

Full Length Research Paper

The clinical study of YiShenTongMai decoction in unstable angina complicated with glucose metabolism disorder

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This study aimed to evaluate the clinical effects of YiShenTongMai decoction working with conventional Western drugs in patients with unstable angina complicated with glucose metabolism disorder. Seventy-six patients with unstable angina complicated with glucose metabolism disorder were randomly divided into two groups: 37 cases were allotted to the control group and were treated with conventional Western medicine; 39 cases were allotted to the experimental group treated with conventional Western medicine and YiShenTongMai decoction (Gold Theragran 20 g, Chinese yam 30 g, Milkvetch root 15 g, *Bombyx mori* 10 g, *Allii macrostemi bulbosus* 10 g, Cassiac torae 30 g, huai *Achyranthis radix* 15 g, notoginseng powder 3 g, *Pheretima asiatica* 15g, Chinese hawthorn 10 g and water 370 ml). The effect of treatment was studied on the indices of electrocardiogram, traditional Chinese medicine (TCM) syndromes, fibrinogen (FIB), C-reactive protein (CRP) levels, standard deviation of Normal-Normal (SDNN), and left ventricular diastolic function (E/A) ratio. There was a significant difference with regards to clinical manifestation improvement in angina control between the experimental group and the control group (94.9% versus 75.7%, $P < 0.05$), as well as in the electrocardiogram profile (84.6% versus 59.5%, $P < 0.05$) and syndrome integral (94.9% versus 70.3%, $P < 0.05$). FIB and CRP decreased while SDNN and E/A increased in both groups but was much higher in the experimental group ($P < 0.05$). The curative effect of combined YiShenTongMai decoction and Western medicine was better than Western medicine alone in patients with unstable angina complicated with glucose metabolism disorder patients.

Key words: Unstable angina, glucose metabolism disorder, YiShenTongMai decoction.

INTRODUCTION

Coronary heart disease (CHD) and diabetes (DM) are both serious health problems in China as well as all around the world. From the 1990s, CHD has become the primary cause of death, and has increased gradually. For DM, there were 194 million patients in 2003, and the number will reach 333 million in 2025 with a higher rate of increase in developing countries than developed countries. DM is an important risk factor for CHD; in DM

patients, the ratio of attack by CHD was much higher (Carneiro, 2004) and the clinical manifestations were much more serious (Alexander et al., 2003). Eighty percent of DM patients died of cardiovascular complications, and 75% died of CHD (Gillum et al., 2000); this ratio was 2 to 4 times higher than that of patients without DM (Juutilainen et al., 2005). It was found that the impaired glucose regulation (IGR) of early DM, including

impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), was involved in metabolic disorder and vascular lesions. IGT and IFG were not regarded as independent diseases, but risk factors of developing into DM and CHD. A study showed that the mortality of IGT and IFG complicating with CHD was significantly higher than the people whose glucose metabolism was normal (Carnethon et al., 2009). Therefore, it has become a serious public health project to control the IGT, IFG and DM combined with CHD.

Unstable angina pectoris (UAP) is one type of CHD. Modern medicine carries out prevention and treatment of glucose metabolism disorder complicated with UAP by controlling blood sugar, blood pressure, lipids and other risk factors, but there are still some patients who could not achieve an optimal end. Chinese traditional medicine has gained more and more attention all around the world (Steven, 1998), the main feature of which was considering the body as a whole, and this was distinguished from the Western medicine, usually acting on a single target organ.

With the collection of clinical progressions about the unstable angina complicated with glucose metabolism disorder (Tao et al., 2002; Zhang et al., 1992; Shen et al., 2002), the status was a combination of "renal deficiency" and "phlegm" and "blood stasis" from Traditional Chinese Medicine (TCM) concept. Depending on this, YiShenTongMai decoction was created by our team, which has the effects of supplementing renal, removing blood stasis and eliminating phlegm. The purpose of this study was to investigate whether the combination of YiShenTongMai decoction and Western medicine could make a better result than western medicine alone. Our study has been approved by the Xi'an Chinese Medicine Hospital Medical research ethics committees review (Approval No.1003).

MATERIALS AND METHODS

Recruitment and exclusion criteria

Seventy-six cases were enrolled from March, 2010 to June, 2011, randomised into an experimental group (n = 39) and a control group (n = 37). The recruitment criteria was according to both "unstable angina and non-ST-segment elevation myocardial infarction diagnosis and treatment guidelines" by the Chinese Medical Association of Cardiology Branch in 2007 (The cardiovascular disease magazine editors committee, 2007) and "Chinese type-2 diabetes prevention and treatment guidelines" by the Chinese Diabetes Association (The Chinese Diabetes Association, 2010). The UAP criteria contained the initial issuance of UAP or deterioration of exertional angina, resting angina, infarction angina, variant angina pectoris: (i) initial issuance of UAP means the angina emerges within 2 months (without angina history or with angina history but has not recurred for at least 6 months); (ii) deterioration of exertional angina means the patient has angina history but the manifestation was worse or the activity that induced angina was mild or nitroglycerin of the same dosage could not control the

progression as before within 2 months; (iii) resting angina lasting much longer or the nitroglycerin of the same dosage could not control the progression as before within 1 month; (iv) infarction angina means the angina occurred within 24 h or 1 month after acute myocardial infarction (AMI); (v) variant angina pectoris, angina occurred with or without activity but with ST segment elevation. The DM criteria: fasting plasma glucose (FPG) ≥ 7.0 mmol/L; 2h PPG ≥ 11.1 mmol/L. At the same time, from Chinese traditional medicine, the differentiation of all the cases was "renal deficiency", "blood stasis" and "phlegm stagnation". The excluding criteria were: diabetes type 1; AMI, NYHA III ~ IV, grade 3 hypertension, serious cardiac arrhythmias, liver and kidney dysfunction, high-risk patients.

Treatment methods

Both the control group and the experimental group received the following prescription for 6 months. During this time, all the subjects were asked to record the extent and duration of chest pain, as well as the nitroglycerin dosage. Then the frequency and severity of chest pain, and the nitroglycerin dosage trend was collected. Electrocardiogram (ECG) changes and TCM syndrome integral were also observed; TCM syndrome included chest distress and pain, cardiopalmus and shortness of breath, languor and debilitation, poor appetite and mouth sticking, dark purple ligula, dizziness, tinnitus, soreness-tiredness of waist and knee, tongue demonstration and pulse tracings. The objective indicators and the detecting methods were as follows: fibrinogen (FIB) was tested with coagulation by Japan sysmex CA-1500; C-reactive protein (CRP) was tested with latex-enhanced transmission turbidimetric immunoassay by American BECKMAN zmmage-800; the standard deviation of Normal-Normal (SDNN) was measured by ECG; left ventricular diastolic function (E/A) was measured by echocardiography. At the same time, liver and kidney function was monitored fully.

In the control group, anti-angina and hypoglycaemic agents of conventional western medicine were administered, including Imdur, Aspirin, Metoprolol/Hebesser, Atorvastatin, Diamicron and Acarbose. Sixteen patients were administered insulin by subcutaneous injection, and IGR patients adopted diet control instead of hypoglycaemic agents.

In the experimental group, YiShenTongMai decoction was administered together with Western medicine as stated earlier. The prescription YiShenTongMai decoction was Chinese yam (origin: Henan) 30 g, Cassiac torae (Hunan) 30 g, Gold Theragran (Shaanxi) 20 g, Milkvetch root (Gansu) 15 g, *Pheretima asiatica* (Guangxi) 15 g, huai *Achyranthis radix* (Henan) 15 g, Chinese hawthorn (Shandong) 10 g, *Bombyx mori* (Hunan) 10 g, *Allii macrostemi bulbis* (Shaanxi) 10 g, notoginseng powder (Yunnan) 3 g, mixed with 370 ml water, boiled by an automatically extracting machine (Beijing Donghuayuan medical equipment limited liability company) for half an hour then squeezed for juice into two bags equally (180 ml, bid). The quality of the drug complied with the standard of Chinese Pharmacopoeia (2005).

In order to avoid bias from psychology, all the patients had no idea about others during the experiment since the patients of different groups were not staying in the same ward.

Evaluation of efficacy

Clinical manifestation

The evaluation of efficacy referred to the clinical research guiding principles of the cardiovascular system by the China Health Ministry

of Pharmaceutical Council in 1993. Excellence: the same degree of exertion does not cause angina after the drug, or the frequency of angina decreased by at least 80%, and/or nitroglycerin consumption decreased more than 80%; Effective: the frequency and/or nitroglycerin consumption decreased by 50 to 80%; Invalid: the frequency and/or nitroglycerin consumption decreased by less than 50%; Aggravation: the frequency and/or nitroglycerin consumption increased.

ECG findings

The evaluation of ECG effect was according to the angina and ECG evaluation standard from 1997 forum about the integrative treatment of angina and cardiac arrhythmias. Excellent: ECG was normal or almost normal. Effective: ST segment rise 0.05 mv or more without reaching the normal degree and T wave is improved. The invalid is that ECG has no obvious changes. The aggravation are that the ST segment is lower by more than 0.05 mv compared to before treatment, the inverted T wave deepens in the main leads (up to 25% or more), straight T wave becomes flattened, flat T-wave becomes inverted, resulting in the emergence of ectopic rhythm, trial ventricular block or intra-ventricular conduction delay.

TCM syndrome

The evaluation of TCM syndrome effect referred to the guiding principles of clinical study in angina by new traditional Chinese drugs in 2002. Excellence: clinical symptoms and signs are improved significantly, and symptom integral decreased by more than 70%. Effective: clinical symptoms and signs are improved, and symptom integral reduced by more than 30%. Invalid: clinical symptoms and signs had no significant improvements, or were even aggravated, symptom integral decreased by less than 30%. Aggravation: clinical symptoms and signs are aggravated, and symptom integral decreased.

Statistical analysis

The gender ratio was analysed with Chi-square test and the mean \pm standard deviation of age and disease course were analysed by t-test, the effect of the decoction was compared with the effective ratio by Chi-square test. All the Statistical analysis was performed by statistical package for social sciences (SPSS) 12.0 software. $P < 0.05$ was considered to be statistically significant.

RESULTS

General information

There was no significant difference of gender with Chi-square test and no significant difference of age and DM or CHD course with t-test between the control and experimental groups ($P > 0.05$) (Table 1).

Clinical manifestation improvement

There was a significant difference in the treatment effect in angina between the two groups: the total effective rate

in the experimental group was 94.9% compared to 75.7% of the control group ($P < 0.05$) (Table 2).

ECG improvement

There was a significant difference between the two groups with total effective rate in the experimental group being 84.6% compared to 59.5% in the control group ($P < 0.05$) (Table 3).

TCM syndrome improvement

There was a significant difference between the two groups with total effective rate in the experimental group being 94.9% compared to 70.3% in the control group ($P < 0.05$) (Table 4).

Biochemical markers

FIB and CRP decreased while SDNN and E/A increased at the end of the treatment in both control and experimental groups, but there was a significant difference between before and after the treatment in the experimental group ($P < 0.05$) but only CRP had a significant difference before and after the treatment in the control group (Table 5).

Side effects

No dysfunction of liver or kidney was attained in all the cases at the end of the treatment. Mild gastrointestinal reactions that could be tolerated occurred in a few patients.

DISCUSSION

Nowadays, DM has become one of the most common chronic non-communicable diseases that has caused a heavy burden globally, and in China there are 92.4 million DM patients (Yang et al., 2010); meanwhile, CHD has become the primary cause of death in China and 40% of deaths were due to CHD or related diseases in 2010 (Moran et al., 2010). Vascular complication was one of the most serious complications of DM, as well as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which also leads to heart dysfunction (Levy, 2002). So it would be difficult to treat patients with concomitant DM and CHD.

UAP belonged to "diabetes" and "thoracic obstruction" in the TCM category while DM belonged to "renal deficiency", "phlegm" and "blood stasis", and the "phlegm" and "blood stasis" would become worse when accompanied by angina, which was "sthenia in origin" and "asthenia

Table 1. General information of the cases in control group and experiment group.

Item	Control group (n=37)	Experiment group (n=39)
Male (n%)	21 (53.85)	20 (54.05)
Age (mean \pm sd, years)	67.0 \pm 7.7	68.0 \pm 7.2
DM course (months)	128.6 \pm 47.8	133.5 \pm 55.3
CHD course (months)	51.6 \pm 23.1	47.3 \pm 21.8

Table 2. The comparison of treatment effects in angina between two groups.

Group	Cases	Excellence	Effective	invalid	aggravation	Total effective rate (%)
Experiment	39	19	18	2	0	94.9
Control	37	14	14	9	0	75.7

Table 3. The comparison of ECG effects between two groups.

Group	Cases	Excellence	Effective	Invalid	Aggravation	Total effective rate (%)
Experiment	39	17	16	6	0	84.6
Control	37	12	10	15	0	59.5

Table 4. The comparison of TCM syndrome effects between two groups.

Group	Cases	Excellence	Effective	Invalid	Aggravation	Total effective rate (%)
Experiment	39	19	18	2	0	94.9
Control	37	15	11	11	0	70.3

Table 5. The comparison of FIB, CRP, SDNN and E/A between two groups.

Group	FIB (g/l)		CRP (mg/dl)		SDNN (ms)		E/a	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experiment	4.91 \pm 0.30	3.10 \pm 0.21 ^{*Δ}	2.80 \pm 1.41	1.32 \pm 0.20 ^{*Δ}	90.10 \pm 19.71	113.40 \pm 23.59 ^{*Δ}	0.79 \pm 0.41	0.98 \pm 0.21 ^{*Δ}
Control	4.83 \pm 0.50	4.56 \pm 0.79	2.62 \pm 1.31	1.82 \pm 0.32 [*]	88.14 \pm 21.90	92.89 \pm 19.98	0.82 \pm 0.39	0.83 \pm 0.32

*P < 0.05 versus before treatment, Δ P < 0.05 versus after treatment of control group.

in superficiality". The "renal deficiency" means fatigue, more frequent urination and spermatorrhea premature ejaculation and so on, which is correlated with aging, adrenal cortex dysfunction and hormone disorders, and from successive promotion/restriction of five "xing" of TCM the "renal deficiency" would lead to the "hyperactivity of liver yang" and the latter one would lead to "spleen-deficiency"; the "blood stasis" means the blood fluidity was poor, which is usually caused by vascular stenosis, leading to atherosclerosis or increased blood viscosity, and so had a relationship with FIB and platelets; the "phlegm" means blood lipids increased with plasma leptin and insulin resistance, which usually caused

caused obesity. YiShenTongMai decoction was created in response to the dialectical symptoms mentioned earlier. The formula was: King drug was Gold Theragran (*Cucurbitaceae gynostemma*), which could tonify the kidney, ministerial drugs were Chinese yam (*Dioscorea opposita*), Milkvetch root (*Leguminous astragalus*), *Bombyx mori* and *Allii macrostemi bulbus* (*Alliaceae allium*) with nourishing qi to invigorate spleen, notoginseng powder (*Araliaceae panax notoginseng*), *Pheretima asiatica*, Chinese hawthorn (*Rosaceae crataegus pinnatifida*) and *Achyranthis radix* (*Amaranthaceae achyranthes*), that could improve the blood fluidity and thoracic obstruction, adjunctive drug was

Table 6. Effects of drugs in YiShenTongMai decoction.

Effect	Gold theragran	Chinese yam	Milkvetch root	Bombyx mori ^[8]	Allii macrosterni bultus ^[8]	Notoginseng power ^[9]	Pheretima asiatica ^[10]	Chinese hawthorn ^[8]	Achyranthis radix ^[8]	Cassiac torae ^[8]
Anti-atherosclerosis	√ ^[4]	√ ^[11]	-	-	√	-	√	√	-	-
Improve myocardial function	√ ^[3]	√ ^[4]	√ ^[7]	-	-	√	-	√	-	-
Anti-inflammation	√ ^[5]	√ ^[5]	-	√	√	√	-	-	√	√
Hypoglycemic	-	√ ^[6]	-	-	-	-	-	-	√	-
Lipid-lower	-	√ ^[11]	-	√	√	√	-	√	√	√
Lower blood pressure	-	√ ^[2]	-	-	-	√	-	√	√	√
Promote blood flow	-	-	√ ^[8]	-	√	-	√	-	-	√
Protect liver	√ ^[6]	-	-	-	-	-	-	-	√	-
Diuresis	-	-	√ ^[8]	-	-	-	-	-	√	-
Analgesic	-	-	-	-	-	√	-	√	√	-
Sedation	-	-	-	√	-	-	-	√	-	√

[1] LiYuFang and HeXuanHua (1997); [2] LUO Rui-zhi et al. (2005); [3] WangNa et al. (1996); [4] Dai-ping et al. (1998); [5] Han-Shen Zhen (1986); [6] ZhaoYanQing and WangAiFeng (2000); [7] Chen Jian and FangZhiZhong (2005); [8] Jiangsu New Medical School Ed. (1987); [9] YangZhiGang et al. (2005); [10] YangMing (2010); [11] WangQian et al. (2005).

Cassiac torae (Cassia) that could calm the liver. All the medicines mentioned have been widely used for thousands of years and the effects have been confirmed by many cases in China, which were recorded in Chinese ancient medical books such as Compendium of Materia Medica. This prescription was helpful indeed to supplement “renal deficiency”, remove “blood stasis” and eliminate “phlegm”, which not only deals with the symptoms but also balances the “Yin” and “Yang”. Furthermore, modern pharmacology has confirmed the functions of drugs used in YiShenTongMai decoction (Table 6).

In recent years, many clinical and epidemiological studies confirmed that plasma FIB level was an independent risk factor of CHD (Becker et al., 1996). FIB is involved in not only blood clotting and stress but also the formation and development of atherosclerosis, which is related with CHD and myocardial infarction. A high level of FIB leads to the hypercoagulable state, induces

erythrocyte aggregation directly, reduces the blood flowability, and affects the shear flow rate of the vessel wall, which accelerates the atherosclerotic damage and thrombus formation significantly. Moreover, the degradation products of FIB can stimulate vascular smooth muscle cell proliferation and migration in the early stage of atherosclerosis formation (Michela et al., 2002).

CRP, as the specific marker of chronic inflammatory reaction, is involved in the atherosclerotic process directly. The increase of CRP is strong evidence of atherosclerotic plaque activity and there is a positive relation of CRP and cardiovascular disease (Ridker, 2003). SDNN is one of the most important indexes in heart rate variability, which is generally acknowledged as the most accurate and sensitive indicator to determine autonomic nerve damage of diabetic patients. The value of SDNN far exceeds the upright test and deep-breathing test, which plays a valuable role in the evaluation of autonomic nervous activity for

cardiovascular patients (Mercedes et al., 2006). The left ventricular diastolic function (E/A ratio) is also a valuable index. The clinical and animal experiments found that the decline of heart function happened in the early stage of diabetes before the occurrence of atherosclerosis. 90% of CHD patients had diastolic dysfunction, which usually occurs before the systolic dysfunction or complications. After the development of nearly two decades, doppler echocardiography has become a most common and important method of non-invasive evaluation in left ventricular diastolic function. In doppler echocardiography, left ventricular diastolic function is evaluated by the analysis of mitral rheogram, pulmonary venous rheogram and ventricular filling way, in which the mitral rheogram was the most common index of left ventricular diastolic function, and diastolic function can be easily identified by analysing the E/A ratio (early/late filling rate) (Bollache et al., 2010). Therefore, these indicators of FIB, CRP, SDNN and E/A will be

helpful to evaluate the treatment effects of unstable angina complicated with glucose metabolism disorder.

The present study showed that both the experimental group and the control group could improve unstable angina complicated with glucose metabolism disorder, and the experimental group with YiShenTongMai decoction showed better effects than the control group in symptomatic improvement. The total effective rates of angina control whether Western clinical symptoms or TCM symptoms and ECG improvement were higher in the experimental group. At the same time, the FIB and CRP decreased while SDNN and E/A increased much more in the experimental group, which showed that YiShenTongMai decoction could reduce blood viscosity and inflammation, improve the cardiac autonomic nervous regulation and left ventricular diastolic function. Since only mild gastrointestinal reactions were attached in a few patients and could be tolerated, the safety may be assured.

The main mechanism may include adjusting glucose metabolism, regulating blood lipid, anti-inflammatory, anti-thrombus to improve myocardial ischemia and cardiac function, which can inhibit or reverse the pathological process of unstable angina complicated with glucose metabolism disorder. Results showed that Western medicine was more effective with YiShenTongMai decoction than without, and the side effects were alike. Since YiShenTongMai decoction could increase the "Yang" so the patients could gain much more profit but none or little liver and kidney toxicity. Considering the medical benefits of short- and long-term, YiShenTongMai decoction may be an alternative supplement for UAP treatment.

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