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The effective evaluation on symptoms and quality of life of chronic obstructive pulmonary disease patients treated by comprehensive therapy based on traditional Chinese medicine patterns☆

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KEYWORDS
Chronic obstructive pulmonary disease;
Tradition Chinese medicine pattern;
Quality of life;
Bu-Fei Jian-Pi granules;

Summary
Objective: To evaluate the efficacy of comprehensive interventions based on the three TCM patterns on symptoms and quality of life of COPD patients.
Design: An open-label, randomized, controlled trial.
Setting: Four hospitals in China.
Intervention: 352 patients were randomly divided into two groups. Patients in the trial group were given conventional Western medicine and Bu-Fei Jian-Pi granules, Bu-Fei Yi-Shen granules and Yi-Qi Zi-Shen granules respectively; patients in the control group were given conventional Western medicine. Data collection was performed at baseline, in the 3rd and 6th month during the treatment period, and the 12th month during the follow-up period.

Abbreviations: COPD, chronic obstructive pulmonary disease; TCM, traditional Chinese medicine; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FEV1%, FEV1 percentage of predicted value; QOL, quality of life; FAS, full analysis set; PPS, per-protocol analysis set.

☆ This trial was registered at Chinese Clinical Trial Register, ChiCTR-TRC-11001406.

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Bu-Fei Yi-Shen granules; Yi-Qi Zi-Shen granules

Outcomes: Symptoms, including cough, sputum, pant, chest tightness, short of breath, lassitude, cyanosis and symptom total score; quality of life, measured by the WHOQOL-BREF questionnaire and adult COPD quality of life questionnaire (COPD-QOL).
Results: Of the 352 patients, 306 fully completed the study. After treatment and follow-up, there were significant differences between two groups in the following: cough, sputum, pant, chest tightness, shortness of breath, lassitude score and symptom total score ($P < .05$); physical, psychological, social and environment domain ($P < .05$) of the WHOQOL-BREF; daily living ability, social activity, depression symptoms and anxiety symptoms domain ($P < .05$) of the COPD-QOL. There were no differences between two groups in cyanosis and adverse events.
Conclusion: Based on the TCM patterns, Bu-Fei Jian-Pi granules, Bu-Fei Yi-Shen granules and Yi-Qi Zi-Shen granules have beneficial effects on symptoms and quality of life of COPD patients.
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Introduction

Chronic obstructive pulmonary disease (COPD) with high prevalence, morbidity, mortality and economic burdens, is a global public health problem.[1] The overall prevalence of COPD in China is 8.2% in individuals 40 years of age or older.[2] And an estimated 65 million people will die of COPD between 2003 and 2033 in China.[3] COPD patients face functional decline and daily life limitations due to the slowly progressive course of breathing discomfort, which can cause dependence, depression, anxiety, and other psychological disturbances overtime.[4] One of the therapeutic goals for COPD management is to improve symptoms and health-related quality of life (HRQOL).[5]

Chronic airway obstruction and airflow limitation are the key physiological characteristics, and the main symptom is breathlessness, although other symptoms such as lassitude and depression are common.[6,7] However, in an early or stable state, breathlessness is not obvious and often overlooked by patients and physicians.[8] In practice the decision to seek medical help is usually determined by the effect of a symptom on a patient's daily life. Therefore, evaluation of the symptom is important to understand health status and to evaluate effects of clinical intervention.[9] HRQOL is a multidimensional concept that includes physical, psychological and social function and well-being.[10,11] In the last decade, the evaluation of QOL has been an important outcome measure and assessment tool in COPD research and treatment.[12] Although lung function is often used as an index of COPD severity,[5] it is not necessarily linked to symptoms, disability or HRQOL; indeed, HRQOL appears more closely linked to the respiratory symptoms than lung function.[13,14]

The remarkable longevity of traditional Chinese medicine (TCM) for COPD implies its potential advantages.[15,16] However, there is limited evidence concerning specific symptoms and disease-specific QOL based on comprehensive TCM interventions that responded to the TCM patterns. According to our previous study, there are three common TCM patterns of stable COPD, and there is one specific herbal intervention responding to each pattern.[17] Therefore, a multi-center randomized controlled study had been carried out to evaluate the efficacy of comprehensive interventions based on the three TCM patterns on COPD patients' symptoms and QOL.

Methods

Participants

Patients included should meet the following inclusion criteria: met the diagnostic criteria of COPD;[7,18] met the TCM pattern criteria of COPD[19] (pattern of lung-spleen qi deficiency, pattern of lung-kidney qi deficiency, pattern of lung-kidney qi and yin deficiency); were stable and met the diagnosis of mild to severe COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD 1,2,3); aged between 40 and 80 years; no experience in other intervention trials in the previous month; received the treatment voluntarily and signed informed consent. COPD patients were excluded if they had confusion, dementia or any type of mental illness; acute exacerbation of COPD or very severe COPD (GOLD 4); bronchial asthma, or bronchiectasis, or active tuberculosis, pulmonary embolism, or diffuse panbronchiolitis; serious diseases such as tumor, heart failure, liver and kidney diseases, or haematopoietic system diseases; allergic to treatment drugs.

Ethical review and entry procedure

The study was approved by the Ethical Research Committees of The First Affiliated Hospital of Henan University of TCM (batch number: YFYKTLL2007-1). Patients were enrolled from out-patient department and through open recruitment. Patients were observed in the First Affiliated Hospital of Henan University of TCM, Jiangsu Provincial Hospital of TCM, Henan Provincial People's Hospital and the Affiliated Hospital of Shandong University of TCM. All patients signed informed consent before inclusion.

Sample size

The frequency of acute exacerbation was considered as the primary outcome. From a previous study, the exacerbation frequency decreased by 0.44 times half year,[20] then exacerbation frequency decreased at least by 1 time and the standard deviation was 1.5 times/year were assumed to reflect the efficacy of TCM comprehensive interventions. The formulae $((2(\mu_\alpha + \mu_\beta)\sigma^2)/\delta^2)$ was based on a comparison between the equal numbers of a two sample mean. The

two-sided alpha level was 0.05, and the beta level was 0.10. Through the calculation, the final sample size was 352, with 176 patients in each group.

Randomization

A stratified and block randomization design was adopted. The number of the groups was 2, the distribution ratio was 1-to-1, and the length of block was four. A random number from 001 to 352 was generated by SAS 9.2 and saved in a sealed envelope. Treatment allocation occurred when the participant met the inclusion criteria and signed the informed consent. The design was provided by the DME Department of Guangzhou University of TCM.

To strengthen the quality control for this open-label trial, an investigator separate from all of the clinical researchers was assigned in each center as the contact person who preserved and recorded the randomization information. Meanwhile, outcome assessments were made by an independent clinical statistician blinded to group allocation and uninvolved in providing intervention or management.

Interventions

COPD patients in the control group were given conventional Western medicine treatment recommended by GOLD and Chinese Treatment Guidelines.[7,18] The specific therapies were: GOLD 1: albuterol sulfate (Ventolin, GlaxoSmithKline), 100 μg/dose, 100 μg each time. GOLD 2: formoterol fumarate dehydrate (Oxis Turbuhaler, AstraZeneca), 4.5 μg/dose, 4.5 μg each time, twice daily. GOLD 3: salmeterol/fluticasone propionate (Seretide, GlaxoSmithKline), 50/250 μg each time, twice daily.

Patients in the trial group, based on conventional Western medicine treatment, were additionally given Bu-Fei Jian-Pi granules, Bu-Fei Yi-Shen granules and Yi-Qi Zi-Shen granules, which were made by a series of process. Firstly, base on our long experience in the clinical practice, combined with expert counseling many times, the initial framework of the three granules was formed. Meanwhile, through the experimental studies, the mechanism of the three granules was explored and its formulas were performed further optimization. In addition, the small sample randomized controlled trial was conducted to evaluate its efficacy. Finally, the three granules were made and used in this study. The granules were compound preparations of TCM and produced by Jiang Yin Tian Jiang Pharmaceutical Co. Ltd. with the authentication quality of Goods Manufacturing Practice (Approval Number: SU J0677).

Bu-Fei Jian-Pi granules for lung-spleen qi deficiency (batch number: 080103), 3.83 g per bag, were mainly composed of Huang Qi (*Astragalus propinquus*), Dang Shen (*Codonopsis pilosula*), Bai Zhu (*Atractylodes macrocephala*), Fu Ling (*Wolfiporia extensa*). Bu-Fei Yi-Shen granules for lung-kidney qi deficiency (batch number: 080102), 4.25 g per bag, were mainly composed of Ren Shen (*Radix Ginseng*), Huang Qi (*A. propinquus*), Shan Zhu Yu (*Fructus Corni*), and Yin Yang Huo (*Herba Epimedii*). Yi-Qi Zi-Shen granule for lung-kidney qi and yin deficiency (batch number: 080104), 5.16 g per bag, were mainly composed of Ren Shen (*Radix Ginseng*), Huang Jing (*Polygonatum sibiricum*), Shu Di Huang (*Rehmannia glutinosa*), Mai Dong (*Ophiopogon japonicus*). The quality of the granules was consistent with the required quality standards. Each type of granule was given orally, three bags each time, twice daily for 6 months.

Outcomes

Symptoms

Symptoms included cough, sputum, pant, chest tightness, shortness of breath, lassitude, cyanosis, and symptom total score. Based on the typical format of a Likert response scale,[21] each symptom had a score from 0 to 3 according to the severity of the symptom. The lower the score was, the better the clinical symptom of the patients. Total scores were got by adding up each symptom score.

Quality of life

The WHOQOL-BREF questionnaire[22] and adult COPD quality of life questionnaire[23] (COPD-QOL) were adopted. The WHOQOL-BREF, a validated questionnaire, contains 26 questions that are loaded on 4 domains, which are physical, psychological, social and environment domain. For each domain, the higher score, the better QOL of the patients. The COPD-QOL was developed by Cai Ying-yun and his study group. To assess whether this questionnaire was appropriate for our study,[24] we re-evaluated it and it had good reliability, content validity and construct validity. There are 35 questions loaded on 4 domains of the COPD-QOL, which are daily living ability, social activity, depression symptoms, and anxiety symptoms domain. For each domain, the lower score, the better QOL of the patients. Both questionnaires were the typical format of a Likert 5-points response scales, in which each question ranged from 1 to 5. The domain score was got by summing each question score.

The symptoms and QOL questionnaire are all the self-complete questionnaires and the questions are all closed questions with a Likert scale. The patients were invited to complete the three questionnaires in the office for this trial through face-to-face survey. The patients can answer each question and check the most appropriate opinion (a specific score) in their standards, hopes, pleasures and concerns. Meanwhile, there is the same investigator in each center was assigned in the office to help the patients. If the patients have difficulty understanding some questions, the investigator can clarify the ambiguous questions to them, however, the patients completed the questionnaires in their own opinions. Then the investigator should check through each completed questionnaire to ensure that the patients answer all the questions. The dates of symptoms and QOL were observed and recorded before treatment (month 0), in the 3rd month (month 3) and 6th month (month 6) during the treatment period, and at the 12th month (month 18) during the follow-up period.

Statistical analysis

All P values were two-tailed and the α level of significance was set at 0.05. Measurement data were analyzed by independent-samples t-tests or Mann—Whitney U-tests based on data distribution to compare differences between the two groups. Repeated measures were used to compare

differences of time continuous observations. The analysis of covariance was used to compare the value differences of center effect. Numerical data were described by absolute frequency. All statistical analyses were undertaken using SAS9.2 (KEY: FQ37-WSB8-7G5C).

Results

Patients enrollment and comparison of general information

Based on the rejection criteria, two patients were excluded because of violating the protocol. Meanwhile, forty-four patients who did not fully complete the study were withdrawn owing to poor compliance, loss during follow-up, or dropped out of the study without explanation. 306 patients fully completed the study. Therefore, the per-protocol analysis set (PPS) population was 306; the full analysis set (FAS) population was 350. Patients enrollment and completion values for the study were shown in Fig. 1.

There was no significant difference in gender, age, the course of disease, lung function, and GOLD classification between the two groups (FAS, PPS: $P > .05$). The comparison of general information at baseline between the two groups was shown in Table 1.

Comparison of symptoms

Before treatment, there was no significant difference in each symptom and total scores between the two groups ($P > .05$). Cough, sputum, pant, chest tightness, shortness of breath, lassitude score and total scores of the trial group all continued to decrease overtime, and the mean scores of the trial group were significantly lower than those of the control group (FAS, PPS: $P < .05$). At the 3rd, 6th and 18th month, the trial group had lower each symptom score and total scores compared with those of the control group, specifically for cough (Fig. 2A, $P \leq .004$), sputum (Fig. 2B, $P \leq .001$), pant (Fig. 2C, $P \leq .047$), chest tightness (Fig. 2D, $P \leq .036$), shortness of breath (Fig. 2E, $P \leq .039$), lassitude (Fig. 2F, $P \leq .023$), symptom total score (Fig. 2H, $P \leq .004$). There was no significant difference in cyanosis score between the two groups ($P > .05$), the results were shown in Fig. 2G.

Comparison of WHOQOL-BREF questionnaire

Before treatment, there was no significant difference in each domain score and its total scores between the two groups ($P > .05$). QOL scores of the trial group all continued to increase over time and were significantly higher than those of the control group ($P < .05$). At the 3rd, 6th and 18th month, the trial group had higher QOL scores compared with those of the control group, specifically for physical (Fig. 3A, $P \leq .022$), psychological (Fig. 3B, $P \leq .049$), environment (Fig. 3C, $P \leq 0.016$), social (Fig. 3D, $P \leq .015$), total score (Fig. 3E, $P \leq .005$).

Comparison of COPD-QOL questionnaire

Before treatment, there was no significant difference in each domain score and its total scores between the two groups ($P > .05$). QOL scores of the trial group continued

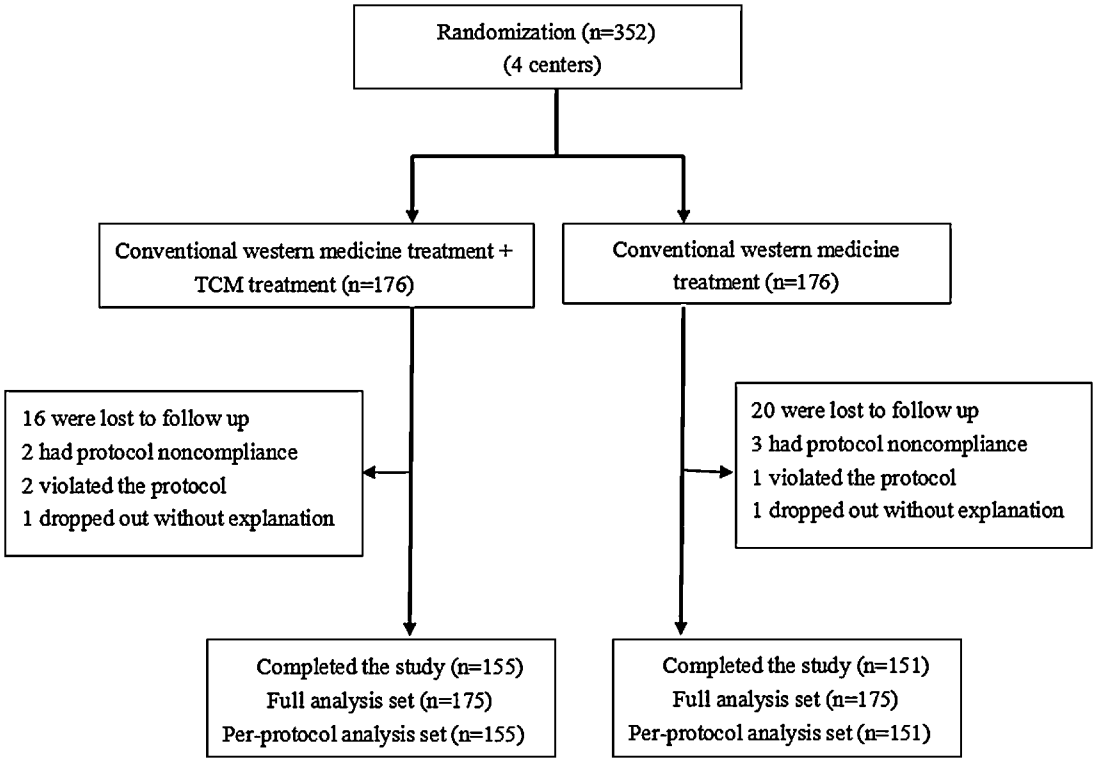

Figure 1 Enrollment of the patients and completion of the study.

Table 1 Comparison of general information between the two groups.

Characteristics	Full analysis set				Per-protocol analysis set			
	Trial $n=175$	Control $n=175$	$t/\chi^2/Z$	P	Trial $n=155$	Control $n=151$	$t/\chi^2/Z$	P
Age (years)	66.33 ± 9.63	64.28 ± 9.42	−.935	.351	62.74 ± 9.87	64.66 ± 8.92	−1.778	.076
Course of disease[a]	169.56 ± 290.63	161.07 ± 128.45	.353	.725	166.86 ± 305.92	163.18 ± 131.84	.136	.892
Exacerbation[b]								
Frequency (times)	3.26 ± 2.27	2.94 ± 2.05	1.378	.169	3.32 ± 2.31	2.95 ± 1.91	1.523	.129
Duration (days)	2.78 ± 2.00	2.73 ± 1.97	.228	0.820	2.82 ± 2.08	2.75 ± 1.81	.319	.750
Lung function								
FVC (liters)	2.91 ± .95	2.81 ± .89	.953	.341	2.95 ± .97	2.81 ± .92	1.239	.216
FEV_1 (liters)	1.46 ± .57	1.35 ± .46	1.465	.144	1.46 ± .57	1.35 ± .46	1.747	.082
FEV_1 (%)	49.89 ± 10.84	49.58 ± 12.07	.244	.807	49.94 ± 10.95	49.58 ± 12.36	.266	.790
Gender								
Male	122	131	1.556	.212	106	116	2.732	.098
Female	54	43			49	35		
GOLD classification[c]								
GOLD 1	14	6	−.093	.926	13	6	−.369	.712
GOLD 2	68	80			61	66		
GOLD 3	94	88			81	79		

[a] The course of disease was calculated in months.
[b] Exacerbations during the 12 months before screening were self-reported.
[c] Classification of lung function were determined by guidelines for COPD

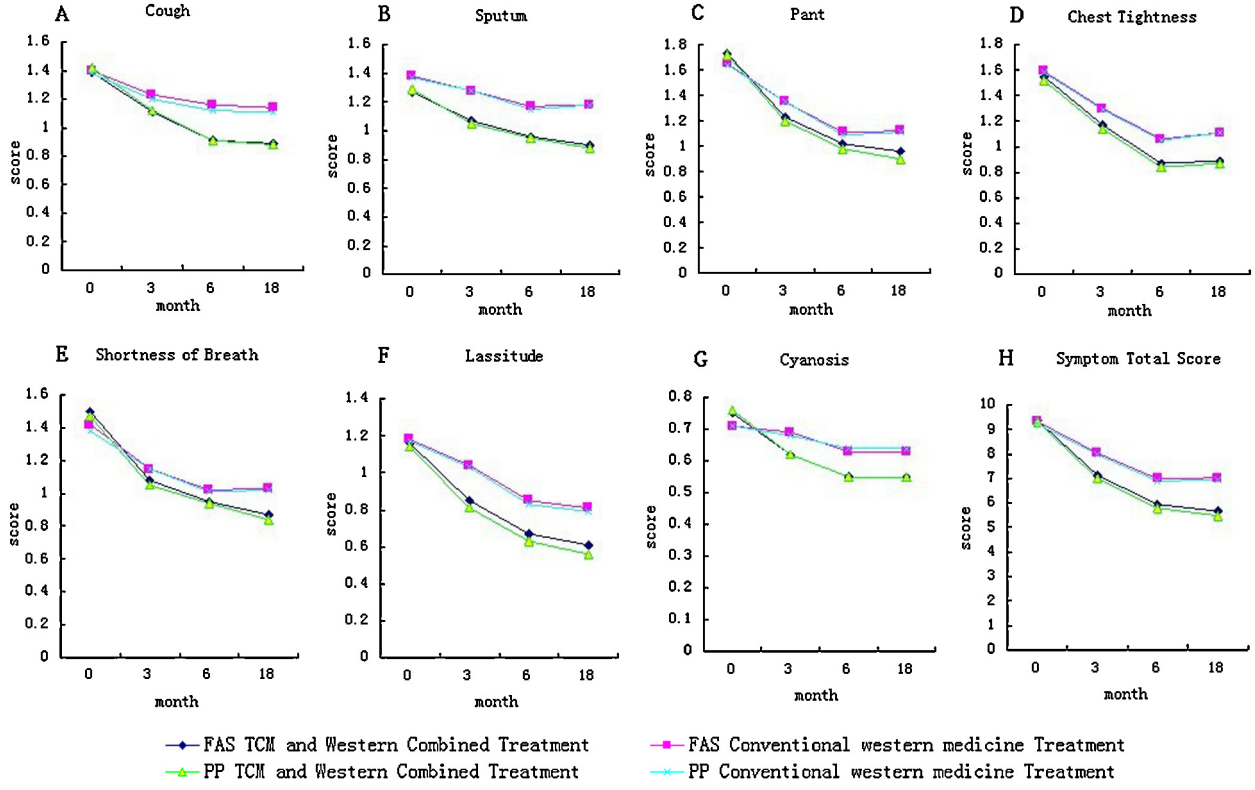

Figure 2 Change in symptoms and comparison of cough, sputum, pant, chest tightness, shortness of breath, lassitude, cyanosis score and symptoms total scores at baseline, 3rd, 6th and 18th month between two groups.

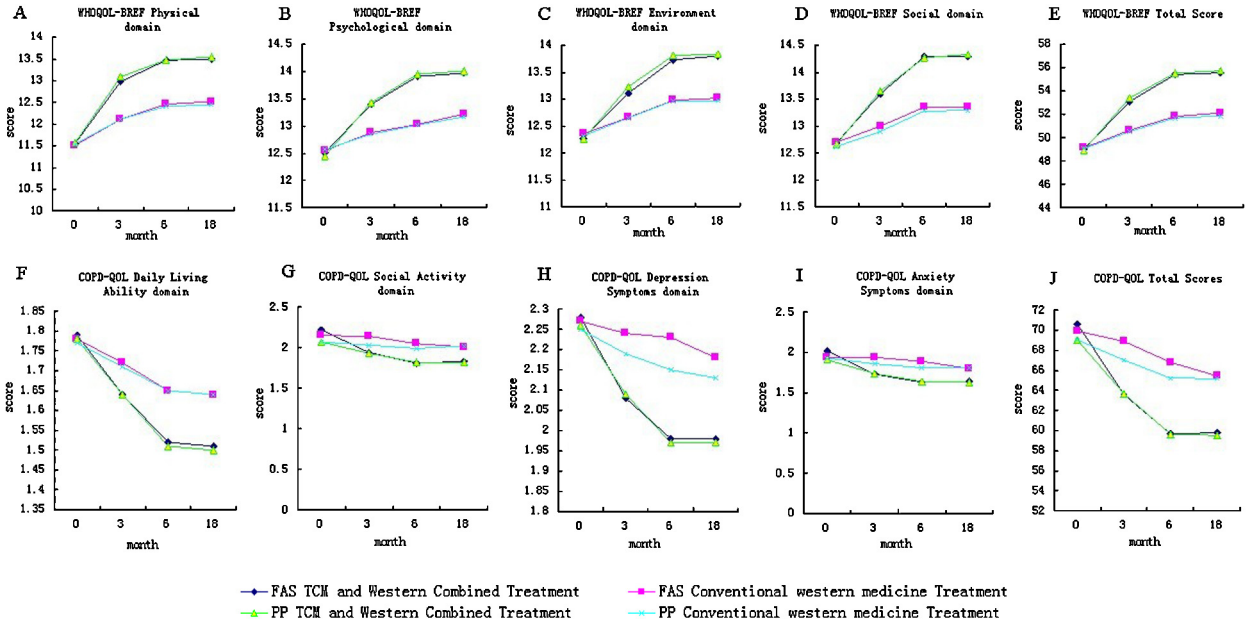

Figure 3 Change in quality of life and comparison of WHOQOL-BREF questionnaire in physical, psychological, environment, society domain and total scores, and COPD-QOL in daily living ability, social activity, depression symptoms, anxiety symptoms domain and total scores at baseline, 3rd, 6th and 18th month between two groups.

to decrease over time and were significantly lower than those of the control group ($P < .05$). At 3rd, 6th and 18th month, the trial group had lower QOL scores compared with those of the control group, specifically for daily living ability (Fig. 3F, $P \leq .003$), social activity (Fig. 3G, $P \leq .002$), depression symptoms (Fig. 3H, $P \leq 0.023$), (Fig. 3I, $P \leq .007$), (Fig. 3J, $P \leq .023$).

Evaluation of safety

There were no significant difference in routine blood, urine and stool tests, liver and kidney function tests and ECG in each group before and after treatment. Adverse events were recorded when happened, however there was no significant difference between the two groups ($P > .05$). Five cases in the trial group with abdominal distension, palpitation, constipation, thirst and insomnia, which may be caused by drug-related effects of TCM treatment. Eight cases with abdominal distension, palpitation, constipation, insomnia, stomach discomfort and dry throat, which may be been caused by drug-related effects of conventional Western medicine.

Discussions

Presently, the classes of medications treatment recommended by GOLD are commonly used in treating COPD. Although more alternative approaches are used in COPD patients, definite effect evidence for TCM treatments is still limited. Hence, based on recommended conventional Western medicine, we conducted the study to evaluate the comprehensive interventions based on three TCM patterns on COPD patients' symptoms and QOL. Over treatment and follow-up, the TCM granules had beneficial effects on the measured outcomes.

The clinical symptoms, regarded as a summary of the body's condition at a certain stage, are the most intuitive feelings came directly from the patient on the disease and treatment, which are important to disease condition judgment, treatment plan adjustment, curative effect evaluation, as well as the main basis of TCM diagnosis, syndrome differentiation and treatment.[25] COPD is characterized by a progressive decline in lung function and an increase in symptoms such as dyspnea, cough, and sputum production. In practice the decision to seek medical help is usually determined by the effect of a symptom on a patient's daily life. Our results showed that the improvement of cough (35.97%), sputum (29.13%), pant (44.51%), chest tightness (42.58%), short of breath (51.33%), lassitude (47.41%), and symptom total score (39.56%) in the trial group was better than those of the control group, in which cough (18.57%), sputum (14.49%), pant (32.12%), chest tightness (30.19%), short of breath (27.46%), lassitude (31.36%), and symptom total score (24.65%). In this study, there lack of evident improvement of cyanosis, the late symptoms of COPD, due to severe hypoxia, for which the process was relatively long and the effect was not obvious. Therefore, TCM granules can alleviate the main symptoms of COPD.

Currently, QOL becomes an indispensable indicator and assessment tool, widely used in the world. As QOL is subjective experience, questionnaire is an important tool for its assessment. There are many kinds of effective and reliable HRQOL questionnaires on COPD. The WHOQOL-BREF questionnaire was widely used to evaluate the generic HRQOL. Disease-specific HRQOL measures for respiratory conditions include the St. George's Respiratory Questionnaire (SGRQ)[26] and the Chronic Respiratory Questionnaire (CRQ).[27] Because of the long course and a progressive lung function decline,

which can cause limited daily activities and lead to COPD patients cannot take care of themselves and rely on family members, coupled with the financial burden, which make them have low self-esteem, depression, anxiety and other damages on psychological emotion and social adaptation ability. As for COPD patients, it is important part to cure them with effective interventions to improve the QOL.

With better reliability and validity, the WHOQOL-BREF and COPD-QOL questionnaire were adopted. As for the WHOQOL-BREF questionnaire, the results showed that after treatment and follow up, the improvement of physical domain (16.88%), psychological domain (11.83%), social domain (12.61%), environment domain (12.47%), and total scores (13.34%) in the trial group was better than those of the control group, in which the improvement was 5.12—8.78%. As for the COPD-QOL questionnaire, the results showed that after treatment and followed up, there was more improvement of daily living ability domain (15.64%), social activity domain (18.47%), depression symptoms domain (10.71%), anxiety symptoms domain (17.27%), and total scores (16.05%) in the trial group than those of the control group, in which the improvement was 4.41—7.87%. For the improvement of QOL, the interventions of TCM granules had better effect than conventional Western medicine.

However, there are some limitations to this study. The placebo of TCM granules and blind methods were not adopted in this study. For this study, three TCM granules were used based on the three TCM patterns in COPD patients. Because of the number of patients in each TCM pattern cannot be got before randomization, it is difficult to have precise number for making three placebos for this study. Add to that the specific blind method for the different TCM patterns in chronic disease were difficulty solving. Therefore, an open-label, randomized, controlled trial was adopted for this study. However, some measures were taken to strengthen quality control and avoid the influence of placebo effect. The randomization, allocation, and data management were handled by independent individuals. The standard operating procedures (SOPs) and periodic monitoring were also implemented. In addition, the culture background was also taken into account. We try our best to avoid the influence of placebo effect to a large extent.

Conclusions

Based on the TCM patterns, TCM treatments have beneficial effects on symptoms and quality of life, with no relevant between-group differences in adverse events. Further studies are required to prove the efficacy and safety of TCM treatments.

Conflict of interest

The authors declare that they have no competing interests.

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