Chin J Integr Med 2011 Feb;17(2):146-149

CLINICAL EXPERIENCE

Clinical Effect of Astragalus Granule of Different Dosages on Quality of Life in Patients with Chronic Heart Failure*

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ABSTRACT **Objective**: To explore the dose-effect relationship of Astragalus granule (AG) on improving the quality of life (QOL) of the patients with chronic heart failure (CHF). **Methods**: Ninety CHF patients of Fei (肺)-qi deficiency and/or Xin (心)-Shen (肾) yang-deficiency syndromes were equally randomized divided with a random number table into three groups; they received the high (7.5 g), moderate (4.5 g), and low dosage (2.25 g) of AG orally taken twice a day, respectively, and 4 mg of perindopril tablet once a day for 30 successive days. The heart function grade, patients' left ventricular ejection fraction (LVEF) and walking distance in 6 min (6mWD) were measured before and after treatment, and the patients' QOL was scored by the Minnesota Questionnaire for QOL evaluation in the patients with CHF at the same time. **Results**: The heart function grades of all the three groups after treatment were improved compared with those before treatment, but the improvements in high-dose group and moderate dose group were better than that in the low dose group (P<0.05). LVEFs were increased significantly in all the three groups, but the improvements in the high-dose group (59.42%±7.50%) and moderate dose group (61.98%±6.82%) were better than that in the low dose group (51.45%±6.80%, P<0.01); the 6mWDs in the all groups were also significantly increased (P<0.01), up to 419.80±36.23 m, 387.15±34.13 m, and 317.69±39.97 m, respectively; and Minnesota scores in them were lowered to 29.59±4.69 scores, 35.74±5.89 scores, and 42.78±6.06 scores, respectively; comparisons in aspects on 6mWD and Minnesota score showed that the effectiveness with high dose is the most effective, moderate dose as the second, and low dose as the lowest (P<0.01). **Conclusions**: AG was sufficient to display an optimal effect on improving heart contraction at the moderate dose. In aspects of improving the QOL of CHF patients, the effectiveness of AG showed a dose-dependent trend. It should be applied discriminatively depending on the actual condition of patients and the aim of treatment in clinic.

KEYWORDS astragalus, heat failure, heart function, quality of life, dose-effect relationship

As a comprehensive index for evaluating condition of health, quality of life (QOL) has become the goal of medicine and social development in present time. Nowadays, in the prevention and treatment of chronic heart failure (CHF), not only are the improving of heart pump function, primary disease, and relevant physical/chemical indices controlling required but also should pay more attention on the patients' QOL elevation and the cutting down of their rehospitalization rate and morbidity[1]. In this study, the effect of astragalus granule (AG) on QOL in CHF patients was observe clinically, taking heart function grade, the walking distance in 6min (6mWD) and the scoring based on "Minnesota Questionnaire for QOL evaluation in CHF patients", and its dose-effect relationship was estimated as well.

METHODS

Standards for Diagnosis, Inclusion, and Exclusion

CHF was diagnosed referring to the standard of "Guidlines for the diagnosis and treatment of chronic heart failure" issued by China Society of Cardiovascular Diseases, Chinese Medical Association, 2007[2].

The patients of CHF fitting to the abovementioned diagnostic standard, whose heart function was classified to NYHA grade Ⅱ–Ⅲ, and their Chinese medicine syndrome patterns were differentiated, according to the "Guiding Principle of Clinical

*Supported by the Funds of Scientific and Technological Research on Traditional Chinese Medicine, Traditional Chinese Medicine Administration of Jiangsu Province, China (No. HL07113)

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DOI: 10.1007/s11655-011-0647-9

Research on New Drugs of Traditional Chinese Medicine"[3], as Fei (肺)-qi deficiency and/or as Xin (心)-Shen (肾) yang-deficiency type were included in this study. They took part in the trial voluntarily and signed the written informed consent.

The patients in the following conditions were excluded: (1) diagnosed as rheumatic, congenital or pulmonary heart disease, or with acute myocarditis; (2) the heart dysfunction was induced by functional failure of important organs other than the heart, as liver and kidney; (3) complicated with severe primary diseases of liver, kidney, endocrine systems, or hemopoietic system or with other severe diseases, such as malignant tumor, grave malnutrition, mental disorder, etc.; (4) the women in pregnant or lactation stage and the patients of allergic constitution or with multiple drug hypersensitivity; (5) incapable to cooperate in the trial, made bold to take or remove the designated drugs, or asked for the possibility quitting in the midway of the trial.

General Materials

A total of 90 patients with confirmed CHF were inpatients of the Department of Cardiaovascular Diseases, Wuxi Municipal Hospital of Traditional Chinese Medicine, from April 2007 to August 2008, and they were randomized with a random number table into three groups (H, M, and L), treated respectively with different dosages of AG. The differences among the groups were insignificant in baseline materials, such as sex, age, course of illness, smoke or not, complication, etc. (P>0.05, Table 1).

Table 1. Baseline Materials of Patients (30 cases in each group)

Item	Group H	Group M	Group L
Sex (Case, M/F)	18/12	14/16	17/13
Age (Year, $\bar{x}\pm s$)	63.0±4.7	62.5±4.3	63.7±3.9
Course (Year, $\bar{x}\pm s$)	5.6±3.4	5.9±4.3	5.0±4.1
Hypertension (Case)	13	15	11
Diabetes (Case)	6	8	7
Blood lipids abnormality (Case)	18	21	17
Smoke (Case, Y/N)	19/11	17/13	16/14

Treatment

The testing drug AG was provided by Jiangsu Tianjiang Pharmaceutical Ltd., Co., China, made of crude *Radix Astragalus* through decocting, concentrating, and drying, packed up to 1.5 g in each bag (equivalent to the extract from 10 g of crude drug).

All patients in the three groups were treated with AG two times a day but at different dosages, namely, high dosage (7.5 g/time) to the Group H, moderate dosage (4.5 g/time) to the Group M, and low dosage (2.25 g/time) to the Group L. In addition, 4 mg of peridopril was administered to all patients once per day. The treatment lasted 30 days. Except the expectant treatment for the patients with acute heart failure attacking, other drugs including cardiotonic, diuretic, etc. were prohibited during the observation period. The related indices, left ventricular ejection fraction (LVEF), walking distance in 6 min (6mWD), and the score of QOL estimated by the patients' self-rating with Minnesota Questionnaire were detected twice at the first and the 30th day of treatment.

Items and Methods of Observation

Evaluation of Heart Function Grade

The heart function grade was evaluated according to New York Heart Association (1982)[4].

Measurement of LVEF

The left ventricular end-systolic volume and end-diastolic volume were measured with color ultrasonocardiography type LOGIQ7 (product of GE Co., USA), with apical four-chamber view monoplane modified Simpson method, and the LVEF was calculated. The mean value of parameters got from three successive cardiac cycles was fetched.

Measurement of 6mWD

The patients were asked to walk quickly in a flat straight hallway under doctor's supervision, and the distance went across in 6 min was recorded as 6mWD.

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Estimation of Scores of QOL

The scores of QOL were estimated by the patients' self-rating with Minnesota Questionnaire, chatted with the patients for clear misgiving up before handing the Questionnaire to them; gave explanation for filling it, or, if necessary, helped them by ghost-writing on their approval. It was completed in 5–10 min.

Statistical Analysis

By using SPSS 11.0 software, the measurement data were expressed as $\bar{x}\pm s$; the analyses were performed with mono-factor variance analyses or t-test

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after data passed normality test and homogeneity of variance test. Rank data were performed with rank sum test.

RESULTS

The observation was completed in all the 90 patients enrolled. During the observation period, 11 patients had acute attack of heart failure; they were three (10.0%) in the Group H, four (13.3%) in the Group M, and four (13.3%) in the Group L. By proportional analysis, the differences among groups in acute heart failure occurrence and the drugs applied were insignificant (P>0.05).

Effects of AG at Different Dosages on Heart Function Grade

After treatment, the heart function grades of all the three groups were improved compared with those before treatment (P<0.05), but the improvements in the high dose group and moderate dose group were better than that in the low dose group (P<0.05), however, the comparison of the index between the high dose group and moderate dose group showed no significant difference (P>0.05, Table 2).

Table 2. Effects of AG at Different Dosages on Heart Function Grade (Case)

Group	Case	Time	Heart function grade			
			Ⅰ	Ⅱ	Ⅲ	Rank sum
H	30	Pre-treat.	0	9	21	58.37
		Post-treat	7	14	9	49.02*△
M	30	Pre-treat.	0	8	22	62.10
		Post-treat	5	15	10	48.78*△
L	30	Pre-treat.	0	10	20	59.97
		Post-treat	6	8	16	70.07*

Notes: *P<0.05, compared with pre-treatment in the same group; △P<0.05, compared with Group L

Effects of AG at Different Dosages on Patients' QOL

After treatment, LVEFs and 6mWDs were increased, and Minnesota scores were lowered in all the three groups, as compared with those before treatment; all were showed statistically significant (P<0.05). The improvements in the Group H and the Group M were better than that in the Group L (P<0.01). However, the comparison of the indices between the Group H and the Group M showed that the high dosage of AG could not further improve the LVEF (P>0.05) but could increase the 6mWD (P<0.01), which suggested the further improvement of exercise tolerance. In addition, Minnesota score in the Group H was lower than that in the Group M (P<0.01), suggesting that the larger dosage AG had a certain superiority in improving the patients' QOL (Table 3).

DISCUSSION

Modern medicine has achieved great successes in present years in aspects of nosogenesis, therapeutic policy, and pharmacological research of CHF; however, the high mortality and progressive deteriorating characteristics prompts that the current "ideal" drug-therapy cannot completely block the developmental course of CHF yet. Chinese medicine has showed its superiority in controlling the symptoms of CHF and improving the QOL of the patients. Particularly, the effectiveness of *Radix Astragalus* such as improving heart function and QOL has been proven by lots of pharmacological researches, and its application in clinical practice is widened unceasingly. However, either Chinese medicine or Western medicine affects the organism depending on a dose-effect relationship to a certain degree, lower dose influencing the efficacy, while large dose inducing the waste of drug resource and even leading to side-toxicity effects due to the accumulation in the body. The dosage of *Radix Astragalus* used is still in a random manner depending on users' experience, and a unified and standardized reference system is absent. To use *Radix Astragalus* rationally and normatively becomes a problem, which should be dissolved with urgency.

Table 3. Effects of AG at Different Dosages on Patients' QOL ($\bar{x} \pm s$)

Group	Case	Time	LVEF (%)	6mWD (m)	Minnesota questionnaire score (Score)
H	30	Pre-treat.	38.08 ± 5.74	238.48 ± 37.22	57.21 ± 3.25
		Post-treat.	59.42 ± 7.50*△	419.80 ± 36.23*△▲	29.59 ± 4.69*△▲
M	30	Pre-treat.	38.65 ± 5.48	230.05 ± 39.04	56.33 ± 4.70
		Post-treat.	61.98 ± 6.82*△	387.15 ± 34.13*△	35.74 ± 5.89*△
L	30	Pre-treat.	37.81 ± 6.25	235.75 ± 35.20	58.19 ± 3.64
		Post-treat.	51.45 ± 6.80*	317.69 ± 39.97*	42.78 ± 6.06*

Notes: *P<0.05, compared with pre-treatment in the same group; △P<0.01, compared with Group L; ▲P<0.01, compared with Group M

Moreover, the occurrences of some symptoms, such as lassitude, edema, exercise tolerance deprivation even unable to lie flatly, and nocturnal paroxysmal dyspnea, are imperfectly identical with the laboratory data obtained, which means that these symptoms might be revealed in some patients with normal physical/chemical parameters[6]. Along with the social development, biomedicine is turning toward the biological/psychological/social medical mode; the traditional therapeutic approaches and effectiveness evaluation criteria, which paid attention only to life preservation and local function improvement, already could not embody the whole intention of health; people beginning to pursue the integrality and entireness of man that possess biological/psychological/social attributive characters and also the understanding of the concrete intention of QOL.

6mWD is a parameter for assessing the exercise tolerance of CHF patients, a classic index for evaluating cardiac function and also a quantitative index for expressing the patients' QOL. Minnesota Questionnaire Score was adopted for many years in assessing QOL of CHF patients; its reliability, efficacy, and responsibility has been confirmed widely worldwide and has been applied in lots of large-scale clinical researches[7].

In this study, those two parameters were used for the patients' QOL assessment, and the effects of AG at different dosages on LVEF and Minnesota Questionnaire Score of CHF patients were observed comparatively. Results showed that the left ventricular contract functions were strengthened after the patients treated with different dosages of AG, even the dosage used was low. However, the effect was not dose-dependent, since the power of strengthening was not increased more in the Group H, in spite of the dosage used, which was much higher than that used in the Group M. This fact suggested that further increase of AG dosage was of no practical meaning for enhancing LVEF.

However, in the other side, the effects of AG showed its effects on extending 6mWDs and reducing Minnesota questionnaire Scores from high to low in the three groups: the high dosage was the most effective, moderate dose the second, and low dosage the lowest, presenting a dose-dependent tendency. The authors considered that which could be related with the effect of AG on improving myocardial ischemia/anoxia and enhancing the immune and auto-regulation function of organism[8]. Whereas it might be also related with the selection criteria in this trial (only the patients with Fei-qi deficiency and/or Xin-Shen/yang-deficiency syndrome were selected). The problem is waiting for further exploring. The limit of the observation is that no Western medicine contro group was set up during the study due to a certain difficulty in selecting the patients with CHF.

Results of the study indicated that AG at moderate dosage (9.0 g per day) could show a favorable effectiveness in improving heart contract function, but in improving QOL, it showed a dose-effect dependent tendency. Therefore, in clinical practice, the dosage of *Radix Astragalus* should be determined discriminatingly depending on the actual condition of patient and the aim of treatment.

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(Received January 18, 2010)
Edited by WANG Wei-xia