Letter to the Editor

Xuezhikang, an extract of cholestin, decreases plasma inflammatory markers and endothelin-1, improve exercise-induced ischemia and subjective feelings in patients with cardiac syndrome X

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Abstract

Previous studies have demonstrated that Xuezhikang, an extract of cholestin, available from Chinese red yeast rice, could effectively modify lipid profile. The present study was undertaken to investigate whether Xuezhikang could modify endothelin-1 (ET-1), interleukin-6 (IL-6), high-sensitivity C-reactive protein (CRP) and exercise-induced ischemia in patients with cardiac syndrome X (CSX). Thirty-six patients with CSX were randomly assigned to 1200 mg/d of Xuezhikang or placebo group (n = 18 respectively). Blood samples were drawn at day 0 and day 90 for measuring above parameters. The treadmill exercise tests and subjective feelings were also assessed at day 0 and day 90. The data showed that Xuezhikang therapy resulted in significant reductions in total cholesterol (TC, 19%), low-density lipoprotein cholesterol (LDL-C) (26%), and triglycerides (TG) compared with baseline (16%, p < 0.01 respectively). The data also showed that Xuezhikang led significantly to reductions in median and log-CRP levels (38% and 44%, p < 0.01 respectively), IL-6 (20%, p < 0.01), and ET-1 (47%, p < 0.01) compared with baseline. The exercise duration, and time to 1 mm ST-segment depression was significantly prolonged after Xuezhikang therapy (9% and 6%, p < 0.05 respectively) accompanied by improvement of subjective feelings. Data suggested that the benefit of Xuezhikang resulted in significant modification vascular function by reduction of ET-1, inflammatory markers and LDL cholesterol, which may be clinically important for patients with CSX.

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1. Introduction

Cardiac Syndrome X (CSX) is a clinical entity characterized by angina-like chest discomfort, positive treadmill exercise test, negative intravenous ergonovine test and angiographically normal. Despite the extensive studies, the pathogenesis of this syndrome, however, is not well known. A large body of evidence has shown that inflammation plays a key role in coronary artery disease, and atherosclerosis is an inflammatory disease [1]. Vascular inflammation contributes to the pathogenesis of atherosclerosis and later in the disease process, and is a major mechanism! for acute coronary syndrome [2,3]. More recently, emerging data suggested that inflammation might also play a key role also in microvascular dysfunction of patients with CSX [4–6]. A large number of investigations including our data have suggested that administration of statin could modify C-reactive protein (CRP) concentration with a concurrent fall in inflammatory markers. Xuezhikang, an extract of cholestin, is a traditional Chinese medication and contains a family of naturally occurring statins (monacolins), one of which is lovastatin [7]. However, limited information is available in respect of effects of Xuezhikang on inflammatory markers.
endothelin-1 (ET-1) and exercise-induced ischemia in patients with CSX. The aim of this study, therefore, is to investigate whether Xuezhikang could modify lipid profile, inflammatory markers, ET-1, as well as parameters of exercise-induced ischemia in patients with CSX.

2. Methods

The study groups included 36 consecutive patients with CSX were enrolled in this study. Entry criteria were typical angina chest pain, normal 12-lead electrocardiogram at rest, a positive exercise test response (>0.1 mV ST-segment depression at 80 ms after the J point in two or more contiguous leads) and a complete normal coronary angiogram. All subjects enrolled in this study had normal hepatic function. Patients with evidence of myocardial infarction, valvular heart disease, left ventricular dysfunction, congestive heart failure, a history of dysphagia, swallowing as well as intestinal motility disorders, untreated thyroid disease, sinus node dysfunction or conduction disturbance, estrogen replacement therapy, lipid-lowering agents were excluded from the study. The other medication was withdrawn at least a week before the study. After baseline determination of lipid profile, interleukin-6 (IL-6), CRP, and exercise test, patients were randomly assigned to either a dose of 1200 mg/d of Xuezhikang group (n=18) or placebo group (n=18) for 3 months. Left ventricular and selective coronary angiography was performed using the standard Judkin’s techniques, and the results were analyzed by at least two interventional physicians according to our previous study. All anti-anginal and anti-ischemic medications, except sublingual nitroglycerin, were withheld for at least a week before the examination. During coronary angiography, to exclude the possibility of coronary spasm, all patients underwent hyperventilation tests, which were performed by asking the patients to breathe quickly and deeply for at least 5 min.

EDTA-anticoagulated peripheral blood sample were taken after 12-hour overnight fast at baseline (day 0), and at the end of the study (day 90). Serum lipid profile [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and High-density lipoprotein (HDL)], ET-1, IL-6, CRP were measured by methods as our previously reported. In the beginning and at the end of the study, patients were asked to report any ischemic symptoms or adverse experience during the past 3 months. The frequency of angina pectoris, both during exercise and at rest, was recorded according to the Canadian Cardiology of Society (CCS) angina classification. Patients’ subjective feelings of chest pain during the treatment periods were also recorded as ‘improve’, ‘unchanged’, or ‘worsened’ in comparison with that before randomization. These interviewed finding were scored on an ordinal scale ranging from 0 (no angina), 1 (mild chest pain at current life), 2 (moderate chest at current life), 3 (serious chest pain at current life, to 4 (serious chest pain at rest). Patients were also subjected to a symptom-limited submaximal end point on a graded exercise treadmill at baseline and at the end of Xuezhikang therapy (Marquette CASE 16) using the modifying Bruce protocol according to our previous study. The data are presented as percentages for discrete variables and as mean±SD for continuous variables unless otherwise indicated. The differences between demographic variables of the groups were assessed using the Mann–Whitney U test for continuous data and Chi-square test for categorical data. The baseline and post-treatment lipid component and other biochemical variables were compared between the two groups with the Mann–Whitney U tests. Because the distribution of CRP is skewed rightward, log transformation was made at baseline and at study completion, and the significance of any difference in distributions was assessed by the Wilcoxon rank-sum test as our previously reported. A p value<0.05 was considered statistically significant.

3. Results

There were no significant differences of baseline clinical variables between the placebo and Xuezhikang group. A 3-month therapy of 1200 mg Xuezhikang per day induced significant reductions in TC (19%), LDL-C (26%), and TG (16%) compared with baseline (p<0.01 respectively). Our data indicated that log-CRP levels decreased from 0.25±0.06 mg/dl at baseline to 0.14±0.02 mg/dl at day 90 after administration of Xuezhikang (44% reduction, p<0.01). Meanwhile, the levels of IL-6 decreased from 10.2±0.09 mg/dl at baseline to 6.4±0.05 mg/dl at day 90 after administration of Xuezhikang (38% reduction, p<0.01). Apparently, this 44% reduction in CRP and 38% reduction in IL-6 at day 90 were attributed to Xuezhikang therapy. In addition, Xuezhikang therapy resulted in the 47% reduction in mean ET-1 levels (3.2±0.8 ng/L versus 1.7±0.4 ng/L, p<0.01). Moreover, the exercise duration, and time to 1 mm ST-segment depression was significantly prolonged after Xuezhikang therapy (578±135 s versus 530±124 s, 9% reduction and 6.31±0.71 min versus 5.94±0.62 min, 6% reduction, p<0.05 respectively). Finally, at the end of the study, patient’s subjective feelings of improvement were more frequently reported with Xuezhikang than placebo (p<0.01). No such changes of above parameters were observed in placebo group.

4. Conclusion

In this small-sample size, randomized, placebo-control study, our data showed, for the first time, that Xuezhikang, an extract of choleslin, could significantly decrease CRP and IL-6 in patients with CSX accompanied by the improvement of subjective feelings. In agreement with the increasing evidence that statin had pleiotropic effects, our data also showed that Xuezhikang could modify the levels of plasma
ET-1, which may shift the balance toward vasodilatation. The levels of plasma ET-1 in patients with CSX treated with Xuezhikang decreased by nearly 2-fold compared with that treated with placebo, suggesting the benefit to the vascular function conferred by Xuezhikang might occur by reduction of inflammatory markers and LDL-C, which may be clinically important for patients with CSX.

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References