Effect of Liandouqingmai recipe on quality of life and inflammatory reactions of patients with coronary heart disease

Hongjun Zhu, Shu Lu, Wei Su, Shaoyu Gong, Zhibin Zhang, Ping Li

Abstract

OBJECTIVE: To observe the effect of Liandouqingmai recipe (Chinese herbal medicine compound preparation) on the quality of life (QOL) and inflammatory reaction of patients with coronary heart disease (CHD).

METHODS: A total of 101 CHD patients were randomized into two groups: treatment group (n=45) receiving standard treatment for CHD plus Liandouqingmai recipe, and control group (n=56) receiving standard treatment only. The control group contained 16 normal healthy subjects. Changes in hs-C-reactive protein (CRP), peripheral blood leukocytes (PBL), and interleukin (IL)-6 and IL-10 levels were measured. The Seattle Angina Questionnaire (SAQ) was used to determine patient QOL before and after treatment for 2 weeks.

RESULTS: Before treatment, SAQ scores [physical limitation (PL), angina stability (AS), angina frequency (AF), treatment satisfaction (TS), and disease perception (DP)] were not statistically different between groups. After treatment, AS and DP levels of controls were significantly increased compared with the other groups, while PL, AS, AF, TS, and DP levels of the treatment group were significantly increased compared with controls. Treatment group SAQ scores (PL, AS, AF, TS, and DP) were significantly higher than for controls. CHD patient IL-6 and IL-10 levels were significantly higher than controls. Before treatment, mean levels of IL-6, hs-CRP and PBL of the two groups were not statistically different. After treatment, mean levels of IL-6, IL-10, hs-CRP and PBL of the two groups were significantly decreased compared with their before treatment values, and levels of IL-6, hs-CRP, and PBL of the treatment group were lower than controls. Although mean IL-10 levels of both groups decreased, there was no significant difference in between-group and in-group comparisons before and after treatment. Mean levels of IL-6 and IL-10 in the normal group were lower than in CHD patients. SAQ scores of QOL were negatively associated with the inflammatory index (IL-6/IL-10), and there was a significant negative association of IL-10 with AS ($r=-0.15, p<0.05$).

CONCLUSION: Inflammatory reactions in CHD patients are related to angina status. Coadministration of CHD standard treatment and Liandouqingmai recipe increased patient SAQ scores by decreasing IL-6, IL-10, hs-CRP, and PBL levels in CHD patients, which might inhibit endothelial inflammation to improve patient QOL.
Key words: Coronary disease; C-reactive protein; Leukocytes; Interleukins; Liandouqingmai recipe; Seattle angina questionnaires

INTRODUCTION

Coronary heart disease (CHD) is a life-threatening disease and atherosclerosis (AS) is the pathological basis of CHD. Our previous studies confirmed that Liandouqingmai recipe, developed by our laboratory, is effective for the prevention and treatment of AS and CHD. It decreases the brachial-ankle pulse wave velocity and increases the ankle-brachial index of atherosclerosis patients when provided as a standard treatment.1 Liandouqingmai recipe also decreases low-density lipoprotein-cholesterol levels and plasma-induced atherosclerosis index of atherosclerosis patients.2 Because it has anti-inflammatory functions that improve arterial rigidity and decrease levels of high-sensitivity C-reactive protein (hs-CRP), peripheral blood leucocytes (PBL), interleukin-6 (IL-6) and IL-10, it is commonly used in clinical practice as a standard treatment.3 This trial was designed to observe the effect of Liandouqingmai recipe on the quality of life of CHD patients and investigate the correlation between SAQ scores and inflammatory reactions.

METHODS

Patient data

One hundred and one CHD patients and 16 healthy volunteers took part in this study. The 101 in-patients of the Heart Internal Medicine Department, Wuxi Traditional Chinese Medicine (TCM) Hospital, Nanjing University of Chinese Medicine were enrolled from June 2007 to December 2009 and were randomized into a Liandouqingmai recipe group (treatment group) and a standard treatment group (control group) according to a random number table. In the treatment group of 45 patients, there were 20 males and 25 females, aged 51-87 years [mean age (71±8) years], with a disease course from 2 h to 28 years [mean (9±11) years]. In the control group of 56 cases, there were 24 males and 32 females, aged 54-86 years [mean age (70±9) years], with a disease course from 1 h to 40 years [mean (9±14) years]. Between the two groups, there was no statistical difference in age, sex, and disease course. The 16 healthy volunteers in the normal control group (normal group) were staff members and workers at posts or retirees of the study hospital after age and sex matching. All persons voluntarily taking part in this research study signed a fact-knowing agreement prior to their inclusion in the study. The study was approved by the Ethics Committee of Wuxi TCM Hospital and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Diagnostic criteria

Diagnostic criteria for CHD followed the naming and diagnostic criteria of ischemic heart disease issued by the World Health Organization.4

Inclusion criteria

Patients met the diagnostic criteria of CHD and any one item of the following conditions: remote myocardial infarction, hemodynamically stable acute non-ST segment elevation myocardial infarction or angina pectoris, with clinical symptoms and signs and a positive result in a sports plate test, and at least one blood vessel or at least one part of a vessel narrowing over 60% found with coronary arteriography.

Exclusion criteria

Patients were excluded from the trial if they had an insufficiency of the spleen-Yang in TCM, hemodynamically unstable angina pectoris and acute myocardial infarction, severe arrhythmia, other inflammatory diseases, severe heart diseases, severe dysfunction of liver and kidney, severe primary diseases of lung and brain, psychosis, or if they refused to sign the fact-knowing agreement.

Treatment methods

Patients of both groups were treated with a standard treatment for CHD, including nitrate drugs such as isosorbide mononitrate tablets (Southern Betty Pharmaceutical Co., Ltd., Linyi, China) 20 mg twice per day; isosorbide dinitrate (Nanjing Baijingyu Pharmaceutical Co., Ltd., Nanjing, China) 5-10 mg, thrice daily; and nitroglycerin (Guangzhou Baiyun Mountain Ming Xing Pharmaceutical Co., Ltd., Guangzhou, China) according to the individual’s condition; aspirin (Bayer Pharmaceutical Co., Ltd., Leverkusen, Germany) 100-300 mg, once per day; statins for regulating lipids such as atorvastatin calcium tablets (Pfizer, New York, NY, USA) 10-20 mg, once per day; and fluvastatin sodium capsules (Beijing Novartis Pharma Company Limited, Switzerland) 40 mg, once per night; angiotensin-converting enzyme inhibitor [Benazepril tablets (Beijing Novartis Pharma Co., Ltd., Beijing, China)] 10 mg, once per day; or peduopril tablets (Les Laboratoires Servier Industrie, Tianjin, China) 4 mg, once daily. For patients with no contraindications, β-receptor blockers [Metoprolol tablets (AstraZeneca Pharmaceutical Co., Ltd., Wuxi, China)] 6.25-100 mg, twice per day; bisoprolol tablets (Merck Co., Ltd., Darmstadt, Germany) 2.5-5.0 mg, once per day were used for long-term treatment over the whole course of the study.

There was no statistical difference between the type of drugs, dose, and administration time-course for the standard treatment in the two groups.

For patients in the treatment group, Liandouqingmai recipe composed of Lianqiao (Fructus Forsythiae) 15 g, Huanglian (Rhizoma Coptidis) 3 g, Yeliaodou (Glycine soja Sieb) 15 g, Chishao (Radix Paeoniae) 10 g,
Laifuzi (Semen Raphani) 10 g, and so on, was added to the standard treatment. The recipe was prepared by the Pharmaceutics Department of our hospital and the herbs were purchased from Tianjiang Pharmaceutical Factory. The decoction (250 mL) was administered orally twice a day, for 2 weeks as one course of treatment.

**Collection and preservation of samples**

Either 4 or 6 mL of venous blood was taken from patients the morning after fasting within 24 h after hospitalization and added to a dry tube and kept for 1 h at room temperature, then centrifuged for 10 min at 3000 r/min. Part of the supernatant was used for IL-6 and IL-10 determination immediately. Another part of the supernatant was used for hs-CRP determination. Finally, 2 mL of venous blood was slowly poured into a tube with 30 μL 10% ethylene diamine tetraacetic acid (EDTA) and mixed for PBL determination.

**Observation indexes and determination methods**

IL-6 and IL-10 were determined by IMMULITE 1000 full-automatic chemiluminescence immunoanalyzer (Siemens Co., Munich, Germany). hs-CRP was determined by AU5800 fully automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA). Five classification XE2100 fully automatic blood analyzers (SYSMEX, Kobe, Japan) were used to determine PBL counts. Before and 2 weeks after treatment, the physical limitation (PL), angina stability (AS), angina frequency (AF), treatment satisfaction (TS), and disease perception (DP) were scored by the same deputy chief physician using paper SAQ scales.

**Statistical analysis**

The data were analyzed with SPSS 17.0 software (SPSS Company, Chicago, IL, USA). Measurement data were expressed as the mean ± standard deviation (\( \bar{x} \pm s \)). Two-sided Student t-test of two independent samples was used for between-group comparisons of therapeutic effects, and paired samples were used for in-group comparisons before and after treatment. Correlation was analyzed by Pearson correlation. A value of \( P < 0.05 \) indicated statistical significance.

**RESULTS**

**Effect of Liandouqingmai recipe on SAQ scores**

Before treatment, there was no significant difference in PL, AS, AF, TS, and DP scores between the two groups (Table 1, \( P > 0.05 \)). After treatment, the AS and DP scores in the control group were significantly increased (\( P < 0.01 \)) compared with the treatment group; however, in the treatment group, the PL, AS, AF, TS, and DP scores were significantly increased (\( P < 0.01 \)).

Effect of Liandouqingmai recipe on IL-6, IL-10, hs-CRP, and PBL. Before treatment, the IL-6 and IL-10 levels of CHD patients were significantly higher than those of the normal group (Table 2, \( P < 0.05 \)). There was no significant difference in the IL-6, hs-CRP, and PBL levels between the treatment group and control group. After treatment, the mean levels of IL-6, IL-10, hs-CRP, and PBL in the treatment and control groups were all decreased although the differences were statistically significant (\( P < 0.05 \)). IL-6, hs-CRP, and PBL lev-

<table>
<thead>
<tr>
<th>Group</th>
<th>PL</th>
<th>AS</th>
<th>AF</th>
<th>TS</th>
<th>DP</th>
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<tbody>
<tr>
<td>Control</td>
<td>Before</td>
<td>60±11</td>
<td>62±22</td>
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<td>After</td>
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<tr>
<td>After</td>
<td>78±10</td>
<td>89±10</td>
<td>85±12</td>
<td>82±12</td>
<td>81±17</td>
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</table>

Notes: treatment group was given standard treatment plus Liandouqingmai recipe twice a day, for 2 weeks; control group was given standard treatment only for 2 weeks. SAQ: seattle angina questionnaire; PL: physical limitation; AS: angina stability; AF: angina frequency; TS: treatment satisfaction; DP: disease perception. Compared with data before treatment, \( * P < 0.01 \); compared with control group, \( ^b P < 0.01 \).

<table>
<thead>
<tr>
<th>Group</th>
<th>T-STD (mv)</th>
<th>IL-6 (pg/mL)</th>
<th>IL-10 (pg/mL)</th>
<th>hs-CRP (mg/L)</th>
<th>PBL (x10^9/L)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-</td>
<td>1.10±0.08</td>
<td>1.09±0.06</td>
<td>1.22±0.34</td>
<td>4.17±0.76</td>
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<td>Control</td>
<td>Before</td>
<td>0.72±0.18</td>
<td>9.22±2.05</td>
<td>1.95±0.32</td>
<td>9.22±4.63</td>
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<td>After</td>
<td>0.29±0.12</td>
<td>5.13±1.85</td>
<td>1.65±0.18</td>
<td>8.92±2.87</td>
<td>6.61±0.47</td>
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<tr>
<td>Treatment</td>
<td>Before</td>
<td>0.73±0.21</td>
<td>9.11±1.36</td>
<td>1.93±0.19</td>
<td>7.38±3.94</td>
</tr>
<tr>
<td>After</td>
<td>0.24±0.10</td>
<td>4.48±1.22</td>
<td>1.82±0.19</td>
<td>3.47±0.03</td>
<td>5.55±0.43</td>
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</table>

Notes: treatment group was given standard treatment plus Liandouqingmai recipe twice a day, for 2 weeks; control group was given standard treatment only for 2 weeks. T-STD: total values of ST segment down on electrocardiogram; IL-6: interleukin-6; IL-10: interleukin-10; hs-CRP: high-sensitivity C-reactive protein; PBL: peripheral blood leukocytes. Compared with data before treatment, \( * P < 0.05 \); compared with control group, \( ^b P < 0.05 \).
els in the treatment group were significantly lower than in the control group ($P<0.05$). The mean levels of IL-10 in the treatment and control groups were decreased and between-group and in-group comparisons showed no statistical significance before and after treatment ($P>0.05$).

**Correlation between SAQ scores and inflammatory indexes**

SAQ scores were negatively correlated with IL-6 and IL-10 levels, and there was a significant negative correlation between IL-10 and AS ($r=-0.15$, $P<0.05$) (Table 3).

**DISCUSSION**

Studies have shown that almost one in three patients with stable angina attending primary care practices had angina at least once a week, which was associated with worse quality of life than those with minimal angina (less than once a week over the preceding 4 weeks).7,8 Herein, the aim of treatment of CHD is not only to ease the clinical symptoms but also to improve the patients’ quality of life. This is an important index to evaluate the effects of drug treatment.

At present, SAQ is widely used to clinically evaluate the quality of life of CHD patients. It contains 11 items in five categories: limited degree of body activities (question 1), stable state of angina pectoris (question 2), heart attacks (questions 3-4), treatment satisfaction (questions 5-8), and disease understanding (questions 9-11). The total score is 100 points. The higher the score, the better the quality of life and body function of the patients. This system has good reliability, validity and reaction,6 and can be used to evaluate the quality of life of CHD patients.

Inflammatory reactions are an important mechanism affecting the stable state of angina pectoris and quality of life of CHD patients. hs-CRP is an important index to calculate cardiovascular events. The risk of cardiac infarction increases with an increase of hs-CRP. An increase in PBLs is an independent risk factor for CHD patients.

IL-6 is a strong inflammatory factor that induces inflammatory responses, which generates increased vascular endothelial active oxygen clusters; thus, oxygen-free radicals evoke oxidative stress and induce dysfunction of vascular endothelium, which accelerate AS.9,10 Plasma IL-6 concentrations in patients with unstable angina pectoris are significantly higher than in patients with stable angina pectoris or normal healthy subjects.11 IL-10 is the main anti-inflammatory cytokine, and directly inhibits the expression of adhesion molecules, prevents ischemia/reperfusion lesions of the myocardium, and protects myocardium. IL-10 also reduces metalloprotease activity in coronary artery plaques.12 IL-10 was negatively associated with AS ($r=-0.15$, $P<0.05$). This indicated that inflammatory reactions are closely related to CHD patient myocardial ischemia and quality of life, especially in AS.

Inflammatory responses are important in the occurrence and development of AS and CHD. Therefore, inhibiting the inflammatory response is very important for the treatment of CHD.

Antibiosis and anti-inflammation effects of Huanglian (Rhizoma Coptidis) and Lianqiao (Fructus Forsythiae), are well known clinically. It was shown that an extract of Huanglian (Rhizoma Coptidis) reduced breaking times of aortic atherosclerotic plaques in ApoE-gene knockout mice, helping stabilize vulnerable atherosclerotic plaques.13 On the basis of standard treatment, Liandouqingmai recipe might decrease IL-6, IL-10, hs-CRP, and PBL concentrations, inhibit the injuring actions of IL-6 on vascular endothelium, improve myocardial ischemia, and thus improve the quality of life of CHD patients.

The standard treatment for CHD improved the AS and DP scores, stabilized the state of angina pectoris, and helped the disease understanding of CHD patients. When the Liandouqingmai recipe was added to the standard treatment, the levels of PL, AS, AF, TS, and DP in the treatment group were all increased, indicating it relieved the limited degree of body activity, improved the stable state of angina pectoris, reduced heart attacks, and enhanced the treatment satisfaction and disease understanding of CHD patients. SAQ scores for PL, AS, AF, TS, and DP in the treatment group were significantly higher than those in the control group.

In conclusion, the Liandouqingmai recipe, on the basis of standard treatment, improved the quality of life of CHD patients.

**REFERENCES**

2. Zhu HJ, Lu S, Su W, et al. Effect of Liandouqingmai reci-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PL</th>
<th>AS</th>
<th>AF</th>
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<tbody>
<tr>
<td>IL-10</td>
<td>-0.01</td>
<td>-0.15</td>
<td>-0.12</td>
<td>0.000</td>
<td>-0.03</td>
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<tr>
<td>IL-6</td>
<td>-0.08</td>
<td>-0.09</td>
<td>0.02</td>
<td>-0.04</td>
<td>-0.02</td>
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</tbody>
</table>

Notes: There was a significant correlation ($P<0.05$) (bilateral). SAQ: seattle angina questionnaire; PL: physical limitation; AS: angina stability; AF: angina frequency; TS: treatment satisfaction; DP: disease perception; IL-6: interleukin-6; IL-10: interleukin-10.


4 International Heart Association/International College of Cardiology and the Named Standardization Joint Task Team of WHO. The naming and diagnostic criteria of ischemic heart disease. Zhong Hua Xin Xue Guan Bing Za Zhi 1981; 9(1): 75-76.


