<td>0.51</td>
<td></td>
<td></td>
<td>0.70±0.23</td>
<td>0.70</td>
<td>0.73</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>


Side effects
Adverse reactions almost did not be seen, and reexamination of live function and creatine kinase (CK) were roughly normal, in Group A, whereas 11 patients had mild gastrointestinal reaction, 12 patients slightly increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), 16 patients higher CK content (below 3 times the normal high value), 2 weeks after treatment, which relieved later with no special treatment, in group B. There were no abnormal blood sugar and coagulation function after in group A and B.

4. Discussion

Patients with prehypertension have kidney impairment, atherosclerosis (AS) and target organ damage related to increased blood pressure. Compared with normotensive groups, incidence of cardio-cerebrovascular events got higher in prehypertension population [1]. Domestic recent studies have shown that detection rate of new carotid artery plaque increased significantly in the prehypertension [5]. Though the need medication in the patients with prehypertension is still controversial, clinically prehypertension and blood lipid metabolic disorder are well-recognized major risk factors for cardio-cerebrovascular diseases.

Chuanxiongsu synthesized with modern technology is an active alkaloidal monomer, and is also one of the mainly biologically active plant substances of Chuanxiong, which is extracted from the Chinese traditional herb Chuanxiong, whose chemical structure is similar to ferulic acid. Because of retaining the natural activity of Chuanxiong, Chuanxiongsu has the effect of Huoxue Huayu. With the in-depth research of Chuanxiongsu, its clinical use is widen day by day, especially its remarkably efficiency to the cardiovascular disease.

The results revealed that Chuanxiongsu has similar lipid-regulating effect with Simvastatin, but the latter were less than the former in terms of the antihypertensive effect and drug safety, in prehypertensive patients with hyperlipemia, thus delaying prehypertension development for hypertension and highlighting traditional Chinese medicine characteristics and advantages.

Published data [6-12] have showed that ligustrazine-aromatic acid derivation, especially compound of ligustrazine and feralic acid, has significant inhibitory effect on adenosine diphosphate (ADP) induced platelet aggregation in the in vitro experiment; ligustrazine reduce the mean arterial pressure, systolic pressure of left ventricle, maximum of left ventricular interior pressure augmenting rate, in rats. And also researchers found that Chuanxiongsu could antagonized calcium ion channel, dilate capillary vessels, improve microcirculation, increase coronary blood flow, reduce capillary permeability and plasma levels of homocysteine (Hcy); Tetramethyl pyrazine (TMP) could exert protective effect on Adriamycin-induced acute heart failure mice, partially by inhibition of cardiomocytes apoptosis and cardiac enzymes. In addition, Chuanxiongsu’s phenolic hydroxy and allyl structure could remove free radicals to
prevent and treat vascular endothelial lipid peroxidation damage, and antagonize endothelin to relieve secondary endothelial injury, respectively. In a word, all of these could contribute to protection of endothelium, as a result, adjusting the balance between the contracting factor and relaxing factor derived from endothelium, which might be antihypertensive action mechanism of Chuanxiongsu.

The mechanism for Chuanxiongsu’s lipid-regulating effect, despite extensive research, has not been established. It is likely that a variety of mechanisms and several explanations contributed to a greater or lesser extent. They [13-18] were as follows: 1) Sodium ferulate could inhibit cholesterol synthesis in liver, enhance the cholesterol esterase activity of vascular smooth muscle and decrease cholesterol ester accumulation; 2) Chuanxiongsu could inhibit angiogenesis and intervene oxidative stress, which might tend to stabilize plaques of AS; 3) Ferulic acid might show the antiatherosclerosis effect by increasing the surface ATP binding cassette transporterA1 (ABCA1) and ATP binding cassette transporterG1 (ABCG1) expression of macrophage foam cells and promoting cholesterol efflux; 4) The combination of tanshinol and TMP could expose synergistic or additive effect on cardiovascular system, which may be related to the antagonism of calcium ion channel; 5) Danshen ligustrazine for injection might reduce hs-CRP and improve blood rheology and fat metabolism. 6) On the basis of SUN Long-fei, et al’s observation, Giving sodium ferulate may stochastically upregulate liver X receptor mRNA and caveolin-1 mRNA expression to mediate inflammatory signaling pathway, which might inhibit inflammatory reaction, reduce the generation of oxidized low density lipoprotein (ox-LDL) and improve cholesterol metabolism.

5. Conclusion

In conclusion, the therapy of Chuanxiongsu, as an alternative to Simvastatin, could markedly improve blood lipid metabolism and reduce the level of blood pressure to some degree, thus leading to relief of symptoms and delaying development of prehypertension. In terms of adverse reactions, Chuanxiongsu was obviously less than Simvastatin, so the former is safer than the latter. Totally, curative effect of Chuanxiongsu is better than Simvastatin’s, highlighting traditional Chinese medicine characteristics and advantages, which was suggested to apply in treatment of prehypertension patients with hyperlipemia. Because traditional Chinese medicine is a health care system with an extensive history of practical clinical experience. In China, traditional Chinese medicine and Western medicine have equal social and culture status in the treatment of disease and health problem (including hypertension management). However, this study has a number of limitations. Because the sample was drawn from a limited population, the results may not generalized to the general population. The relatively low sample size may also affect the study’s generalizability. And the best dose, best course of treatment and lipid individualized dose adjustment strategy after achieving blood lipid control of evidence-based with Chuanxiongsu therapy remain to be researched and further perfect. And the curative effect of its molecular biology mechanism also is worth in-depth study.

References


