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Full Length Research Paper

Efficacy of a Chinese herbal formula in patients with stable angina pectoris based on doctor and patient reported outcomes

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This research aimed at evaluating the clinical curative effect of Blood Mansion Stasis-Expelling Decoction and its refining prescription on stable angina pectoris through double-blind randomized controlled trial based on doctor and patient reported outcomes. Patients (92) were randomly grouped into Groups A, B, and C, and were separately given Blood Mansion Stasis-Expelling Decoction, refined Blood Mansion Stasis-Expelling Decoction and placebo, and they were evaluated before and after treatment, though, doctor and patient reported outcomes. The results showed that in doctor reported outcomes (DRO) aspect Blood Mansion Stasis-Expelling Decoction and its refining prescription had significant curative effect on angina ($P < 0.05$) when compared with placebo and reduced the patients' nitroglycerin consumption ($P < 0.01$), blood viscosity, platelet adhesion rate (PAR), and serum IL-6 level ($P < 0.05$ or $P < 0.01$), and raised their NO level ($P < 0.05$), while Blood Mansion Stasis-Expelling Decoction could raise the patients' erythrocyte deformation rate (EDR) and tissue plasminogen activator (t-PA) level ($P < 0.05$). In patient reported outcomes (PRO) aspect, Blood Mansion Stasis-Expelling Decoction and its refining prescription could improve angina stability of the stable angina pectoris patients, angina frequency and the satisfaction about the whole treatment ($P<0.01$ or $P<0.05$), and especially, work better on the patients' angina frequency than placebo ($P < 0.05$). The result showed that Blood Mansion Stasis-Expelling Decoction and its refining prescription have significant curative effect on stable angina pectoris through reducing inflammatory mediators and improving hemorheology condition and vascular endothelial function. Double-blind randomized controlled trial based on doctor and patient reported outcomes is an effective method to evaluate the curative effect of Chinese herbal formulae.

Key words: Blood Mansion Stasis-Expelling Decoction, patient reported outcomes, doctor reported outcomes, stable angina pectoris, Seattle Angina Questionnaire (SAQ), traditional Chinese medicine, double-blind randomized controlled trial.

INTRODUCTION

Coronary artery disease (CAD) is one of the most serious diseases around the world, which endanger human health. Thus, cardiovascular disease is on the top of the list of causes for population death in China, half of which is caused by coronary artery disease (National Center for Cardiovascular Diseases, 2009). In China, Chinese Medicinal Herb (CMH) is widely used in the clinical treatments and is considered with fine application value. The application value of CMH should be presented through acceptable objective evaluation system.

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Different from pharmaceutical chemicals, clinical application of CMH mainly relies on formulae and the components and mechanism of Chinese herbal formulae are quite complicated and difficult to specify, causing ordinary biomedicine evaluation system and standard cannot give a full and appropriate evaluation of CMH, and it is not satisfying, using physicochemical indexes and function evaluation.

As the medical model is being transferred from disease-centered to patients-centered, more scholars are using patient reported outcomes (PRO) for the analysis and research of the effects of diseases and medicine on patients. PRO is an all-round measurement of healthy status of patients by the patient itself (Food and Drug Administration, 2006). Generally, the Chinese herbal formulae are considered to have the characteristic of targeted therapy and integral adjustment, that is, improvement of both specified curative effect and health status, which proves that PRO could present the improvement of the patients after CMH treatment. All other evaluation from doctors, radiology diagnosing reports and experimental results are referred as doctor reported outcomes (DRO). Combining both DRO and PRO, the evaluation of Chinese herbal formulae with double-blind randomized controlled trial based on doctor and patient reported outcomes can reflect the effect of Chinese herbal formulae in clinical treatment of angina pectoris better. According to this idea, the most popular prescription was chosen on stable angina, Blood Mansion Stasis-Expelling Decoction, and choose curative effect on angina, nitroglycerin consumption, hemorheology index, inflammation index and vascular endothelial function index as DRO and Seattle Angina Questionnaire (SAQ)score as PRO to observe the clinical effect on stable angina pectoris of Blood Mansion Stasis-Expelling Decoction and its refining prescription through double-blind randomized controlled trial based on doctor and patient reported outcomes.

MATERIALS AND METHODS

Preparation of plant extracts

All medicinal herbs required were provided by Hebei province, Anguo City Longlian prepared by Chinese Medicinal Herb CO. Ltd., and were identified by Medicine Research Laboratory of Xiyuan Hospital. Blood Mansion Stasis-Expelling Decoction consists of 11 medicinal herbs as *Rhizoma Chuanxiong* (Chuanxiong), *Semen Persicae* (Taoren), *Flos Carthami* (Honghua), *Radix Angelicae Sinensis* (Danggui), *Radix Rehmanniae* (Dihuang), *Radix Paeoniae Rubra* (Chishao), *Radix Bupleuri* (Chaihu), *Fructus Aurantii* (Zhiqiao), *Radix Achyranthis Bidentatae* (Niuxi), *Radix Platycodonis* (Jiegeng), and *Radix et Rhizoma Glycyrrhizae* (Gancao) with the portion of 4:8:6:6:6:4:2:4:6:3:4 and were produced by Medicine Research Laboratory of Xiyuan Hospital through decoction and alcohol sedimentation technique. Extraction technology: all herbs were decocted with water twice, 2 h for the first time and 1.5 h for the second time before combining the filter, and then, the filtrate was concentrated until its relative density was about 1.15 to 1.20(50℃) and ethanol was added to produce a solution containing 60% of ethanol, and it was stirred well, and was left standing for 24 h, filtered, thus, ethanol was recovered for later use. Mixed liquid was adjusted to a pH value of 7.0, and was heated up to boiling, filtered, potted and was sterilized. Crude drug was 1500 g/L with the color of yellow-brown, spicy air and bitter taste.

The refining Blood Mansion Stasis-Expelling Decoction consists of 6 medicinal herbs as *Rhizoma Chuanxiong* (Chuanxiong), *Semen Persicae* (Taoren), *Flos Carthami* (Honghua), *Radix Paeoniae Rubra* (Chishao), *Radix Bupleuri* (Chaihu), and *Fructus Aurantii* (Zhiqiao) with the proportion of 2:4:3:2:1:2, and the same extraction technology was used as the previous decoction. Maltose was used as placebo with the same extraction technology as the previous decoction.

Blood Mansion Stasis-Expelling Decoction and refining Blood Mansion Stasis-Expelling Decoction and placebo had no difference in packing, and they were all labeled as Blood Mansion Stasis-Expelling Decoction oral liquid and were numbered by Medicine Research Laboratory with blind code. All medicines had passed all qualification tests with test reports. The voucher specimens were deposited in the laboratory for future reference.

Clinical data

In this study, 98 patients were collected with stable angina pectoris treated by Xiyuan Hospital of China Academy of Chinese Medical Sciences and Fuwai Hospital of Chinese Academy of Medical Sciences from June 2003 to January 2004.

Diagnostic and inclusion criteria

The diagnostic standard of stable angina referred to the nomenclature and criteria for diagnosis of ischemic heart disease (World Health Organization, 1979), and all patients were voluntarily collected as observed case and signed informed consents.

Exclusion criterria

Patients excluded comprised those who had intellectual disturbance and mental disturbance, and could not finish the questionnaire, those who had acute myocardial infarction, and acute heart failure; patients with complication of severity hypertension, and serious arrhythmia (maintaining rapid atrial fibrillation, atrial flutter, ventricular premature beat, ventricular tachycardia); patients with complication of diabetic ketoacidosis; patients with complication of serious primary disease of liver, kidney or hematopoietic system; pregnant or breast feeding women or patients with allergic condition.

Grouping and treatment

All patients were randomly grouped into 3 groups (labeled I, II and III). Group A (I) was treated with Blood Mansion Stasis-Expelling Decoction of 10 ml tid; Group B (III) was treated with refining Blood Mansion Stasis-Expelling Decoction of 10 ml tid; Group C (II) was treated with placebo of 10 ml tid. All patients maintained previous standard treatment and used nitrate esters, calcium antagonist, β-blocker, small dose of aspirin according to clinical requirements and excluded all other CMH treatment and were observed for 4 weeks.

Doctor reported outcomes

Therapeutic effect for angina pectoris

Curative effect on angina was judged by the standard of Guiding

Table 1. Curative effect on angina.

Group	n	Markedly effective	Effective	Ineffective	Aggravated
Group A	31	11	16	3	1
Group B	31	10	15	6	0
Group C	30	0	18	8	4

Principles of Clinical Study on new drug of Traditional Chinese Medicine (State Food and Drug Administration of China, 2002).

Hemorheological index

Blood viscosity, plasma viscosity (mpa·s) were measured with LBY-N6 rotational viscometer produced by Beijing Precil Company. Platelet adhesion (PADT, %) was measured through the rotating glass sphere method to calculate platelet adhesion rate (PAR) with XSN-R II platelet adhesion determinator produced by Jiangsu Wuxi, the second Electronic Instruments Plant. Erythrocyte deformability (%) was measured through laser diffraction method with LBY-BX2 erythrocyte function laser determinator produced by Beijing Precil Company.

Inflammation marker

IL-6 and IL-8 were measured through immunoassay, using kits produced by the Immunity Research Institute of Chinese PLA General Hospital, batch number of 040112-06 and 040113-08, using SN-682 radio-immune γcounter produced by Shanghai Radiation Instrument Co, Ltd. Hs-CRP was measured through enzyme linked immunoassay, using kits from American HOPE E&E LAB Company, batch number of 03111403, using Alisce MX automated immune analyser.

Vascular endothelial function index

Endothelial (ET) was measured through radioimmunoassay, using kits produced by the Immunity Research Institute of Chinese PLA General Hospital, batch number of 040115-01, using SN-682 radio-immune γcounter produced by Shanghai Radiation Instrument Co, Ltd. Nitride oxide (NO) was measured through enzymatic determination and t-PA was measured through enzyme linked immunoassay, using kits from Jingmei biological engineering Beijing Co. Ltd, batch number of 040110, using Wellscan MK3automated immune analyser produced by Labsystems Dragon in Finland.

Patient reported outcomes

When using SAQ to evaluate, the measuring scale was divided into 5 parts and 19 items, including physical limitation (PL, item 1), angina stability (AS, item 2), angina frequency (AF, items 3 to 4), treatment satisfaction (TS, items 5 to 8) and diseases perception (DP, items 9 to 11). Each item was graded and the grade was summed by parts and was converted to standard grade. Standard grade = (actual grade – lowest grade) / (highest grade – lowest grade) × 100.

Higher grade implied better living quality and physical condition. After essential explanation of the doctors to grouped patients about SAQ questionnaire, the patients should finish the questionnaire independently.

Statistics analysis

All data were presented by $\bar{x} \pm s$ and were processed with SAS 6.12. Measurement data were analyzed with t test and variance analysis, enumeration data were analyzed with χ^2 test and ranked data were analyzed with rank test.

RESULTS

The clinical trial expulsed 6 cases with the rate of 6.1% and finished 92 cases, with 1 patient in Group C of untoward effect of bellyache, diarrhea and dizziness, and the patient applied and quitted the trial after being approved. In all accomplished cases, Group A had 31 cases, 16 males and 15 females, of 43 to 74 age with the average of (61.29 ± 7.57); Group B had 31 cases, 15 males and 16 females of 45 to 73 age with the average of (62.58 ± 7.15); Group C had 30 cases, 16 males and 14 females of 42 to 75 age with the average of (63.57 ± 7.49). Age, sexuality and symptom of the 3 groups had comparability in statistical analysis ($P > 0.05$).

Curative effect on angina and nitroglycerin consumption

The groups ranked by the curative effect from the best to the worst were Group A, Group B and Group C. The difference of curative effect on angina had statistical significance after rank test ($P < 0.05$). All the 3 groups were treated with less nitrorectal after treatment with statistic significance ($P < 0.01$ or $P < 0.05$). Nitroglycerin consumption between the 3 groups had statistical significant difference ($P < 0.01$ or $P < 0.05$) (Tables 1 and 2).

Effects on hemorheological index

Blood viscosity of Groups A and B reduced significantly after the treatment ($P < 0.05$), while that of Group C had no significant different ($P > 0.05$). For all groups, plasma

Table 2. Effect on nitroglycerin consumption.

Group	n	Consumption of nitroglycerin (tablets per week)		
		Before treatment	After treatment	P
Group A	31	3. 96 ± 1. 27	1. 15 ± 0. 58	P < 0.01
Group B	31	3. 79 ± 0. 57	1. 54 ± 0. 38	P < 0.01
Group C	30	3. 79 ± 0. 77	2. 20 ± 0. 49	P < 0.05

Table 3. Effects on hemorheological index-1.

Group	n	Whole blood viscosity (mpa·s)			Plasma viscosity (mpa·s)		
		Before treatment	After treatment	P	Before treatment	After treatment	P
Group A	31	4.95 ± 1.01	4.25 ± 1.26$^{\Delta}$	0.026	1.74 ± 0.03	1.72 ± 0.03	0.086
Group B	31	5.09 ± 0.95	4.65 ± 0.78$^{\Delta}$	0.019	1.73 ± 0.04	1.73 ± 0.03	0.836
Group C	30	5.17 ± 0.99	4.92 ± 0.90	0.331	1.73 ± 0.03	1.72 ± 0.03	0.157

$^{\Delta}$P < 0.05 versus before treatment.

Table 4. Effects on Hemorheological index-2.

Group	n	Platelet adhesion (%)			Erythrocyte deformation (%)		
		Before treatment	After treatment	P	Before treatment	After treatment	P
Group A	31	29.43 ± 3.31	26.51 ± 3.25$^{\Delta}$	0.002	33.58 ± 13.24	39.00 ± 8.13$^{\Delta}$	0.047
Group B	31	30.08 ± 2.93	27.14 ± 3.37$^{\Delta}$	0.006	36.76 ± 9.07	36.79 ± 9.27	0.988
Group C	30	29.37 ± 3.27	27.02 ± 3.76$^{\Delta}$	0.006	31.95 ± 13.62	37.32 ± 10.58$^{\Delta}$	0.039

$^{\Delta}$P < 0.05 versus before treatment.

viscosity had no significant change (P > 0.05). Platelet adhesion rate (PAR) reduced significantly after treatment of all the 3 groups (P < 0.01). The Erythrocyte Deformation Rate (EDR) of Groups A and C increased significantly after treatment (P < 0.05), while no significant difference was found for Group B (P > 0.05). Blood viscosity level of Group A was lower than that of Group C (P < 0.05). Difference of plasma viscosity, PAR and EDR of all the 3 groups had no significant difference after treatment (P > 0.05) (Tables 3 and 4).

Effects on IL-6, IL-8 and Hs-CRP

Judging by inflammation markers, IL-6 of Groups A and B was significantly lower after treatment (P < 0.05), while no significant change was found for Group C, IL-8 and Hs-CRP for all the 3 groups (P > 0.05) (Table 5).

Effects on NO, ET and t-PA

NO level of Groups A and B rose significantly after treatment (P < 0.05) and t-PA of Group A also rose significantly (P < 0.05). ET level of the 3 groups had no significant difference (P > 0.05) (Table 6).

SAQ score

AS, AF and TS of Group A got improved significantly after treatment (P < 0.01 or P < 0.05). AS, AF, TS and DP of Group B got improved significantly after treatment (P < 0.01 or P < 0.05). PL, AS, AF, TS and DP of Group C had significant change after treatment (P > 0.05). Comparing all the 3 groups, AF of Groups A and B was higher than Group C significantly (P < 0.05), and other items had no significant difference between each of the two groups (P > 0.05) (Table 7).

DISCUSSION

Generally speaking, there are varieties of evaluation method for curative effect on stable angina pectoris, including angina curative effect, electrocardiogram curative effect, treadmill exercise, cardiac function evaluation, radiological reports (like echocardiography) and laboratory examination results (hemorheological index, inflammation markers, vascular endothelial function index, blood lipid, etc), and the most popular standard of angina is the improvement of heart function and motion test of New York Heart Association (NYHA). In a broad sense, all these evaluation methods belong to DRO

Table 5. Effects on IL-6, IL-8, and Hs-CRP.

Group	n	IL-6		IL-8		Hs-CRP	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	31	89.54 ± 7.41	70.95 ± 5.48$^{\Delta}$	0.44 ± 0.03	0.42 ± 0.02	30.42 ± 5.12	25.98 ± 4.20
Group B	31	84.76 ± 7.16	62.70 ± 5.50$^{\Delta}$	0.44 ± 0.05	0.36 ± 0.02	31.71 ± 5.76	26.75 ± 5.09
Group C	30	81.47 ± 6.58	99.98 ± 11.15	0.43 ± 0.02	0.37 ± 0.02$^{\Delta}$	28.14 ± 5.04	27.88 ± 5.04

$^{\Delta}P < 0.05$ versus before treatment.

Table 6. Effects on NO, ET, and t-PA.

Group	n	NO		ET		t-PA	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group A	31	70.24 ± 8.34	76.79 ± 8.48$^{\Delta}$	61.42 ± 12.27	64.16 ± 17.70	0.033 ± 0.004	0.039 ± 0.004$^{\Delta}$
Group B	31	73.38 ± 9.98	78.47 ± 13.96$^{\Delta}$	60.95 ± 14.78	67.48 ± 21.06	0.034 ± 0.004	0.035 ± 0.005
Group C	30	69.96 ± 9.47	70.30 ± 9.31	64.78 ± 12.35	66.08 ± 14.43	0.033 ± 0.003	0.034 ± 0.004

$^{\Delta}P < 0.05$ versus before treatment.

Table 7. Effect on SAQ Score.

Group	n		PL	AS	AF	TS	DP
Group A	31	Before treatment	64.80 ± 3.87	39.80 ± 3.10	65.50 ± 4.10	56.40 ± 3.30	48.45 ± 3.82
		After treatment	70.55 ± 3.41	61.11 ± 3.85$^{\Delta\Delta}$	78.51 ± 2.81$^{\Delta\Delta\blacktriangle}$	65.04 ± 3.81$^{\Delta}$	52.16 ± 3.57
Group B	31	Before treatment	64.23 ± 3.50	44.00 ± 3.61	68.40 ± 5.43	60.00 ± 3.98	46.99 ± 3.59
		After treatment	68.11 ± 2.90	65.00 ± 4.33$^{\Delta\Delta}$	80.40 ± 4.01$^{\Delta\Delta\blacktriangle}$	71.50 ± 3.71 $^{\Delta\Delta}$	50.99 ± 3.48$^{\Delta}$
Group C	30	Before treatment	65.41 ± 3.60	45.19 ± 3.11	64.61 ± 4.08	55.53 ± 4.62	50.64 ± 3.83
		After treatment	68.12 ± 3.17	57.69 ± 4.75$^{\Delta}$	67.69 ± 4.01	58.65 ± 4.69	51.96 ± 3.47

$^{\Delta}P<0.05$, $^{\Delta\Delta}P<0.01$ versus before treatment; $^{\blacktriangle}P<0.05$ versus after treatment of Group C.

system, while PRO from patients themselves reflect symptoms, physical sign, psychological and physiological adaption to the environment, using measuring scale. The quality of life is one of the main part of PRO and popular measuring scales for angina living quality are Nottingham Health Profile (NHP) (Hunt et al., 1981), CLASP, SF-36, SF-8, SAQ, etc. SAQ reflect the limitations of physical movement for angina patients, stability of angina and paroxysm condition, satisfactory treatment and the recognition of the disease, and it is repeatable and reliable. Therefore, this research used combined DRO methods and SAQ as evaluation method for Blood Mansion Stasis-Expelling Decoction.

DRO of this research shows that Blood Mansion Stasis-Expelling Decoction and its refining prescription and placebo all have curative effect on stable angina pectoris. Blood Mansion Stasis-Expelling Decoction has the best curative effect on angina and the most significant nitroglycerin consumption reduction, and the refining Blood Mansion Stasis-Expelling Decoction comes second and placebo third. Blood of coronary heart disease patients usually shows a hypercoagulable state and the result of this research shows that Blood Mansion Stasis-Expelling Decoction can improve blood viscosity, PAR and EDR of angina pectoris patients and refining Blood Mansion Stasis-Expelling Decoction can improve blood viscosity and PAR, while placebo can improve EDR of the patients. Inflammation markers shows that Blood Mansion Stasis-Expelling Decoction and its refining prescription can reduce IL-6 level of angina patients significantly; however, no significant influence on IL-8 and Hs-CRP and placebo can reduce IL-8 level significantly. Formation and development of coronary atherosclerosis relates to inflammation reaction. IL-6 is the main regulatory

factor of inflammation cell differentiation and the effect on IL-6 of Blood Mansion Stasis-Expelling Decoction and its refining prescription shows their curative effect on coronary heart disease to certain extend. For endothelial function, the balance between ET and NO stabilizes the base tension of blood vessel and some research data shows that angina pectoris patients have lower NO level than normal people and Blood Mansion Stasis-Expelling Decoction and its refining prescription could improve NO/ET balance through raising NO level of serum. Though, there is no unified recognition of t-PA level of angina patients, Blood Mansion Stasis-Expelling Decoction can improve the activity of t-PA of patients. According to all DRO, Blood Mansion Stasis-Expelling Decoction and its refining prescription have better curative effect than placebo, improve hemorheology condition and endothelial function, reduce inflammation and explain their curative effect and mechanism of action on stable angina pectoris from the view of the disease.

On the other side of PRO, Blood Mansion Stasis-Expelling Decoction and its refining prescription and placebo can significantly improve angina stability of angina pectoris patients and there is no significant different between each two of them. Blood Mansion Stasis-Expelling Decoction and its refining prescription can improve angina frequency and the satisfaction of the treatment, while placebo has no improvement. Blood Mansion Stasis-Expelling Decoction and its refining prescription cannot improve physical limitation. As a whole, through PRO analysis, Blood Mansion Stasis-Expelling Decoction is an effective cure for stable angina pectoris, and especially, it has satisfactory effect on reducing pain paroxysm condition of patients.

Referring to DRO and PRO analysis, PRO can show that Blood Mansion Stasis-Expelling Decoction has good total clinical curative effect and the patients get improved from physical status to psychological status, while DRO can evaluate drug effect from certain aspects and have limited application in clinical curative effect of Chinese herbal formulae. For pharmaceutical chemicals which have single component and single target, DRO can reflect the curative effect more efficiently, while for Chinese herbal formulae which have complicated components and varieties of mechanism of action, PRO maybe a better way for curative effect evaluation. However, DRO can reflect potential mechanism of action when evaluating drug effect, for example, in this research, Blood Mansion Stasis-Expelling Decoction and its refining prescription may work through reducing inflammatory mediators, improving hemorheology condition and endothelial function, and set up a basement for further improvement, refining and research on Pharmaco-mechanism of Chinese herbal formulae. Meanwhile, PRO have certain subjectivity and can be affected by different effects. SAQ used in this research have good repeatability and double-blind setting can reduce the effect of grouping on patients' psychology, so PRO for this trail is reliable and it also illustrates that psychological impacts of patients should be paid attention to in PRO research. There is a relation between DRO and PRO: DRO is the base of PRO and both of them reflect the curative effect of CMH from different aspects. In brief, double-blind randomized controlled trial, based on doctor and patient reported outcomes can reflect the curative effect of Chinese herbal formulae appropriately and makes a good evaluation method to show their clinical value.

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