Effectiveness and safety of acupoint application for chronic obstructive pulmonary disease
A protocol for updated systematic review and meta-analysis
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Abstract

Background: Acute exacerbation is a primary cause of repeated hospitalization and death in chronic obstructive pulmonary disease (COPD) patients. Therefore, how to control the symptoms of COPD at stable stage and reduce the number of acute exacerbation is a hot spot of medical research. Acupoint application (AA) is a significant part of external treatment of traditional Chinese medicine (TCM), Previous researches have reported that AA can be applied to the treatment of COPD. Nevertheless, its effectiveness is still inconclusive. This systematic review (SR) and meta-analysis is designed to appraise its effectiveness and safety for the treatment of patients with COPD.

Methods: Eight databases will be systematically retrieved from their inceptions to February 2021. Inclusion criteria are randomized control trials of AA combined with routine western medicine interventions in the treatment of COPD at stable stage. The primary outcomes we focus on comprise clinical effective rate, TCM symptom score, quality of life, dyspnea, exercise capacity, lung function, frequency of acute exacerbation, adverse events. The research screening, data extraction, and risk of bias assessment will be conducted by 2 individuals independently, and divergence will be adjudicated by a third senior investigator. The Stata 13.1 software will be used for meta-analysis. The confidence of evidence will be classified adopting grading of recommendations assessment, development and evaluation (GRADE) algorithm and methodological quality of this SR will be assessed using assessment of multiple systematic reviews-2 (AMSTAR-2) tool.

Results: This SR will provide evidence-based medical proof for the treatment of COPD at stable stage by AA combined with conventional western medicine interventions. The findings of this SR will be presented at relevant conferences and submitted for peer-review publication.

Conclusions: The findings of this SR will provide up-todate summary proof for evaluating the effectiveness and safety of AA for COPD.

Registration number: INPLASY 202140080.

Abbreviations: AMSTAR-2 = assessment of multiple systematic reviews-2, COPD = chronic obstructive pulmonary disease, GRADE = grading of recommendations assessment, development and evaluation, INPLASY = International Platform of Registered Systematic Review and Meta-analysis Protocols, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs = randomized controlled trials, SR = systematic review.

Keywords: acupoint application, chronic obstructive pulmonary disease, meta-analysis, systematic review

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable respiratory disease characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities. The pathological changes are mainly airway and/or alveolar abnormalities, which are usually associated with significant exposure to harmful particles or gases. Many host factors such as genetic susceptibility, abnormal inflammatory response, and abnormal lung development are involved in the pathogenesis. Serious complications may affect the performance and mortality of the disease.

COPD is 1 of the 4 major chronic diseases in the world with high morbidity, mortality and disability. Chronic obstructive pulmonary disease (COPD) is a common disease that seriously endangers human health and severely affects the quality of life of patients. COPD is an important cause of death, and brings heavy economic burden to patients, their families, and society. According to the latest World Health Organization prediction on mortality and causes of death, with the increase of smoking rate in developing countries and the aging of population in high-income countries, the
prevalence of COPD will continue to rise in the next 40 years.\[^6\]\ It is predicted that by 2060, more than 5.4 million people will die of COPD and its related diseases every year.\[^7\]\ In recent years, with the increasingly serious environmental pollution and aging problem, the incidence rate of COPD is increasing, with a higher disability rate and mortality in China.\[^8\]\ Epidemiological studies have shown that the prevalence rate of people over 40 years old in China is 13.7%, with nearly 100 million patients, ranking the third cause of death in China. In terms of disability adjust life year, its disease burden has ranked second in China.\[^9\]\

The risk factors of COPD are diverse, which can be summarized as individual susceptibility factors and environmental factors. Individual factors included genetic factors, age and gender, lung growth and development, bronchial asthma and airway hyperresponsiveness, and low body mass index.\[^10\]\ Environmental factors mainly include smoking, fuel smoke, air pollution, occupational dust and infection, chronic bronchitis, and social economic status.\[^11\]\

The pathogenesis of COPD is complex and has not been fully elucidated. Inhaling tobacco smoke and other harmful particles or gases can cause airway oxidative stress, inflammatory reaction, and protease/antiprotease imbalance, which are involved in the pathogenesis of COPD.\[^12\]\ In addition, autoimmune regulation mechanism, genetic risk factors, and lung development related factors may also play an important role in the occurrence and development of COPD.\[^13\]\ The combination of above mechanisms can lead to the formation of COPD. The main pathophysiological changes of COPD include airflow limitation, gas entrapment and abnormal gas exchange. It can be associated with mucus hypersecretion, airway epithelial cilia dysfunction, and systemic adverse effects. Severe cases may be complicated with pulmonary hypertension, chronic pulmonary heart disease, and respiratory failure.\[^14\]\

COPD patients often have multiple systemic complications at the same time, which are related to the severity of the disease.\[^15\]\ The main symptoms of COPD are chronic cough, expectoration, and dyspnea. Cough and expectoration usually appear in the early stage of the disease, and dyspnea is the main manifestation in the later stage.

Phase of COPD can be divided into acute exacerbation stage and remission stage. In acute exacerbation stage, COPD mainly occurs in the elderly and is prone to respiratory failure, which is an important reason for patients’ repeated hospitalization and death.\[^15\]\ Therefore, how to control symptoms in stable stage and reduce the number of acute exacerbations is a hot spot in medical research.\[^16\]\

At present, conventional treatment for stable COPD includes pharmacological and non-pharmacological interventions. Pharmacological medications mainly contain β2-agonists, inhaled corticosteroids, methylxanthines, and anticholinergics, which are applied to relieve and control the symptoms. Nevertheless, no clinical evidence have shown that the current drug treatment can postpone the long-term decline in lung function of patients with COPD.\[^17\]\ Furthermore, nonpharmacological interventions mainly include integrative care, self-management, oxygen therapy, pulmonary rehabilitation, ventilatory support, and interventional therapy. However, it should consider the risk of adverse reactions, the inconvenience, and cost of the prolonged course of the therapy.\[^18\]\

Acupoint application (AA) is an important part of external treatment of traditional Chinese medicine (TCM). It is a noninvasive therapy based on the theory of meridian science of TCM, which directly applies herbs to acupoints to treat diseases and it is widely used in the prevention and treatment of chronic respiratory diseases.\[^19\]\ AA has the characteristics of simple operation, significant curative effect, and less adverse reactions, which has been widely recognized by the society.\[^20\]\ In the stable period of disease, AA can stimulate the body’s healthy qi, dredge the channels and collaterals, regulate qi and blood to enhance the body’s antievil ability, and control the recurrence of disease.\[^21\]\ This idea also fully embodies the concept of “treating pre-disease” in TCM. AA in the treatment of COPD is a typical application of this concept.\[^22\]\

There are many effective components and targets in the herbs of AA, and the mechanism of action is more complex. The mechanism of western medicine mainly focuses on the regulation of immunity and inflammation.

1. Inflammatory cells and mediators: some studies have shown that AA can significantly reduce the expression of IL-6, IL-2, MCP-1, and other inflammatory factors in the lung of COPD rats\[^23\]; others have shown that AA can alleviate the symptoms of patients with COPD, improve the quality of life, reduce the secretion of systemic inflammatory factors and the levels of IL-8 and CRP inflammatory factors.\[^24\]\ 2. Cellular immunity and humoral immunity: some studies have shown that AA can reduce the levels of CD3+, CD4+, CD4+/CD8+ in peripheral blood, and BALF of COPD rats, but increase the level of CD8+ significantly, thus promoting the recovery of balance of both. Some studies have confirmed that AA can gradually improve the IgA, IgG, IgM levels in serum of patients with COPD, reduce the content of IgE, not only enhance the body’s cellular immunity and humoral immunity, but also reduce the IgE mediated hypersensitivity.\[^23\]\ 3. NK cell activity: the expansion of NK cells and the enhancement of anti-infection immunity are directly affected by IFN-γ and TNF-α. Studies have shown that AA can significantly reduce the levels of IFN-γ and TNF-α, improve the activity of NK cells, and improve the quality of life of patients.\[^26\]\

A number of clinical studies have shown that AA combined with conventional western medicine interventions has a good clinical effect on COPD.\[^27\]\ For patients with COPD in stable stage, compared with conventional western medicine measures, AA combined with routine western medicine interventions can improve clinical efficiency, reduce clinical symptoms, improve quality of life, and reduce the number of acute exacerbations.\[^28\]\ For patients with AECOPD, it can improve pulmonary ventilation function, quality of life, and clinical symptoms.\[^29\]\ With the increasing number of clinical trails on AA in the treatment of COPD, reliable evidence is needed. Presently, although several reviews have addressed this issue, none of them have further assessed the effectiveness and safety of AA for COPD after more new randomized controlled trials have been published.\[^30-33\]\ Therefore, in this study, we will provide latest and updated evidence of systematic review to evaluate the effectiveness and safety of AA for COPD.

2. Methods and analysis

2.1. Objective

The purpose of this systematic review (SR) and meta-analysis is to evaluate the effectiveness and safety of AA combined with conventional western medicine interventions in the treatment of COPD in remission stage.
2.2. Study registration

It is registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY no. 202140080, https://inplasy.com/). The procedure of this protocol will be conducted according to the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidance.

2.3. Inclusion and exclusion criteria

2.3.1. Type of study. Only the randomized controlled trials (RCTs) of AA combined with routine western medicine interventions in the treatment of COPD in remission stage will meet the inclusion criteria of in this SR regardless of blinding, publication type or language. Quasi-RCTs, duplicated publications, case reports, editorials, animal publications, narrative publications, editorials, animal experiments will be excluded.

2.3.2. Type of participants. The participants should be diagnosed with COPD in stable phase by using clearly defined or internationally recognized criteria and aged at least 18 years old. There are no restrictions on race or gender. The cases with following diseases will not meet selection criteria:

1. respiratory disease like asthma, bronchiectasia, pulmonary fibrosis, and so on;
2. severe liver, kidney, heart disease, and so on;
3. patients were in the acute exacerbation period of COPD.

2.3.3. Type of interventions. Acupoint application combined with conventional western medicine therapeutic measure should be applied in the treatment group. No restrictions were applied to the herbal regimen, acupoints selected, patching time. The same conventional western medicine therapeutic measure must be used in the comparator arm.

2.3.4. Type of outcome measurements. Clinical effective rate; TCM symptom score; quality of life (COPD assessment test, St. George respiratory questionnaire, chronic respiratory questionnaire, etc); dyspnea (borg scale, visual analog dyspnea scale, modified British medical research council respiratory difficulty questionnaire, etc); exercise capacity (6-minute walking test, shuttle walking test, etc); lung function (FEV1, FVC, FEV1/FVC, TLC, RV, etc); frequency of acute exacerbation; adverse effects.

2.4. Search strategy

We will conduct a comprehensive retrieval on the following 8 databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, China National Knowledge Infrastructure, WangFang Database, Chinese Science and Technology Periodical Database, SinoMed. The retrieval time range is from their inceptions of each database to February 2021. We will also retrieve the following databases to confirm ongoing or completed clinical trials: current controlled trials, WHO clinical trials registry, Clinical Trials.gov trials registry, The Australian New Zealand Clinical Trials Registry, Centre Watch, and Chinese Clinical Trial Registry. Grey literature will also be searched to avoid omission. The language is limited to Chinese and English. In addition, we will manually search for relevant studies according to references from previously published SRs. If any, we will try to contact the correspondence author to obtain the data we need. Subject words combined with free words method will be used for retrieval. The search strategy in PubMed is as follows and it will be adjusted according to the characteristics of each database.

2.4.1. Search strategy in Pubmed. ((((((((((( COPD) OR Chronic Obstructive Pulmonary Disease) OR COAD) OR Chronic Obstructive Airway Disease) OR Chronic Obstructive Lung Disease) OR Airflow Obstruction, Chronic) OR Airflow Obstructions, Chronic) OR Chronic Airflow Obstructions) OR Chronic Airflow Obstruction) OR Respiratory Tract Diseases) OR Respiratory Tract Diseases Obstructive Lung Disease) OR Obstructive Airway Disease)) OR “Pulmonary Disease, Chronic Obstructive”[Mesh]) AND (“Transdermal Patch”[Mesh]) OR ((((((((((((((((((((((( Acupoints) OR Acupoint) OR Patch)Transdermal) OR Patches) Transdermal) OR Transdermal) OR Patches) OR Transdermal) OR Patches) OR Point Application) OR Acupoint Application) OR Acupoints Sticking) OR Acupuncture Point Paste) OR Point Application Therapy In Dog Days) OR Acupoint Sticking Therapy) OR Emplastrum Therapy) OR External Application) OR Sanfu (OR Sanfu Patches) OR Sanfu Herbal Patch) OR Sanfu Stickers) OR Tianju Therapy) OR Treating The Winter’s Disease In Summer) OR Acupoint Herbal Patching) OR Sanfu Acupoint Herbal Patching)) AND (((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR random[Title/Abstract]) OR drug therapy[MeSH Subheading]) OR trial[Title/Abstract]) OR groups[Title/Abstract]) NOT (“Animal-s”[Mesh]) NOT (“Humans”[Mesh]) AND “Animals”[Mesh])

2.5. Studies selection

All retrieved studies were imported into the Note Express software (version 3.0) to delete any duplicates. Two researchers (Zhang HY, Huang H) independently screened the titles and abstracts against the established inclusion and exclusion criteria and then downloaded the remaining studies for further screening by reading the full text. If any disagreements occurred, a consensus was reached through discussion or adjudication by a third senior researcher (Pang LJ). The reviewers will record all studies that do not meet the inclusion criteria and provide the rationale for their exclusion. Details of the selection process will be presented in the PRISMA flow chart (Fig. 1).

2.6. Data extraction

The key characteristics of the included articles were extracted independently by 2 reviewers (Zhang HY, Huang H) using a predefined form. The following data items were collected from each study: the first author, publication year, primary locality of the study, sample size (research group/control group), outcomes, range of age (research group/control group), sex distribution (male/female), diagnostic criteria, and funding. If any important information elements were missing, we attempted to contact the authors for the desired data. If any disagreements occurred during this process, the 2 reviewers reached a consensus through consultation or adjudication by a third senior investigator (Pang LJ).

2.7. Risk of bias assessment

We will use the Cochrane risk of bias assessment tool version 2.0 (RoB 2.0) to assess the methodologic quality of RCTs. RoB 2.0 was published by the Cochrane methodology working group in 2016 and published and modified on the official website of
Cochrane in 2018. This SR will evaluate the possibility and sources of bias in RCT from 5 areas, including risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, risk of bias in selection of the reported result. Each module sets up several signal questions, and the reviewers will answer “yes,” “probability yes,” “possible no,” “no,” “not applicable” or “no information.” The overall risk of bias of RCT can be rated as low risk, high risk, and possible risk.

Two researchers (Zhang HY, Huang H) will use ROB 2.0 to evaluate the included RCTs independently. In case of disagreement, it will be decided through discussion or by the third senior researcher (Pang LJ).

2.8. Dealing with missing data
In case of missing data exist in included RCT, we will contact the corresponding authors. In the event of missing data are unobtainable, intention-to-treat (ITT) analysis will be conducted, if possible, and sensitivity analysis will be performed to address the potential impact of missing data, which will be discussed if necessary.

2.9. Strategy for data synthesis
The Stata13.1 software (Stata-Corp LP, College Station TX77845) was used for the meta-analysis. The Q-test and $I^2$ values were applied to measure the inter-study heterogeneity. When the $P$ value of Q test $>.1$ and $I^2<50\%$, a fixed effects model was applied; otherwise, a random-effects model was used. Binary variables were expressed using the odds ratio with 95% confidence interval (CI) and continuous variables by the standardized mean difference with 95% CI. Subgroup analysis will be performed to analyze potential factors that may cause high heterogeneity. If the heterogeneity remains substantial, a narrative summary will be conducted.
2.10. Subgroup analysis
Where heterogeneity is significant, subgroup analysis will be implemented based on specified effect modifiers as follows: different interventions, controls, publication year, sample size, course of treatment, publication language, risk of bias.

2.11. Sensitivity analysis
Different levels of the risk of bias of clinical research may affect the overall effects. According to the risk of bias assessment results, we will eliminate the low-quality literature to carry out sensitivity analysis to judge the robustness of the conclusion.

2.12. Publication biases
If the number of included RCTs is sufficient (n ≥ 10), this SR will adopt inverted funnel plot to detect publication bias. Besides, Peters regression test will be applied for binary variables, and Egger for continuous variables to provide quantitative evidence of any publication bias.

2.13. Rating the confidence in estimates of the effect
Grading of Recommendations Assessment, Development and Evaluation (GRADE) algorithm will be used to assess the confidence in estimates of the effect. Five factors may downgrade the level of proof, namely inconsistency, imprecision, limitations/risk of bias, publication bias and indirectness. The overall quality of evidence may be rated as “high,” “moderate,” “low,” or “very low.”[36] The certainty of proof was independently by 2 reviewers (Zhang HY, Huang H) who had received GRADE training, and divergences in this process will be resolved through discussion or decided by a third senior reviewer (Pang LJ).

2.14. Assessment of methodological quality
Assessment of multiple systematic reviews-2 (AMSTAR-2) is a comprehensive critical appraisal instruments developed to measure the methodological quality of systematic review, which has been demonstrated relatively simple, reliable and effective for methodological assessment.[37] It appraise all considerable steps in systematic review conduction, which contains 16 items covering topic selection, design, registration, information extraction, data statistical analysis, and discussion. The overall methodological quality can be classified as “high,” “moderate,” “low,” and “critically low” according to AMSTAR-2 guidance document. Online AMSTAR-2 checklist (http://www.amstar.ca/Amstar_Checklist.php) will be used to calculate and complete the scores in this study.

This process will be completed independently by 2 reviewers (Zhang HY, Huang H), and divergences in this process will be resolved through discussion or decided by a third senior reviewer (Pang LJ).

2.15. Ethics and dissemination
This systematic review will not require ethical approval because there are no data used in our study that are linked to individual patient data. In addition, findings will be disseminated through peer-review publications.

2.16. Strengths and limitations of this study
1. This study will be the latest SR to summarize the relevant evidence of AA combined with routine western medicine interventions in the treatment of COPD in remission stage.
2. This study will use the GRADE method to rate the confidence of evidence.
3. In this study, AMSTAR-2 tool will be used to evaluate the methodological quality of SR to ensure the integrity and transparency of the literature.
4. The search language is limited to Chinese and English, which may lead to omission.

3. Discussion
Chronic obstructive pulmonary disease has a high morbidity, mortality, and disability rate. It is a difficult problem to control recurrence in modern medicine. Acupoint application has a great benefit in the prevention and treatment of chronic recurrent respiratory diseases. Previous clinical studies have proved that AA combined with conventional western medicine treatment can reduce the number of acute exacerbations, improve symptoms and improve the quality of life in patients with stable COPD. This study will evaluate the effectiveness and safety of AA for stable COPD. Although several previous reviews have addressed this issue, a number of high-quality clinical trials on the efficacy and safety of AA for stable COPD have been published after them. This SR will provide the up-to-dated evidence on the effectiveness and safety of AA for COPD. It will provide helpful evidence for both clinical practice and future studies.

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