Bufei Yishen Granule combined with acupoint-sticking therapy in patients with stable chronic obstructive pulmonary disease: study protocol of a multicenter, randomized, double-blind, active-controlled trial

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Background: Chronic obstructive pulmonary disease (COPD) is a serious disease constituting a major threat to public health. Current popularity of traditional Chinese medicine (TCM) in treating COPD implies its potential advantage in improving symptoms, reducing the frequency of acute exacerbation and improving the patients' quality of life. This study is to evaluate the efficacy and safety of a comprehensive intervention, Bufei Yishen Granule combined with acupoint-sticking therapy, in patients with stable COPD.

Methods and design: A multicenter, double-blind, double-dummy and randomized controlled design will be adopted. A total of 244 cases meeting the inclusion criteria will be enrolled into this study with 122 cases in the trial group and 122 in the control group, respectively. Patients in the trial group will receive Bufei Yishen Granule combined with acupoint-sticking therapy and dummy sustained-release theophylline, while patients in the control group will receive sustained-release theophylline and dummy Bufei Yishen Granule combined with dummy acupoint-sticking therapy. The frequency and duration of acute exacerbation, lung function, clinical symptoms, six-minute walking distance, dyspnea grade and quality of life will be observed during a four-month treatment period and a further six-month follow-up.

Discussion: It is hypothesized that Bufei Yishen Granule combined with acupoint-sticking therapy will have beneficial effects in reducing the frequency and duration of acute exacerbation, ameliorating the symptoms, and improving the quality of life of patients with stable COPD. The results of this study will provide evidence for developing a TCM-based regimen for patients with COPD.

Trial registration: ChiCTR-TRC-11001409.

Keywords: pulmonary disease, chronic obstructive, traditional Chinese medicine therapy; acupoint sticking therapy; clinical trial; clinical protocols
Chronic obstructive pulmonary disease (COPD) is a major serious disease threatening public health. The incidence, prevalence and mortality of COPD are increasing, and the economic burdens and harmful consequences cannot be ignored. It was reported that the incidence of COPD in Chinese urban populations over 40 years old was 8.2%\(^{[1]}\). Due to tobacco smoking, solid-liquid use and other reasons, between 2003 and 2033 an estimated 65 million people will die of COPD in China\(^{[2]}\). The clinical study of prevention and treatment of COPD has become an important subject for contemporary research. At present, health education, low-dose and slow-release theophylline, inhaled \(\beta_2\)-agonists and corticosteroids, home oxygen therapy and pulmonary rehabilitation exercises are used to prevent and treat COPD. However, there are still difficulties in helping people control their symptoms as well as eliminating medication-induced side effects or adverse events\(^{[3]}\).

The current popularity of traditional Chinese medicine (TCM) in the treatment of COPD implies its potential advantage in improving symptoms, reducing the frequency of acute exacerbation and improving patients’ quality of life\(^{[4-6]}\). Bufen Yishen Granule is made from highly concentrated Chinese herbs. A previous study demonstrated that Bufen Yishen Granule can ameliorate the functions of the lung and the kidney and can be administered easily\(^{[6]}\). Acupoint-sticking therapy by externally applying herbal paste to the acupoints, is used for many lung diseases in TCM clinical practice. The paste is made from different formulas according to the intended purpose of treatment. Acupoint-sticking therapy is suitable for wide application in the community due to its practical and convenient application and rare side effects\(^{[7]}\). In routine clinical practice, Chinese herbal medicine combined with acupoint-sticking therapy can improve the therapeutic effect on COPD. Therefore, a randomized, double-blind, active-controlled clinical trial will be carried out to evaluate the efficacy and safety of Bufen Yishen Granule combined with acupoint-sticking therapy in patients with stable COPD.

1 Methods and design

1.1 Participants

1.1.1 Diagnostic criteria for COPD Stable COPD is diagnosed according to the Global Strategy for the Diagnosis, Management, and Prevention of COPD\(^{[8]}\), and the Chinese Treatment Guidelines of COPD\(^{[9]}\).

1.1.2 Inclusion criteria (1) Patients meet the diagnostic criteria. (2) Patients meet the patterns of deficiency of lung and kidney qi (TCM diagnosis), with symptoms of dyspnea, shortness of breath, weakness and spontaneous sweating, which are aggravated during exhalation, and have the symptoms of tinnitus, vertigo, frequent micturition, frequent urination at night, soreness and weakness of waists and knees\(^{[9]}\). (3) Patients should be in the stable state of COPD and the severity grade of pulmonary function should be in a level of grade I to III. (4) Patients are aged between 40 and 80 years. (5) Patients should receive treatment voluntarily and sign informed consent.

1.1.3 Exclusion criteria (1) Patients with acute exacerbation of COPD or with severe grade of pulmonary function in a level of grade IV. (2) Patients with confusion, dementia or any kind of mental illness. (3) Patients with bronchial asthma, bronchiectasis, active tuberculosis, pulmonary embolism or diffuse panbronchiolitis. (4) Patients with serious diseases such as tumor, heart failure, liver and kidney diseases, or hematopoietic system diseases. (5) Patients with congenital or acquired immune deficiency. (6) Patients participating in other clinical intervention research program. (7) Patients allergic to the treatment drugs.

1.1.4 Entry procedure Patients with stable COPD will be enrolled from either the out-patient departments or open recruitment and be observed in four centers, namely, the First Affiliated Hospital of Henan University of TCM, the First Affiliated Hospital of Anhui College of TCM, the Third...
Affiliated Hospital of Henan University of TCM and Kaifeng Hospital of TCM. All patients will sign the informed consent before inclusion.

1.2 Study design

1.2.1 Sample size A total of 244 patients will be enrolled into this study with 122 in each group, respectively. The frequency of acute exacerbation is considered as the primary outcome measure. According to the previous study results, the exacerbation frequency decreased by 44% every six months using the TCM comprehensive interventions compared with the Western medicine treatment. Assume that there would be promotional value only when the exacerbation frequency decreased at least once for one patient every six months. The standard deviation (SD) value is 1.25 times per year, the two-sided α is 0.05, and β is 0.10. Based on the formula \( \frac{2(\mu_1 + \mu_2)}{\delta^2} \) of the comparison between the means of the two samples, the sample size in each group is 33. Considering a 20% dropout rate over the course of the study, 40 patients will be enrolled in each group. The severity of disease (I, II and III) is considered as the stratification factors, then there will be 120 patients in each group and the total sample size will be 240. As one of the four centers is a relatively small hospital, considering the recruitment process, four cases are added to this center and the total sample size will be 244.

1.2.2 Randomization The stratified and block randomization design will be adopted. The random number will be generated by the SAS 9.12 software and saved in a sealed envelope by statistical professionals and the director of the study.

1.2.3 Double blinding The patients and investigators will be blinded. All the drugs will be in unified packaging. Neither the patients nor the clinical trial investigators will know the types of drugs taken by each patient. The blind code will be saved in a sealed envelope by the directors of each center who are responsible for the study. For each blind code, an emergency envelop is prepared. Investigators could uncover the emergency envelop with the monitor if there is a serious adverse event.

1.3 Interventions The trial group patients will take Buefei Yishen Granule combined with acupuncture-sticking therapy and dummy sustained-release theophylline, while the control group patients will take sustained-release theophylline and dummy Buefei Yishen Granule combined with dummy acupuncture-sticking therapy.

Buefei Yishen Granule is a compound extract of Renshen (Radix Ginseng), Huangqi (Radix Astragali Mongolici), Gouqi (Fructus Lycii), Shanzhu (Fructus Corni) and Yinyanghuo (Herba Epimedi Brevicornus); 1 g of the extract is equivalent to about 5 g of the original herbs. Dummy Buefei Yishen Granule is mainly composed of dextrin and a bitter agent. Both the granule and the dummy are packaged 4.25 g per bag and both are produced by Jiangyin Tianjiang Pharmaceutical Co. Ltd. The test results of drug quality are consistent with the required quality standards.

Shufei Tie ointment for acupoint-sticking therapy is a compound extract of Baijizai (Semen Sinapis), Yanhusuo (Rhizoma Corydalis Yanhusuo), Ganjiang (Rhizoma Zingiberis), Xixin (Herba Asari Mandshurici) and Yunnanhu (Flos Genkwa); 1 g of the extract is equivalent to approximately 3 g of the original herbs. Dummy Shufei Tie ointment is mainly composed of carbopol, diatomaceous earth and glycerine. Both the ointment and the dummy are packaged 3 g per unit and both of them are produced by the First Affiliated Hospital of Henan University of TCM.

The sustained-release theophylline (approval number: H10940037), 24 pills per bag, each pill containing 100 mg, is produced by Hangzhou Minsheng Pharmaceutical Co. Ltd., and repacked by the First Affiliated Hospital of Henan University of TCM. The dummy sustained-release theophylline, with starch as the main component, 24 pills per bag, each pill containing 100 mg, is produced by the First Affiliated Hospital of Henan University of TCM.

Buefei Yishen Granule (or its dummy) would be administered orally with three bags each time and twice a day for four months; the ointment for acupuncture-sticking (or its dummy) would be applied for 6 to 12 h each patching time and once every 7 d for two months; sustained-release theophylline (or its dummy) would be given orally with 100 mg each time and twice a day for four months.

The practitioner will be required to provide a brief description of every adverse event and what action should be taken, including details of any investigations and treatments. They will be also asked to state whether, in their opinion, the event was related to the TCM therapy.

1.4 Outcome measures

1.4.1 Primary outcome measures

1.4.1.1 Frequency and duration of acute exacerbation of COPD The frequency and duration of acute exacerbation of COPD each time within the treatment will be counted for four months and followed up for six months. If the interval between two onsets of acute exacerbation is less than one week, it can be counted as one occurrence of acute exacerbation. The data will be recorded before treatment, each month during the treatment period, and the third month and the sixth month during the follow-up period.

1.4.1.2 Lung function The indicators of forced vital capacity (FVC), forced expiratory volume in one second (FEV1, ) and FEV1, percentage of predicted value (FEV1, %) will be measured before and after treatment, respectively.

1.4.2 Secondary outcome measures

1.4.2.1 Symptoms Symptoms including cough,
sputum, shortness of breath, dyspnea, gasping and cyanosis, etc, will be observed and recorded before treatment, each month during the treatment period, and the third month and the sixth month respectively during the follow-up period. The Dyspnea Scale Questionnaire, which is first developed by the British Medical Research Council (MRC), and later revised by the American Thoracic Society, will be used before treatment, in the second month and the fourth month during the treatment period, and in the sixth month during the follow-up period.

1.4.2.2 Quality of life The WHOQOL-BREF questionnaire and adult COPD quality of life scale (COPD-QOL) will be adopted, and will be used before treatment, in the second month and the fourth month during the treatment period, and in the third month and the sixth month during the follow-up period.

1.4.2.3 The six-minute walking distance The six-minute walking distance (6MWD) will be observed and recorded once respectively before treatment, in the second month and the fourth month during the treatment period, and the sixth month during the follow-up period.

1.4.3 Safety The routine blood test, routine urine test, routine stool test, liver and kidney function test and electrocardiograph will be undertook before and after treatment, respectively. Adverse events will be observed and recorded at any time during the treatment period as well as the follow-up period.

1.5 Statistical analysis

1.5.1 Statistical analysis set Full analysis set (FAS): patients who go through randomization and receive treatments and get observation at least one related record on time point will be included in FAS. Per-protocol analysis set (PPS): patients who fully complete the trial with better compliance will be included in PPS. Safety set (SS): all patients who take the trial medicine at least once will be included in SS.

1.5.2 Data processing and statistical analysis methods All P values will be two-tailed and the significance will be set at 0.05. Measurement data will be presented as mean ± SD or median ± interquartile range. The paired-sample t test or signed rank sum test will be used to compare the difference between pretreatment and posttreatment within one group. The analysis of variance will be used to compare the difference between the trial group and control group. The analysis of covariance will be used to compare the differences of center effect. The repeated measures will be used to compare the differences of several continuous observations. The numeration data will be described by absolute frequency or constituent ratio. The Chi square test will be used to compare the value differences between the trial group and control group. All statistical analyses will be undertaken by using SPSS 19.0 (License number: 6fd84e801f1e6010dc). See Figure 1 for procedure of this study.

![Figure 1](image-url)
2 Discussion

Current therapies in the treatment of COPD have limitations. Alternative approaches are therefore required in some patients with COPD. There is limited evidence concerning comprehensive TCM interventions for patients with stable COPD. As the results are with poor comparability and less scientific evidence, it is difficult to fully reflect the efficacy, characteristics and advantages of TCM therapy\[16\]. Therefore, based on TCM theory of lung and kidney deficiency and previous study of Buefei Yishen Granule and Shuifei Tie acupoint-sticking therapy\[17,18\], this study will be conducted in order to evaluate the efficacy and safety of the combination therapy.

Sustained-release theophylline is selected as the active control drug because the low-dose, slow-release oral theophylline is effective and well-tolerated in the long-term treatment of stable COPD\[17,18\]. Considering the influence of seasonal factors on COPD and time requirements of traditional acupoint-sticking therapy which should be applied in hot summer days, the therapeutic course will be in summer and autumn, and the follow-up period will be in winter and spring. The variation of the exacerbation frequency in different seasons is taken into account. Whether the frequency of acute exacerbation can be reduced by comprehensive TCM interventions in winter and spring will be observed.

COPD is a disease characterized by restricted airflow that is not fully reversible and progressively developing. Lung function test is important to the diagnosis, assessment of severity, progression and prognosis of COPD. Yet in early stage and stable state, it is not obvious and often overlooked by patients and physicians. Thus evaluation of the degree of breathing difficulty and the 6MWD is important to understand the severity of the disease and the health status of patients and to evaluate the clinical intervention effects\[15,20\]. Acute exacerbation of COPD is a main factor in deterioration. It can accelerate the progression of the disease, reduce the lung function, aggravate the symptoms and affect the quality of life of patients. To reduce the frequency and duration of acute exacerbation is a major goal of treatment and also a key indicator for evaluating the treatment effects of patients with stable COPD. Meanwhile, the observation of lung function, symptoms and quality of life of patients is also important.

However, there are some limitations of the study. On the one hand, single treatment of Buefei Yishen Granule group and single treatment of acupoint-sticking group are not set; the relative contribution of either the granule or the acupoint-sticking therapy in relieving the symptoms of COPD patients cannot be evaluated. On the other hand, the observation time and follow-up time of the interventions are not long enough.

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5 Competing interests

The authors declare that they have no competing interests and they don’t receive any funding by any pharmaceutical company.

REFERENCES


“补肺益肾方联合穴位贴敷治疗慢性阻塞性肺疾病稳定期患者的多中心随机、双盲、阳性药平行对照临床试验”的研究方案

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背景：慢性阻塞性肺疾病（chronic obstructive pulmonary disease，COPD）是一种严重危害公众健康的疾病，加强 COPD 防治的临床研究已成为重要的研究内容。中医药治疗 COPD 具有明显的特色和优势，能够改善患者的症状和体征，减少急性加重次数，提高生存质量。因此，在补肺益肾方或“舒肺贴”穴位贴敷单一干预措施研究的基础上，本试验旨在研究两种干预措施联合使用对 COPD 稳定期患者的疗效。

方法与设计：采用多中心、随机、双盲、阳性药平行对照的临床试验方法。以 COPD 稳定期患者为研究对象，治疗 4 个月，随访 6 个月。观察研究方案实施前后患者急性加重次数及持续时间、肺功能、临床症状、6 分钟步行距离、呼吸困难分级和生存质量等指标的变化，并进行随访，以评价研究方案的有效性和安全性。

讨论：本次试验研究补肺益肾方联合穴位贴敷综合干预措施对 COPD 患者的疗效和安全性，为制定适合 COPD 患者的中西医干预方案提供临床依据。

临床试验注册号：ChiCTR-TRC-11001409。

关键词：肺疾病，慢性阻塞性；中医疗法；穴位贴敷法；临床试验；临床方案