Systematic Review and Meta-analysis of Shenfu Injection on Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Jian-Guo Lin a,b, Jian Lyu a, Meng-Hua Sun c, Xing Liao b, Yan-Ming Xie a

a Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China; b Guang’anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Abstract

The objective of the study was to systematically evaluate the efficacy and safety of Shenfu injection in the treatment of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). A total of 15 randomized controlled trials involving 1198 patients were included. The results of meta-analysis showed that compared with the control group, the experimental group can improve the total clinical effective rate in AECOPD patients (relative risk = 1.15, 95% confidence interval [CI] [1.09, 1.21], P < 0.000 01), improve the pulmonary function levels: forced expiratory volume in one second (FEV1) (standardized mean difference = 1.88, 95% CI [0.89, 2.88], P = 0.000 2) and the FEV1/forced vital capacity (FVC) ratio (FEV1/FVC) (mean difference [MD] = 0.96, 95% CI [0.24, 1.68], P < 0.000 01); improve the arterial blood oxygen partial pressure (MD = 6.03, 95% CI [4.58, 7.48], P < 0.000 01), and reduce the arterial blood partial pressure of carbon dioxide (MD = −4.59, 95% CI [−6.91, −2.26], P = 0.000 01), and the white blood cell count in pulmonary infection may be improved (MD = −1.16, 95% CI [−1.63, −0.68], P < 0.000 01). The study showed that the efficacy of experimental group in the treatment of AECOPD is better than control group. Due to the limitation of the number and quality of included studies, this conclusion needs more high quality studies to confirm.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, meta-analysis, Shenfu injection, systematic review

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease, which is characterized by persistent respiratory symptoms and airflow restriction due to exposure to toxic particles or gas. [1] Acute exacerbation of COPD (AECOPD) refers to the continuous deterioration of the patient’s condition beyond daily life and the need to change the basic medication. Usually, it is manifested as short-term cough, expectoration, shortness of breath and/or wheezing exacerbation, increased sputum volume, purulent or mucopurulent, and can be accompanied by fever and other inflammation. [2] The prevalence of COPD was 8.6% in adults aged 20 and over, 13.7% in people aged 40 and over, and over 27% in people aged 60 and over. The total number of COPD patients nationwide was 99.9 million or about 100 million. [3] COPD is currently the third leading cause of death in the world and is expected to be the third leading cause of death and the fifth largest economic burden in 2020. [4] The morbidity and mortality of COPD in China are increasing year by year, and the situation of prevention and treatment is grim. COPD belongs to the category of “lung distension,” “asthma syndrome,” and “cough” in Chinese medicine. Evidence indicates that the occurrence, treatment, and prognosis of AECOPD are related to cold drinking, phlegm–dampness, deficiency syndrome, and blood stasis. [5] Clinical treatment of AECOPD with Chinese medicine on the basis of routine Western medicine treatment can significantly improve the

Access this article online

Quick Response Code: www.wjcm.net

Website:

DOI: 10.4103/wjcm.wjcm_30_20

Address for correspondence: Prof. Yan-Ming Xie, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China. E-mail: kizu2018@163.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2020 World Journal of Traditional Chinese Medicine | Published by Wolters Kluwer - Medknow

Received: 25-12-2019, Accepted: 19-03-2020, Published: 05-08-2020

How to cite this article: Lin JG, Lyu J, Sun MH, Liao X, Xie YM. Systematic review and meta-analysis of shenfu injection on treating acute exacerbation of chronic obstructive pulmonary disease. World J Tradit Chin Med 2020;6:276-83.
curative effect, shorten the course of disease, and reduce complications, in which the beneficial Yang-warming drugs improve lung function, reduce symptoms, signs, and so on have a good effect. Shenfu injection (SFI) is prepared from Shenfu decoction (red ginseng and black aconite) of Complete Effective Prescriptions for Women’s Diseases by modern technology. The main components of SFI are ginsenoside and aconite alkaloids, which have the effects of restoring yang, relieving adverse effects, invigorating qi, and strengthening immunity, and have good effects on improving hemodynamics, anti-inflammation, anti-coagulation, and anti-apoptosis, improving metabolism, and enhancing immunity. In recent years, there have been many clinical studies of SFI in the treatment of AECOPD, but there is no systematic review and analysis related to it because of its single report, small sample size, and lack of rigorous persuasion. Therefore, according to the method of systematic evaluation, this study conducted a systematic evaluation and meta-analysis on the randomized controlled trials (RCTs) of SFI in the treatment of AECOPD, providing evidence-based medical evidence for clinical practice.

DATA AND METHODS

Screening criteria

(1) Type of study: SFI in the treatment of AECOPD RCT, blind method, is not limited. (2) Subjects: Patients who complied with the diagnostic criteria of AECOPD. Diagnostic criteria may refer to Global Initiative for Chronic Obstructive Lung Disease (GOLD). Guidelines for the diagnosis and treatment of COPD[11,12] or other recognized diagnostic criteria at home and abroad. (3) Intervention: Experimental group: SFI combined with Western medicine treatment, the treatment dose, and the course of treatment was not limited. Control group: Western medicine routine treatment: Western medicine routine treatment for anti-infection, asthma, expectoration, routine continuous low-flow oxygen inhalation, and other comprehensive treatment. (4) Exclusion criteria: Repeated literature, false or incomplete research data, unable to get a full text, and patients with other organ complications.

Outcome indicators

Main outcome measures were the total clinical effective rate; secondary outcome indicators were pulmonary function indicators, including the forced expiratory volume in one second (FEV₁) and the FEV₁/forced vital capacity (FVC) ratio (FEV₁/FVC); blood gas analysis included arterial blood partial pressure of oxygen (PaO₂) and arterial blood partial pressure of carbon dioxide (PaCO₂); and pulmonary infection indicators were white blood cell count (WBC) and adverse reactions.

Retrieval methods

A total of seven databases including VIP Database for Chinese Technical Periodicals (VIP), China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Biomedical Literature Database (CBM), Cochrane Library, Medline, and EMBase were searched by computer. Retrieval time of each database ranged from the earliest date of the database to April 2019. The Chinese keywords were “Shenfu injection,” “chronic obstructive pulmonary disease,” “chronic obstructive pulmonary,” and “COPD.” In English, subject words and free words are used for retrieval. The keywords are “Shenfu Injection,” “COPD,” and “chronic obstructive pulmonary disease.” The comprehensive retrieval of subject words and free words is carried out in accordance with the characteristics of the database. Take CNKI retrieval strategy as an example, CNKI: SU = (“Shenfu Injection” + “Shenfu”) and SU = (chronic obstructive + “COPD” + “chronic obstructive pulmonary disease”).

Literature screening and data extraction

The literature selection, data extraction, and literature quality evaluation were carried out independently by two persons, and the literature that is difficult to judge was evaluated through discussion between the two parties or intervention of a third party. During the screening, the reasons for excluding the literature were judged and recorded according to the way of reading the abstract and the full text. The basic information extraction table of literature was drawn up during data extraction, including researchers, years of publication, diagnostic criteria, number of cases of the experimental group and the control group, age and sex composition, intervention measures, outcome indicators, adverse reactions, and randomized methods.

Evaluation of the quality of the studies included

According to the risk bias assessment tool in Cochrane Reviewers Handbook 5.1,[13] the quality of the included literature was evaluated in the following seven aspects: random sequence generation, random allocation hiding, double blindness of implementers and subjects, blindness in outcome assessment, the integrity of outcome data, selective reporting of results, and other biases. Finally, the literature is evaluated one by one and judged according to the results of “low risk,” “high risk,” and “uncertainty.”

Statistical methods

RevMan 5.3 software provided by Cochrane Collaboration Network was used for the statistical analysis. Relative risk (RR) was used to express the effect statistics for the counting data. When the measurement method or unit of the effect of the same intervention is exactly the same, the mean difference (MD) is used to represent the effect statistics. When different measurement methods or units are used for the effect of the same intervention, the standardized MD (SMD) is used for representing the effect statistics, and both use the effect value and 95% confidence interval (CI) to represent the combined result. Q-test was used for the heterogeneity test. If $I^2 \leq 50\%$, the statistical homogeneity was considered good. A fixed-effect model was used. If $I^2 > 50\%$, the statistical heterogeneity was large. Sensitivity analysis was first carried out to find the cause of heterogeneity. Random effect model was used when the clinical and methodological heterogeneity was not large, and the results were expressed by the forest plot. If the study is not appropriate for a meta-analysis, a descriptive
results

Retrieval and filtering results
A total of 263 related papers were initially retrieved and 97 papers remained after NoteExpress (NE) software and manual duplicate checking. A total of 21 papers were excluded after reading the abstract, 61 papers were excluded after reading the full text, and finally, 15 papers were included in the RCT, as shown in Figure 1.

Basic characteristics and quality evaluation of the study
A total of 1198 patients were enrolled in 15 studies[14-28] including 607 in the experimental group and 591 in the control group. The basic characteristics of the included studies are shown in Table 1. Of the included studies, five studies[14,16,18,19] used random number tables, one study[24] used simple random sampling, three studies[23,25,27] were randomly assigned in order of attendance, and the remaining six studies did not explicitly mention specific random allocation methods, and one study[15] had dropouts and the absence of data was unlikely to affect the true outcome. The quality of the included literature was assessed using the Risk Bias Assessment Tool[13] in Cochrane Reviewers Handbook 5.1, as shown in Figure 2.

Total clinical effective rate
A total of 14 studies[14,15,17-28] involving 1112 patients reported the comparison of total clinical effective rate and heterogeneity test results ($I^2 = 0\%$, $P = 1.00$), using fixed-effect model. The results showed that the experimental group was superior to the control group in improving the total clinical effective rate of AECOPD (RR = 1.15, 95% CI [1.09, 1.21], $P < 0.000 01$), as shown in Figure 3.

Pulmonary function
Comparison of forced expiratory volume in one second
A total of 6 study[15,17,20,21,26,28] reported that comparison of FEV$_1$ and heterogeneity test results ($I^2 = 95\%$, $P < 0.000 01$), using random-effect model, because of the difference of SD more than 10 times, using SMD. The results showed that experimental group was better than control group in its ability to increase FEV$_1$ (SMD = 1.88, 95% CI [0.89, 2.88], $P = 0.000 2$), as shown Figure 4. Since $I^2$ is comparatively large, a sensitivity analysis was performed, and it was found that the SD value in the FEV$_1$ value in the Zhang[20] study differed from other studies by dozens of times. Considering that heterogeneity may be related to different statistical methods or uneven conventional intervention, this study was excluded, the heterogeneity test results ($I^2 = 41\%$, $P = 0.15$), a fixed effect model was used. The conclusion is the same as before (MD = 4.16, 95% CI [3.06, 5.25], $P<0.000 01$).

Comparison of forced expiratory volume in one second/forced vital capacity
A total of six studies[15,17,20,21,26,28] reported the comparison of FEV$_1$/FVC, excluding the Zhang Qianli study[20] and including five studies[15,17,21,26,28] and heterogeneity test results ($I^2 = 33\%$, $P = 0.20$), using a fixed-effect model. The results show that experimental group is better than control group in improving FEV$_1$/FVC (MD = 3.96, 95% CI [2.74, 5.19], $P < 0.000 01$), as shown Figure 5.

Blood gas analysis
Comparison of partial pressure of oxygen
A total of 6 studies reported PaO$_2$ comparison and heterogeneity test results ($I^2 = 40\%$, $P = 0.14$). Fixed effect model was used. The results showed that experimental group was superior to control in improving PaO$_2$ (MD = 6.03, 95% CI [4.58, 7.48], $P < 0.000 01$), as shown Figure 6.

Comparison of partial pressure of carbon dioxide
A total of six studies reported PaCO$_2$ comparison and heterogeneity test results ($I^2 = 88\%$, $P < 0.000 01$), using a randomized effect model. The results showed that experimental group was superior to control group in reducing PaCO$_2$ (MD = −4.59, 95% CI [−6.91, −2.26], $P = 0.000 1$), as shown in Figure 7.
Indicators of pulmonary infection

A total of two studies\(^{[14,16]}\) reported WBC comparison and heterogeneity test results (\(I^2 = 0\), \(P = 0.72\)), using a fixed-effect model. The results showed that experimental group was superior to control group in improving pulmonary infection indicators (MD = -1.16, 95% CI [-1.63, -0.68], \(P < 0.0001\)), as shown Figure 8.
Sensitivity analysis
The sensitivity analysis of clinical total effective rate, pulmonary function, and blood gas analysis indexes was carried out by changing statistical model. The results showed that the evaluation results of the two statistical models were similar, indicating that the meta results were basically robust, as shown in Table 2.

Publication of bias funnel diagram
The total clinical response rate of the 15 included studies was inverted in funnel plots. The results showed that the inverted funnel was asymmetrical from left to right, suggesting the possibility of publication bias, which may be due to the low quality of the included studies, small sample effect, and partial negative results not yet published or not yet published, as shown in Figure 9.

Adverse reactions
Of the 15 studies included, three[15,19,27] reported adverse events and one study[17] reported no adverse events. Two adverse events reported in the Jin Wei study[15] all of which occurred...
in the treatment group but were not specified. Chi Yong sheng study[19] reported one case of an adverse reaction, which occurred in the treatment group, with slight skin pruritus and self-relief after stopping transfusion, while no adverse reaction was found in the control group. Zi-Ran Wang study[27] reported four adverse reactions, all of them occurred in the treatment group, three cases had dry mouth, and one case had irritability, but the symptoms were mild, the patients were tolerable, no special treatment was given, and the symptoms disappeared after the treatment. Yali’s and Baoyong[17] reported no adverse reactions.

**DISCUSSION**

**Validity and theoretical analysis**

AECOPD is commonly observed in autumn and winter. Most of AECOPD patients were old and insufficiency of yang qi. Deficiency of lung-yang, difficult to assist the heart blood flow. Deficiency of spleen-yang, phlegm-fluid retention is born out. Deficiency of kidney-yang leads to decline of vital gate fire. These reasons induce the disease to continue to attack and circulate repeatedly. More deficiency of yang qi, the stronger the pathogenic qi, and form a vicious circle.

SFI is mainly used for the treatment of syndrome of sudden yang collapse (infectious, hemorrhagic, anhydrous shock, etc.) It is composed of *Radix Ginseng Rubra* and *Radix Aconiti Lateralis Preparata*. *Radix Ginseng Rubra* is a cooked product of ginseng. It has sweet taste, slight bitterness, warm temperature, belonging to the spleen, lung, heart, and kidney meridians, and has the effects of invigorating vital energy, restoring pulse and removing blood stasis, and has the effects of anti-tumor, anti-aging, anti-fatigue, improving the cardiovascular and cerebrovascular systems, regulating the central nervous system, and improving immunity.[29] *Radix Aconiti Lateralis* is pungent, sweet, and great warm, belonging to heart, kidney, and spleen Meridian, has the effect of rescuing from collapse by restoring yang, invigorating fire and supporting yang, has immunomodulation, antitumor, antiaging, anti-shock, anti-asthma, heart strengthening, and other activities.[30] SFI can warm yang and supplement kidney, invigorate qi and relieve asthma, generate internal yang, promote triple energy gasification, improve water metabolism, eliminate phlegm and blood stasis in the chest, soothe qi in the lungs, relieve asthma, cough and fullness,[31] and has certain effects on AECOPD.

A total of 15 studies were included in this study, with a total of 1198 cases. The efficacy of SFI in the treatment of AECOPD was systematically evaluated from the aspects of total clinical effective rate, pulmonary function, blood gas analysis, and pulmonary infection index systematic evaluation. Meta-analysis showed: experimental group compared with control group can improve the total clinical effective rate and lung function FEV$_1$ and FEV$_1$/FVC, increasing PaO$_2$, reducing PaCO$_2$, and improving the pulmonary infection indicator WBC, indicating that the efficacy of SFI combined with Western medicine for AECOPD is worthy of recognition. But it is worth noting that the main outcome indicator of this study is the total clinical efficiency. The indicator depends
on subjective feelings of patients or subjective judgments of doctors, lacking objective quantitative criteria and difficult to be recognized. Objective indicators generally have a relatively strict error range and result reporting standards, not easily influenced by subjective factors of patients or doctors, however there are only six indexes of pulmonary function and blood gas analysis in this study, which are small in sample size and poorly representative, so it is difficult to comprehensively respond to the effectiveness of intervention measures, and it is difficult to objectively and systematically analyze the data because of the differences of instrument types, doctors’ operation level, and statistical methods. In addition, only three of the studies included in the study were given to patients according to Traditional Chinese Medicine (TCM) syndrome differentiation. The blind application of SFI may lead to lower curative effect, ineffective treatment, aggravated disease, and other consequences.

Safety analysis
Of the 15 studies included, three studies reported adverse reactions, one study reported no adverse reactions, one study referred to safety observations, and the rest did not mention safety or adverse reactions/events. The symptoms of adverse reactions were mild and did not affect the normal treatment. The patients could tolerate the adverse reactions or relieve the adverse reactions themselves after stopping the treatment. No serious adverse reactions were found. However, we should still pay attention to the safety of Chinese medicine injection; Adverse Drug Reactions (ADRs) of Chinese medicine injection accounted for more than half of ADRs of Chinese medicine, which should be paid attention to by the administrative department, medical personnel, and the public. Studies have shown that the incidence of ADRs of SFI is mainly related to whether the patient has a history of drug allergy and whether the drug is used rationally in clinical practice. Clinicians should try their best to avoid using SFI in patients with a history of drug allergy and should strictly follow the indication, solvent, and dosage indicated in the instructions.

Methodological quality evaluation
Only by reporting and publishing the best research evidence in a standardized way can the dissemination and recognition of high-quality evidence be promoted. The poor quality of clinical trials of Chinese medicine is a fundamental problem in the development of evidence-based Chinese medicine, and the literature included in this study is no exception. (1) The number of literature included in this study was small, totaling 15 articles; the sample size was small, the maximum sample size was 144 cases, the minimum sample size was 54 cases, the difference was obvious, the representative was poor, and the risk of bias was high. (2) All the studies included in this study were Chinese literatures, and all of them were positive results. Due to geographical and linguistic limitations, there may be bias in reporting. (3) The quality of methodology was generally low, and the description of the random method simply refers to the word random; the description is not clear, detailed steps are not specified, the hidden and blind methods are assigned, and the sample size estimation basis is not mentioned. Studies have shown that improper selection of randomization and blind methods may erroneously exaggerate the efficacy of traditional Chinese medicine, such as random hiding is not objective or not. Using the blind method will increase the treatment effect by 15%–50%, which is worthy of attention. (4) Most of the literatures did not mention adverse reactions, and only a few of them were mentioned, and no specific causal relationship determination process was reported.

Clinical significance
It should be kept in mind that SFI is usually used in severe or critically ill patients, not in common AECOPD patients. It is suitable for the syndrome of sudden yang collapse or deficiency of Yang qi.

This study provides a new idea for the treatment of AECOPD. This suggests that in the future clinical treatment, clinical workers in the treatment of syndrome differentiation can consider using SFI combined with Western medicine for the treatment of AECOPD.

In addition, in view of the low quality of the literature, we hope and suggest that future clinical studies should try to improve the quality of research methodologies and reporting. We should strictly perform random grouping, distribution concealment and blind methods, sample size estimation methods, pay attention to safety indicators, establish a core outcome indicator set, standardize the selection of outcome indicators in clinical studies, and report results were strictly in accordance with the international CONSORT standard. As far as possible, we should carry out high-quality RCT with a large sample, multicenter, and long-term follow-up. To scientifically express the high-quality research evidence produced by the evidence-based practice of TCM in the internationally used language, and to continuously promote the benign development of TCM discipline.

Financial support and sponsorship
This study was funded by the Special Fund for Basic Scientific Research Expenses of Public Welfare Research Institutes at the central level (Z0597).

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017. Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195:557-82.
2. Cui HS, Zhang WJ, Yang JY, Li Y. Guidelines for diagnosis and treatment of chronic obstructive pulmonary disease. Chinese journal of traditional Chinese medicine 2011;9:115-6.
3. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): A national cross-sectional study. Lancet 2018;391:1706-17.
4. WHO. Global Health Estimates Summary Tables: Deaths by Cause, age and Sex by Variable. Regional Grouping 2013.
Lin, et al. Meta-analysis of Shenfu injection on AECOPD

5. Chen XA, Li SY, Wang MH, Li XJ, LiHX. Research progress on prognostic factors of acute exacerbation of chronic obstructive pulmonary disease. Chin J Tradit Chin Med 2017;35:799-802.
6. Li JS, Li SY, Yu XQ. Guidelines for TCM diagnosis and treatment of chronic obstructive pulmonary disease (2011 edition). J TCM 2012;53:80-4.
7. Li XY, Peng SL, Tang Q. Theoretical thinking on internal cause of acute exacerbation of chronic obstructive pulmonary disease due to deficiency of qi and yang. Accident Chin Med 2017;26:1964-6.
8. Wang ZY, Song WH, Jia P, Wang CX, Feng M, Zhang YX. Wang cheng-xi’s experience in treating chronic obstructive pulmonary disease in stable stage by tonifying yang and warming kidney. Hunan J Tradit Chin Med 2017;33:23-4.
9. Zhong GW, Wang DS, Chen Q, Fang X, Li YH. Clinical study on treatment of chronic obstructive pulmonary disease complicated with pulmonary hypertension with prescription of invigorating yang, warming yang, activating blood circulation and removing phlegm. China J Tradit Chin Med 2015;30:3771-4.
10. Zhang Y, Ren CH, Wu XD, Yang Y. Clinical application and pharmacological mechanism of Shenfu Injection. Pharmaceut Evalut Res 2018;41:1141-6.
11. Chronic obstructive pulmonary Disease Group, Chinese thoracic society. Guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease (2013 Revision). Chin J Frontier Med (Electronic Edition) 2014;6:67-80.
12. Chronic obstructive pulmonary Disease Group, Chinese thoracic society. Guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease (2007 Revision). China J Tubercul Respir Dis 2007;30:8-17.
13. Green JP. Cochrane Handbook for Systematic Reviews of Intervals Version 5.1.0 [EB/OL] [2019-5-11]. Available from: http://handbook-5.1.cochrane.org.
14. Geng JF. Clinical observation of Shenfu Injection in the treatment of acute exacerbation of chronic obstructive pulmonary disease. Accident Tradit Chin Med 2018;27:1234-6.
15. Jin W, Song Y, Luo XQ, Li YQ, Li YW. Clinical study on the effect of Shenfu Injection on cellular immune function in patients with AECOPD. Accident Tradit Chin Med 2018;27:1182-5.
16. Tang Q, Ao SH, Li XY. Evaluation of therapeutic effect of shenfu injection in adjuvant treatment of 86 patients with acute exacerbation of chronic obstructive pulmonary disease. J Southwest Med Univ 2018;41:372-6.
17. Zhang YL, Han BY. Adjuvant treatment of Shenfu Injection in acute exacerbation of chronic obstructive pulmonary disease. Int J Geriatrics 2017;38:63-6.
18. Bao CM, Bao LJ. Effect of Shenfu Injection in the treatment of acute exacerbation of COPD and its influence on serum high-sensitivity C-reactive protein. Pharmaceut Frontiers 2015;5:116-7.
19. Chi YS. Effect of Shenfu Injection on acute exacerbation of chronic obstructive pulmonary disease. Chin J Emerg Med 2015;24:553-4.
20. Zhang QL, Ma YH, Ye HJ. Clinical efficacy and mechanism of Shenfu Injection in patients with acute exacerbation of chronic obstructive pulmonary disease. Liaoan J Tradit Chin Med 2014;41:1446-8.
21. Han, Li AQ, Tang ZJ, Liu SW, Liu XL. Clinical study on the treatment of acute exacerbation of chronic obstructive pulmonary disease with fire-inducing therapy. J Modern Integrated Tradit Chin Western Med 2013;22:1825-7.
22. Ren YJ, Li XM, Zhang CM. Observation of therapeutic effect of Shenfu Injection on acute exacerbation of chronic obstructive pulmonary disease. Inner Mongolia Tradit Chin Med 2013;32:58-9.
23. Xu GL. Clinical observation of Shenfu Injection in the treatment of acute exacerbation of chronic obstructive pulmonary disease. J Liaoning Univ Tradit Chin Med 2012;14:193-4.
24. Gao SY. Clinical effect of Shenfu Injection on acute exacerbation of chronic obstructive pulmonary disease in 28 cases. J Practical Med 2011;18:285-6.
25. Zheng GY, Chen YH, Zeng ZY, Lin Y. Clinical analysis of 35 cases of acute exacerbation of chronic obstructive pulmonary disease treated with Shenfu Injection. Chin J Med 2010;29:27-9.
26. Qin HJ, Liu GP, Zhang F, Shen JM, Sun H. Clinical observation of Shenfu Injection in the treatment of acute exacerbation of chronic obstructive pulmonary disease. Chin J Clin Med 2010;17:659-60.
27. Wang ZR. Clinical observation of Shenfu Injection combined with Western medicine in the treatment of 60 patients with acute exacerbation of COPD. Med Informat (Second Edition) 2009;8:119.
28. Liao WS, Li WQ, Chen SW, Hu QS. Effect of Shenfu Injection on inflammatory cytokines and pulmonary function in patients with acute exacerbation of chronic obstructive pulmonary disease. Chin J Integrat Tradit Western Med 2008;3:149-51.
29. Yu XN, Feng XG, Zhang JM, Huang JJ, Zhang Q. Recent advances in studies on chemical constituents and pharmacological actions of ginseng. Studies on Ginseng 2019;1:47-51.
30. Yang RJ. Chemical Constituents of Shenfu Injection. Jilin University.
31. Ye WB, He RX, Ma XH, Wang WR. Treatment of chronic obstructive pulmonary disease by triple-jiao gasification. Chin J TCM 2017;32:1618-21.
32. Kimberlin CL, Winterstein AG. Validity and reliability of measurement instruments used in research. Am J Health-Syst Pharmacy 2008;65:2276-84.
33. Yan BH, Peng C, Xie YM, Wang YY. Comparison and analysis of clinical safety evaluation methods of traditional Chinese medicine Injections. Chin J Tradit Chin Med 2013;38:2979-82.
34. Wang ZF, Zhao W, Zhang Y, Xie YM. Analysis of adverse drug reactions of Shenfu Injection based on large-scale prospective safety monitoring. Chin J Tradit Chin Med 2015;40:4746-51.
35. Fu YK, Xie YM. Clinical application and literature analysis of Shenfu Injection. Chin J Tradit Med 2012;37:2796-9.
36. Zhang XY, Chen SQ, Li CY, Tian GH, Zhao C, Qiu RJ. Theoretical research and application of evidence-based Chinese medicine. Chin J Evidanc Based Med 2018;18:86-91.
37. Zhang HY, Liu JP. Blind methods in clinical trials. J Tradit Chin Med 2007;05:408-10.
38. Qiu RJ, Sun Y, Hu JY, Li M, He TM, Huang Y, et al. Methods of selecting outcome measures in clinical studies. Chin J Evidence Based Med 2018;18:238-43.
39. Moher D, Hopewell S, Schulz KF, Montori, V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials Int J Surg. 2012;10:28-55.
40. Hu JY, Zhao C, Tian R, Li J, Chen YL, Zhang XY, et al. Study on the standardized system of clinical research reports on traditional Chinese medicine. Chin J Evidence Based Med 2018;18:1151-7.