Effects of the Clearing the Lung and Dissipating Phlegm Method in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Abstract

Objective: The objective of this study is to evaluate the efficacy and safety of the clearing the lung and dissipating phlegm method in the treatment of acute exacerbation of chronic obstructive pulmonary disease (COPD) and to provide evidence for the treatment of the disease. Materials and Methods: Literature was searched from the United States National Library of Medicine (PubMed), Embase, Cochrane Library, China National Knowledge Infrastructure, Wanfang Database (Wanfang), and the Full-Text Database of Chinese Scientific and Technical Periodicals (VIP). A comprehensive collection was made of randomized controlled trials (RCTs) before June 2018, in which the treatment groups used either the clearing the lung and dissipating phlegm formulas only or combined it with routine Western medicine therapy, and the control group adopted routine Western medicine therapy only for the acute exacerbation of COPD. The Cochrane risk of bias method was used to evaluate the quality of the literature. The data were analyzed and retrieved independently by two reviewers before meta-analysis was carried out with RevMan 5.3 software to evaluate the primary outcome measures, including the total clinical effective rate, and the secondary outcome measures such as the pulmonary function (forced vital capacity [FVC], forced expiratory volume in the 1 st [FEV1], percentage of FEV1 [FEV1%], and FEV1/FVC) and blood gases (PaO₂ and PaCO₂). Results: A total of 13 RCTs involving 990 patients (496 in the treatment group and 494 in the control group) were included in this study. Meta-analysis revealed significant difference in the efficacy of the group that adopted solely the routine Western medicine method and the group that combined the Western medicine with the clearing the lung and dissipating phlegm method. Outcome measures including the pulmonary function (FVC, FEV1, FEV1%, and FEV1/FVC) and the blood gases (PaO₂ and PaCO₂) were significantly improved as compared to the control group (P < 0.00001). However, adverse effects in the treatment group using combined traditional Chinese medicine were not reported due to the short observation time of the study. Conclusion: The clearing the lung and dissipating phlegm method can improve the efficacy in the treatment of acute exacerbation of COPD, the outcome measures of the pulmonary function and the blood gases, as well as the life quality of the patients. However, due to the fact that the existing studies are generally of poor quality in which randomization and its implementation were not properly carried out, more high-quality RCTs are necessary to confirm the findings of this study.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, clearing the lung and dissipating phlegm method, meta-analysis, systematic review

INTRODUCTION

The 2018 Global Initiative for Chronic Obstructive Lung Disease (COLD) has re-defined the chronic obstructive pulmonary disease (COPD) as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] According to the estimations by the Burden of Obstructive Lung Diseases and other large scale epidemiological studies, there were a total of 384 million patients with COPD in 2010, with a prevalence of...
11.7% globally.[2] With the smoking population in developing countries and the aging population in developed countries increasing and the deteriorating of the environment, the prevalence of COPD is expected to rise continuously in the years to come.[3] COPD affects the pulmonary functions of the patients, impairs significantly their movement endurance or even further deprives them of the abilities to work. In addition, COPD is also associated with significant economic burden, especially the costs on the outpatient and inpatient treatments during the acute exacerbation of COPD (AECOPD).

An AECOPD is a phenomenon when a patient with COPD experiences an acute increase in cough, production of purulent or mucopurulent sputum, and shortness of breath and/or dyspnea, which may be accompanied by fever and require additional treatment. AECOPD is a characteristic reaction of worsened respiratory inflammation potentially caused by bacteria and/or virus infections,[4] manifested by pulmonary hyperinflation, aggravated air trapping, reduced expiratory flow, increased difficulty in breathing, and hypoxemia induced by further decreased ventilator/perfusion ratio.[5] Routine Western treatment plan includes oxygen therapy, respiratory support technology, antibiotics, glucocorticoids, bronchodilators, and mucus regulators, which are effective in alleviating the symptoms of AECOPD but costly. Besides, the patients’ sensitivity to the antibiotics tends to decrease after receiving treatment for multiple times. An alternative method is needed to treat the disease and reduce the occurrence. The routine treatment of Western medicine included in this study was oxygen therapy (2l/min), antibiotics (cephalosporins and quinolones), glucocorticoid bronchodilators (salmeterol/fluticasone and budesonide/formoterol), and expectorant (ambroxol) are common adverse reactions such as antibiotic allergy, hoarseness after hormone use, and oral Candida infection.

COPD is categorized as the “lung distension disease” by traditional Chinese medicine due to its clinical symptoms of cough, sputum, and wheezing. AECOPD is primarily caused by bacteria or virus infections and leads to many symptoms of the phlegm-heat syndrome, such as fever, coughing with yellow sputum, yellow and greasy tongue coating, and slippery and rapid pulse. Therefore, the clearing the lung and dissipating phlegm method should be adopted correspondingly.[6] The prescription for clearing the lung and dissipating phlegm method in the literature included in this paper is Qingjin prescription for clearing the lung and dissipating phlegm in the treatment of AECOPD so as to provide empirical evidence for the treatment approach in discussion.

**Materials and Methods**

**Inclusion criteria**

**Subjects**

The participants included in the study were patients with AECOPD diagnosed based on the GOLD criteria, excluding those with severe complications. There were no specifications for race, gender, or age. No obvious abnormalities were observed from the auxiliary examinations, such as the liver and renal function checks and the electrocardiogram.

**Interventions**

The patients in the treatment group were treated with traditional Chinese clearing the lung and dissipating phlegm herbal formulas and routine Western therapies, whereas the control group adopted the same Western treatment plan only.

**Types of study included**

All RCTs, in which AECOPD was treated with the clearing the lung and dissipating phlegm method were included, regardless of the use of allocation concealment and blinding. The reports included were written in either Chinese or English.

**Outcome measures**

The primary outcome measures included the total clinical effective rate, and the pulmonary function (forced vital capacity [FVC], forced expiratory volume in the 1 s [FEV1], percentage of FEV1 as predicted [FEV1%], and FEV1/FVC) and blood gases analyze (PaO2 and PaCO2) were taken as secondary outcome measures.

**Exclusion criteria**

The exclusion criteria include the following:

(a) Non-RCTs such as reviews or animal experiments, (b) Studies where no comparison can be established among the participants due to the huge variation in basic profiles, (c) Studies in which extra treatments such as acupuncture or acupoint plastering were given to the control group besides the expected interventions, (d) Studies where the outcome measures were inconsistent with the inclusion criteria, (e) Of the papers that have been published multiple times, the one with the lowest risk was selected, and (f) Studies with incomplete data or evaluation criteria.

**Retrieval strategy**

**Databases**

Literature searches were performed in the United States National Library of Medicine (PubMed), Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database (Wanfang), the Full-Text Database of Chinese Scientific and Technical Periodicals (VIP), and China Biology Medicine disc (CBMdisc).
Key terms for searching
Chinese terms included “chronic obstructive pulmonary disease” and “Qingfei Huatan” as the Medical Subject Headings. To search the English literature, “chronic obstructive pulmonary disease,” “clearing lung and eliminating phlegm,” and “Qingfei Huatan” were used as the key words. Another round of searching using jointly the subject headings and the key words was performed and was adjusted based on different databases.

Literature screening and selection
The studies searched were imported into the Note express version 3.0 (Aegean Haile Technology Co., Ltd., Beijing, China) by two reviewers independently, from which the repetitive ones and ones that failed to meet the inclusion criteria were deleted after reading the title, abstract and full text. Cross-check was performed and when there was an agreement over the inclusion of the studies, the decision was made after discussion or by the superior of the two reviewers.

Quality assessment and data extraction of the literature
The quality assessment of the included literature was conducted by the Cochrane Risk Assessment Tool, which considered the following: (a) whether randomization was performed correctly, (b) whether there was allocation concealment, (c) whether there was blinding, (d) whether data were complete, (e) whether there was selective reporting, and (f) other biases. The data extracted included: (a) general information: title of the article, name of the author, date of publication and the journal; (b) characteristics of the study: basic information of the participants, number of randomized cases, details of the methodological quality of the research, interventions, the control method, course of treatment, change in the outcome measures, and the effective rate of the treatment; and (c) outcome measures. The bias risk of each study was rated “high,” “unclear,” or “low.”

Statistical analysis
The commonly used software for meta-analysis, Review Manager 5.3, was employed in this study. Enumeration data were summarized using relative risk (RR) and measurement data were summarized using standard mean difference, with a 95% confidence interval (CI) for both. The heterogeneity of the original studies was evaluated with the Chi-squared test. When \(I^2 \leq 50\%\) and \(P \geq 0.05\), the heterogeneity test was considered to be statistically insignificant and a fixed-effect model was used to pool the results. If \(I^2 > 50\%\) and \(P < 0.05\), the test was statistically significant and a random-effect model was used for analysis. Two people performed data entering and analysis at the same time in order to ensure accuracy, and when there were differences, a third person would review the results.

Results
Screening results
The initial search yielded 548 studies from databases such as PubMed, Embase, Cochrane Library, CNKI, Wanfang, and VIP, of which 153 repetitive ones were excluded. Further scanning of the title and the abstract led to the exclusion of 343 studies that failed to meet the inclusion criteria. Another 36 ones were removed after reading the full text. A total of 13 papers[8-20] were included for meta-analysis [Table 1 and Figure 1].

Selected literature and risk of bias assessment
A total of 13 RCTs[8-20] were included, in which correct method of randomization was used, including random sequence generation, table of random digit, and random drawing. Two studies[13,14] indicated the employment of blinding method, whereas whether allocation concealment was adopted failed to be reported by the remaining studies. One study[13] reported subject withdrawal cases, and as a result, analysis of data sets and intention-to-treat analysis were carried out. No data incompleteness or missing were observed in the remaining studies, and the interventions of the treatment and control groups, as well as the corresponding outcomes were described in detail [Figure 2].

Outcome measures
Primary outcome measures – Efficacy rate
A total of 13 RCTs[8-20] involving 990 patients (496 in the treatment group and 494 in the control group) were included in this study. All the studies reported outcome measures. All the 13 studies had statistical heterogeneity (\(P = 0.03, F = 48\%\) so were analyzed with a random-effect model. Meta-analysis revealed significantly greater efficacy of the group that combined the clearing the lung and dissipating phlegm method with the routine Western treatment than the group that adopted...

Table 1: Baseline characteristics of the included studies

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Number of cases (Nc/Nt)</th>
<th>Course of treatment (days)</th>
<th>Interventions</th>
<th>Outcome measures</th>
<th>Subject withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu Tao., 2015</td>
<td>25/27</td>
<td>14</td>
<td>Routine treatment</td>
<td>Pulmonary function</td>
<td>0</td>
</tr>
<tr>
<td>Huang Qingyuan., 2012</td>
<td>40/40</td>
<td>14</td>
<td>Routine treatment plus modified Qingjin Huatan Decoction</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Chen Yi., 2013</td>
<td>32/32</td>
<td>14</td>
<td>Routine treatment plus Qingfei Huatan Granules</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Kou Yan., 2008</td>
<td>31/31</td>
<td>14</td>
<td>Routine treatment plus self-prescribed Qingre Huatan Decoction</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Li Jiansheng., 2011</td>
<td>65/69</td>
<td>14</td>
<td>Routine treatment plus placebo</td>
<td>Pulmonary function and blood gas analysis</td>
<td>6</td>
</tr>
<tr>
<td>Gao Yali., 2016</td>
<td>41/41</td>
<td>14</td>
<td>Routine treatment plus placebo</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Qu Dachun., 2013</td>
<td>36/36</td>
<td>14</td>
<td>Routine treatment plus Qingfei Huatan Decoction</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Yu Yan., 2016</td>
<td>42/42</td>
<td>21</td>
<td>Routine treatment plus Jianpi Qingfei Huatan Decoction</td>
<td>Blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Ying Huana., 2017</td>
<td>40/40</td>
<td>7</td>
<td>Routine treatment plus self-prescribed Qingre Xuanfei Huatan Decoction</td>
<td>Pulmonary function</td>
<td>0</td>
</tr>
<tr>
<td>Fan Rongwei., 2016</td>
<td>50/50</td>
<td>14</td>
<td>Routine treatment plus self-made Huatan Qingre Formula</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Luo Liwen., 2007</td>
<td>30/30</td>
<td>10</td>
<td>Routine treatment plus modified Qingjin Huatan Decoction</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Chen Xiaoying., 2011</td>
<td>32/28</td>
<td>7</td>
<td>Routine treatment plus Tanreqing Injection</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
<tr>
<td>Zhao Mei., 2016</td>
<td>30/30</td>
<td>14</td>
<td>Routine treatment plus Qingjin Huatan Decoction</td>
<td>Pulmonary function and blood gas analysis</td>
<td>0</td>
</tr>
</tbody>
</table>

solely the routine Western medicine method, with the difference being statistically significant (RR = 1.24, 95% CI [1.17, 1.31], P < 0.00001) [Figure 3]. Funnel plots were used to analyze the 13 included RCTs and obvious unsymmetrical distribution could be observed. Two studies[13,20] were found to have potential publication bias. The assessment of bias with Egger reported P = 0.32, suggesting potential publication bias [Figure 4].

Secondary outcome measures – Forced expiratory volume in the one second

A total of 4 studies[9,13,14,19] included used FEV1 as one of the outcome measures, involving 376 cases (190 of the treatment group and 186 of the control group). The comparison of FEV1 between the two groups was shown in the three-lined table. All the studies were checked for heterogeneity (P = 0.03, I² = 67%) and meta-analysis was carried out with a random-effect model, which showed WMD of 0.28 and improved FEV1 of the group that combined the clearing the lung and dissipating phlegm method with the routine Western treatment as compared to the group that adopted solely the routine Western method, with the difference being statistically significant (95% CI [0.18, 0.39], P < 0.0001) [Figure 6].

Secondary outcome measures – Percentage of forced expiratory volume in the one second

A total of 10 studies[8-12,14,15,18-20] included used FEV1 (%) as one of the outcome measures, involving 712 cases (357 of the treatment group and 355 of the control group). The comparison of FEV1 (%) between the two groups was
shown in the three-lined table. All the studies were checked for heterogeneity ($I^2 = 78\%, P < 0.00001$) and meta-analysis was carried out with a random-effect model. Results showed WMD of 2.39 and improved FEV1 (%) of the group that combined the clearing the lung and dissipating phlegm method with the routine Western treatment as compared to the group that adopted solely the routine Western method, with the difference being statistically significant (95% CI [1.60, 3.17], $P < 0.0001$) [Figure 7].

**Secondary outcome measures – forced expiratory volume in the one second/forced vital capacity**

A total of 7 studies[^1-13,15,18,20^] included used FEV1/FVC as one of the outcome measures, involving 524 cases (265 of the treatment group and 259 of the control group). The comparison of FEV1/FVC between the two groups was shown in the three-lined table. All the studies were checked for heterogeneity ($I^2 = 97\%, P < 0.00001$) and meta-analysis was carried out with a random-effect model. Results showed WMD of 4.52 and improved FEV1/FVC of the group that combined the clearing the lung and dissipating phlegm method with the routine Western treatment as compared to the group that adopted solely the routine Western method, with the difference being statistically significant (95% CI [3.75, 5.29], $P < 0.00001$) [Figure 8].

**Secondary outcome measures – $P_{O_2}$**

A total of 11 studies[^9-19^] included used $P_{O_2}$ as one of the outcome measures, involving 858 cases (429 of the treatment group and 429 of the control group). The comparison of $P_{O_2}$ between the two groups was shown in the three-lined table. All the studies were checked for heterogeneity ($I^2 = 89\%, P < 0.00001$) and

Secondary outcome measures – PaCo$_2$

A total of 9 studies [9-12,14-18] included used PaCo$_2$ as one of the outcome measures, involving 624 cases (310 of the treatment group and 314 of the control group). The comparison of PaCo$_2$ between the two groups was shown in the three-lined table. All the studies were checked for heterogeneity ($F = 86\%$, $P < 0.00001$) and meta-analysis was carried out with a random-effect model. Results showed WMD of $-5.42$ and improved PaCo$_2$ of the group that combined the clearing the lung and dissipating phlegm method with the routine Western treatment as compared to the group that adopted solely the routine Western method, with the difference being statistically significant (95% CI $[-6.14, -4.71]$, $P < 0.00001$) [Figure 10].

**Discussion**

COPD is characterized by respiratory symptoms such as persistent cough with sputum and shortness of breath caused by chronic inflammation of the respiratory tract and airflow limitation. The main diagnostic criterion is the decline of the pulmonary function, which deteriorates on each AECOPD. Therefore, both the traditional Chinese and Western medicine aim at reducing the frequency of AECOPD onsets and maintaining a stable pulmonary function as the main treatment goals. COPD has been covered by the medical insurance of chronic diseases in some regions. With greater importance being attached to the traditional Chinese medicine and massive recognition of its effectiveness, an increasing number of patients are willing to use Chinese herbal therapies to prevent AECOPD.

**Summary of the research results**

The systematic review and meta-analysis of the 13 selected studies shows that the efficacy of the clearing the lung and dissipating phlegm method used in conjunction with routine Western treatment is significantly better than Western medicine only. It is capable of alleviating respiratory symptoms and enhancing the quality of life by improving measures such as the pulmonary function and blood gases. However, the severity of the conditions, the GOLD grade, and the baseline data of...
the patients were not reported during the study, thus failing to reflect the actual effectiveness of traditional Chinese medicine. In addition, deficiencies in research methodologies, such as missing placebo, blinding or allocation concealment, largely hindered the inclusion of high-quality RCTs. This research only included studies in Chinese. Finally, the original studies only took patients with phlegm-heat syndrome as the subject, leading to the exclusion of many nonphlegm-heat syndrome cases. The research result fails to be applied universally due to the small size of the samples and a lack of multicenter cooperation.

**Confirmation of the research results**

Clinically characterized by “cough, sputum, and wheezing” that exist throughout the disease, COPD is categorized as the lung diseases by traditional Chinese medicine. According to the fundamental theories of traditional Chinese medicine, the lungs have the physiological characteristics of preference for dryness and aversion to dampness. Dryness belongs to the yang...
pathogen and external yang pathogen that invades the lungs tends to transform into heat. Therefore, heat syndromes are common in lung diseases. It is also evidenced by the clinical practices of the respiratory department that phlegm-heat syndrome occurs more frequently than other syndromes in any lung diseases and among all the outpatients and the inpatients. According to Fan and Qu,[18,19] during the course of AECOPD, the deteriorating inflammation of the respiratory tract could result in a significantly larger amount of sputum which is often yellow. It tends to be categorized as the syndrome of phlegm-heat obstructing the lung by pattern differentiation of traditional Chinese medicine. The modern pharmacology also proves that Qingre Huatan formulas are effective in clearing heat and dissolving phlegm. For example, herbs such as Bulbus Fritillariae Thunbergii, Folium Eriobotryae, Cortex Mori, and Herba Houttuyniae have the functions of controlling the inflammatory cells, inhibiting the release of inflammatory mediators, and alleviating the inflammation in the lungs and the whole body, which helps reduce the secretion of mucus in the respiratory tract and expel the sputum. Unobstructed expulsion of sputum in the airway contributes to the recovery of the lungs’ ventilation functions. Thus, FEV1 (%) has been chosen by a good number of studies on AECOPD as one of the outcome measures. As the lungs’ ventilation function restores, more air enters the lungs for gas exchange and thus improves the oxygen partial pressure and lowers that of carbon dioxide. It is evident that the use of clearing the lung and dissipating phlegm formulas in the treatment of AECOPD could not only boost the effective rate, reduce the inhospitalized time, improve the pulmonary functions, and blood gas analysis but also inhibit the inflammation of the respiratory tract, reduce the frequency of acute exacerbation, improve life quality, and enhance long-term efficacy.

Limitations

There are still several limitations in the research: (1) Randomization was not carried out properly. Most studies failed to present in detail the process of randomization or failed to use the correct randomization method; (2) There was no placebo group or allocation concealment, which may lead to some biases or even improper or incorrect research results; (3) It was not clear whether stratified sampling was carried out based on the baseline characteristics of the patients. Potential risk of bias in efficacy assessment may exist due to the variance in each group of patients; (4) Subject withdrawal, its cause and the corresponding actions were not reported; (5) Important adverse reactions, such as drug allergy or impairment to the liver and kidneys, failed to be reported.

Conclusion

In summary, the clearing the lung and dissipating phlegm formula has certain effect in the treatment and prevention of AECOPD, but further research is necessary to confirm the results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References


