Original Article
The effect of adjuvant therapy with ambroxol hydrochloride in elderly chronic obstructive pulmonary disease patients

Zheng Li

Department of Respiratory Medicine, Affiliated Hospital of Hebei University, Baoding 071000, Hebei Province, China

Abstract: Objective: To investigate the influence of adjuvant therapy with ambroxol hydrochloride (ABH) on the clinical symptoms and pulmonary function of elderly chronic obstructive pulmonary disease (COPD) patients. Methods: From September 2018 to September 2019, 142 elderly COPD patients admitted to the Affiliated Hospital of Hebei University were recruited as the research cohort. Based on different treatment method each patient underwent, they were assigned to the control group (CG, n=69) or the research group (RG, n=73). In the CG, the patients were treated with routine symptomatic treatment, and the patients in the RG were treated with ABH in addition to the treatment administered in the control group. Results: After the therapy, the clinical symptom scores in the RG were significantly lower than they were in the CG (P<0.05), and the total effective rate of the clinical treatment was significantly higher than it was in the CG (P<0.05). The 6MWT scores in the RG were higher than they were in the CG (P<0.001), and the CAT scores were significantly lower than they were in the CG (P<0.001). The inflammatory factor levels in the RG were markedly lower than they were in the CG (P<0.001), and the pulmonary function and immune function indexes were better than they were in the CG (P<0.05). There was no significant difference in the adverse effects between the two groups (P>0.05). Conclusion: ABH can effectively relieve the clinical symptoms and improve the pulmonary function of elderly COPD patients, with a significant clinical effectiveness and high drug safety, so it is worthy of promoting.

Keywords: Chronic obstructive pulmonary disease, ambroxol hydrochloride, clinical symptoms, lung function, curative effect

Introduction

COPD is a heterogeneous and multi-system disease. The air in the lungs is difficult to discharge due to the narrowing of the respiratory tract, and COPD's morbidity and mortality are on the rise [1, 2]. COPD affects about 300 million people all over the world. Air pollution is the main risk factor of COPD, and 3 billion people are in this dangerous environment [3], which has caused a huge burden to the medical and health systems [4]. With the increasing aging of the domestic population, COPD has been prevalent in the elderly population and has become a major public health problem [5]. However, most chronic respiratory burdens can be prevented and improved by treatment [6], so it is of great significance to seek effective treatment methods.

Dyspnea is a common symptom of patients with COPD, and it leads to limited activity and decreased motor function, and it affect patients' psychology and quality of life, so it needs effective intervention [7]. Drug therapy and smoking cessation are the main treatment measures, and some patients can be considered for lung rehabilitation, long-term oxygen therapy, and surgery [8]. Inhalation bronchodilators are the main treatment for COPD at present [9, 10]. However, bronchodilators are bound up with an increased risk of severe cardiovascular disease, they are expensive, and many patients still develop symptoms after treatment [11, 12]. ABH is a new active metabolite of bromhexine, and it can specifically bind to lung tissue, stimulate phospholipid synthesis, promote the production and secretion of pulmonary surfactants, reduce lung injuries, alleviate

inflammatory reactions, and dissolve sputum [13]. ABH is widely used in the clinical therapy of respiratory distress syndrome (RDS) due to its simple operation, low cost, and high safety [14, 15]. However, there is a lack of clinical research on the therapeutic effect of ABH in COPD, so its clinical effectiveness in COPD is still unclear.

Therefore, this research was designed to treat elderly COPD patients with ABH and to investigate its ability to improve their clinical symptoms and lung function.

Clinical data and methods

Collection of the patients' clinical data

From September 2018 to September 2019, 142 elderly patients with COPD admitted to Affiliated Hospital of Hebei University were recruited as the research cohort. Based on different treatment methods each patient underwent, they were divided into the CG (n=69) or the RG (n=73). In the CG, the patients were treated with the routine symptomatic treatment, and the patients in the RG were treated with ABH in addition to the routine symptomatic treatment.

Inclusion criteria: All the patients were diagnosed with COPD, and the diagnostic criteria were based on the relevant guidelines in 2017 [16]; All the patients were ≥65 years old, their clinical data were complete, they had not been treated with bronchiectasis drugs in the previous month, and they had not taken any anti-infective medication for nearly two weeks. The patients and their dependents were informed of the study and signed the informed consent.

Exclusion criteria: Patients allergic to the drugs used in this study, patients comorbid with malignant tumors, other lung diseases, liver or kidney insufficiency, diabetes, or hypertension, patients with communication barriers and patients with poor compliance.

This research was approved by the Medical Ethics Committee of the Affiliated Hospital of Hebei University.

Therapeutic methods

In the CG, the patients were treated with routine therapy. The patients were given symptom-atic treatment such as oxygen uptake, antitussives, antiasthmatics, antiinfectives, and the correction of water and electrolyte disorders according to their condition. In addition to the treatment administered to the CG, the patients in the RG were also administered an intravenous infusion of ABH (Hebei Ideal & Hightech Pharmaceutical Co., Ltd., SFDA Approval no. H20113062), 90 mg/time, twice a day. In both groups, the patients were treated for 14 days.

Measurement methods

Serum inflammatory factors: Before and after the therapy, 5 ml of fasting venous blood was drawn from all the patients, stored at room temperature for 30 min and centrifuged at 3000× g at 4°C for 10 min. Then, the supernatant was obtained and stored in a freezer at -80°C for later examination. Enzyme-linked immunosorbent assays (ELISA) were used to test the serum IL-6, IL-8, and TNF-α levels. The kits were provided by Wuhan Moshake Biotechnology Co., Ltd., and the operation was carried out strictly in accordance with the specifications. The absorbance (OD value) was measured with an enzyme-labeling instrument at a wavelength of 450 nm, and the corresponding concentration was converted from the standard line.

Lung function indicators: Before and after the therapy, the peak expiratory flow rate (PEF), the forced expiratory volume in one second (FEV1), and °C forced vital capacity (FVC) were measured using the chest lung function tester HI801.

Immune function indexes: Before and after the therapy, the CD3+, CD4+ and CD8+ levels were tested using flow cytometry (Flow Cytometer, ACEA Biosciences, the States).

Outcome measures

The main outcome measures: Clinical symptom scores were used to evaluate the improvement in the clinical symptoms in both groups, and the evaluation criteria are shown in **Table 1**. The clinical effectiveness was analyzed in both groups, and the efficacy evaluation criteria are shown in **Table 2**. The changes in the pulmonary function (pulmonary function indexes: PEF, FEV1, and FVC) were observed before and after the therapy.

Table 1. Scoring criteria for the clinical symptoms and signs

Symptoms	Scoring criteria			
	0	1	2	3
Coughing	No coughing	Occasional coughing	Frequent coughing	Severe coughing
Expectoration	No phlegm	The amount of expectoration was less than 15 ml	The amount of expectoration ranged from 15 ml to 50 ml	The amount of expectoration was more than 50 ml
Dyspnea	The patient did not have dyspnea until he continued to exercise vigorously	The patient had dyspnea until he continued to walk quickly on flat ground	The patient had dyspnea and it stopped when he walked quickly on flat ground	The patient was unable to walk long distances and had severe dyspnea
Pulmonary rales	No rales	Occasional rales	Scattered rales	Full-lung rales

Table 2. Evaluation criteria of efficacy

Efficacy	Evaluation criteria
Markedly effective	The clinical symptoms improved significantly and disappeared completely. The sputum was easy to cough up. The respiratory function improved significantly.
Effective	The clinical symptoms were improved. The sputum was easy to cough up. The respiratory function was improved.
Ineffective	The symptoms and respiratory function were not improved.

Secondary outcome measures: The six-minute walking test (6MWT) [17] and the COPD assessment test (CAT) [18] were used to evaluate the conditions of the patients in both groups. Before and after the therapy, the changes in the serum inflammatory factor levels (IL-6, IL-8 and TNF-α) and the immune function (immune function indicators: CD3+, CD4+ and CD8+ of T lymphocytes) were observed in both groups.

Statistical analysis

In this research, SPSS 23.0 (SPSS Co., Ltd., Chicago, USA) was used to analyze the collected data statistically. GraphPad Prism 8 (GraphPad Software Co., Ltd., San Diego, United States) was used to draw the figures of the collected data. The enumeration data were expressed as percentages (%), tested using chi-square tests and represented as χ^2. The quantitative data were represented as the mean ± standard deviation (x(Qu)). Independent samples t-tests were used for the comparisons between the two groups, which were expressed by T. P<0.05 indicated a significant difference.

Results

Basic information of patients

By collecting the patients' baseline data in both groups, we found that there were no significant differences in terms of age, gender, BMI, course of the disease, stage, dust contact history, smoking history, alcoholism history, or place of residence between the two groups (P>0.05), so they were comparable (**Table 3**).

Improvement of the clinical symptoms

The clinical manifestations and sign scores were used to evaluate the improvement in the clinical symptoms in both groups after the therapy. The results indicated that there was no significant difference in the scores between the two groups before the therapy (P>0.05). After the therapy, the sign scores in both groups were lower than they were before the therapy (P<0.001), and the scores in the RG were markedly lower than they were in the CG (P<0.001) (**Figure 1**).

Comparison of the clinical efficacy

By evaluating the clinical efficacy in both groups, it was found that the overall effective rate of the clinical treatment in the RG was significantly higher than it was in the CG (P<0.05) (**Table 4**).

Comparison of the 6MWT and CAT scores

In this study, 6MWT and CAT were used to evaluate the patients' conditions. The results revealed that there were no significant differences in the 6MWT and CAT scores in the two groups before the therapy (P>0.05). After the therapy, the 6MWT scores in both groups were higher than they were before the therapy (P<0.001), and the CAT scores were lower than

Table 3. Baseline data

Factors		CG (n=69)	RG (n=73)	t/χ^2	P
Age/years old		74.25±5.16	75.28±5.10	1.196	0.234
Gender	Male	45 (65.22)	53 (72.60)	0.905	0.342
	Female	24 (34.78)	20 (27.40)		
BMI (kg/m²)		22.31±2.07	21.78±2.14	1.499	0.136
Course of disease (years)		9.68±1.64	9.36±1.57	1.188	0.237
Staging					
	Stationary phase	47 (68.12)	58 (79.45)	2.366	0.124
	Acute exacerbation period	22 (31.88)	15 (20.55)		
Dust contact history					
	Yes	39 (56.52)	33 (45.21)	1.817	0.178
	No	30 (43.48)	40 (54.79)		
Smoking history					
	Yes	42 (60.87)	49 (67.12)	0.603	0.438
	No	27 (39.13)	24 (32.88)		
Alcoholism history					
	Yes	38 (55.07)	42 (57.53)	0.087	0.768
	No	31 (44.93)	31 (42.47)		
Place of residence					
	City	29 (42.03)	41 (56.16)	2.836	0.092
	Rural area	40 (57.97)	32 (43.84)		
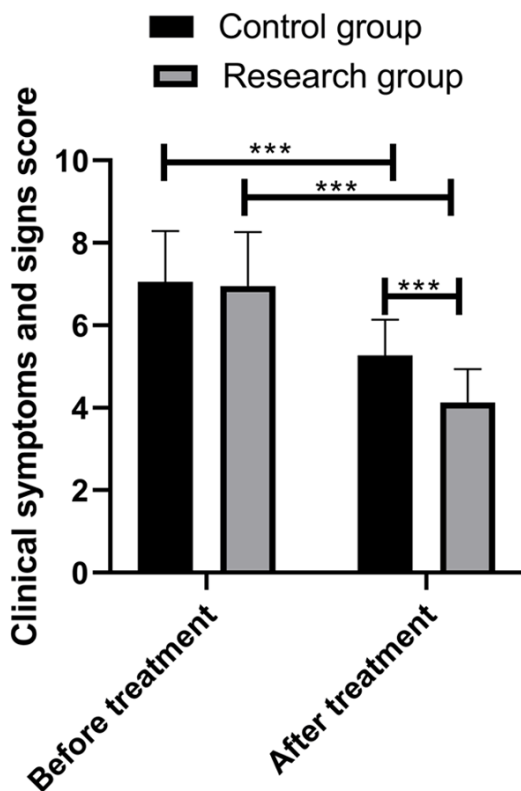
Figure 1. Changes in the clinical symptoms and signs scores. Before the therapy, there was no significant difference in the scores between the two groups. After the therapy, the scores of the signs in both groups were lower than they were before the therapy, and the scores in the RG were significantly lower than they were in the CG. ***P<0.001.

they were before the therapy (P<0.001). The 6MWT scores in the RG were higher than they were in the CG (P<0.001), and the CAT scores were significantly lower than they were in the CG (P<0.001) (**Table 5**).

Changes in the serum inflammatory cytokine levels

By measuring the serum inflammatory cytokine levels in both groups, it was found that there was no significant difference in the IL-6, IL-8, and TNF-α levels between the CG and RG before the therapy (P>0.05). After the therapy, the IL-6, IL-8, and TNF-α levels in both groups were lower than they were before the therapy (P<0.001), and the IL-6, IL-8, and TNF-α levels in the RG were significantly lower than they were in the CG (P<0.001) (**Figures 2**, **3**).

The improvement of lung function in both groups

There were no significant differences in the PEF, FEV1, or FVC levels in the two groups before the therapy (P>0.05). After the therapy,

Table 4. The clinical efficacy in both groups

Grouping	Markedly effective	Effective	Ineffective	Total effective rate
CG (n=69)	21 (30.43)	29 (42.03)	19 (27.54)	50 (72.46)
RG (n=73)	34 (46.58)	32 (43.84)	7 (9.59)	66 (90.41)
X^2				7.639
P				0.006

Table 5. Changes in the 6MWT and CAT scores

Grouping	6MWT		CAT	
	Before treatment	After treatment	Before treatment	After treatment
CG (n=69)	237.47±48.25	318.65±45.62*	26.27±2.75	16.14±2.23
RG (n=73)	248.75±51.23	362.16±44.86*	25.92±2.87	12.37±2.51
t	1.349	5.729	0.741	9.442
P	0.180	<0.001	0.460	<0.001

Note: *indicates P < 0.05.

the PEF, FEV1, and FVC levels were higher than they were before the therapy in both groups (P<0.05), and the index levels in the RG were markedly higher than they were in the CG (P<0.05) (**Table 6**).

Improvement of the immune function

ELISA was used to test the changes in the immune function indexes. The results indicated that there were no significant differences in the serum CD3+, CD4+, or CD8+ levels in the two groups before the therapy (P>0.05). After the therapy, the CD3+ and CD4+ levels in the RG were markedly higher than they were in the CG (P<0.001), but the CD8+ level was significantly lower than it was in the CG (P<0.001) (**Figure 4**).

Comparison of the incidences of adverse reactions

Through the analysis, it was found that there was no significant difference in the incidences of adverse effects between the two groups (P>0.05) (**Table 7**).

Discussion

The pathogenesis of COPD is complex. Although progress has been made in the treatment and prevention of disease, there has been little progress in improving patient prognosis, confirming that COPD is still a major health care problem at present [19]. If a patient is not treated effectively, the patient will progress to an acute exacerbation of COPD. Respiratory viruses and bacteria can infect the lower respiratory tract, aggravate respiratory inflammation, exacerbate the patient's symptoms, decrease lung function, seriously affect the quality of life, and increase medical expenditures [20]. Therefore, it is very important to seek effective treatment to prevent the progression of the disease.

Bronchodilators are the key to the symptomatic treatment of COPD [21]. However, bronchodilators are relatively expensive and may increase the incidence of adverse complications, especially in elderly patients [22, 23]. ABH combined with antibacterial drugs is an effective way to prevent drug-resistant bacterial infections, and the combination can decrease drug dose demand, reduce drug toxicity, and prevent or delay the emergence of drug resistance [24]. Based on the above research, it is considered that ABH is a more appropriate choice for adjuvant symptomatic treatment, so we will verify its therapeutic effect. In this study, the clinical symptoms and sign scores were compared between the two groups. The results indicated that the sign scores in both groups were decreased after the therapy compared with the pretreatment scores, indicating that the treatment in both groups effectively relieved the patients' clinical symptoms. However, the patients' scores in the RG were significantly lower than they were in the CG, indicating that ABH adjuvant therapy has a better effect at relieving the clinical symptoms. Then, the therapeutical effective rates were analyzed in both groups, and the results indicated that ABH combined treatment is more effective for elderly patients with COPD. ABH, a drug used for dissolving bronchial sputum, is widely used in respiratory diseases [25]. Studies have revealed that ABH has an excellent clinical effectiveness at preventing and treating RDS. It can improve patients' symptoms such as dyspnea, and it can effectively prevent neonatal death in prenatal applications [26, 27], a conclusion similar to the results of our research.
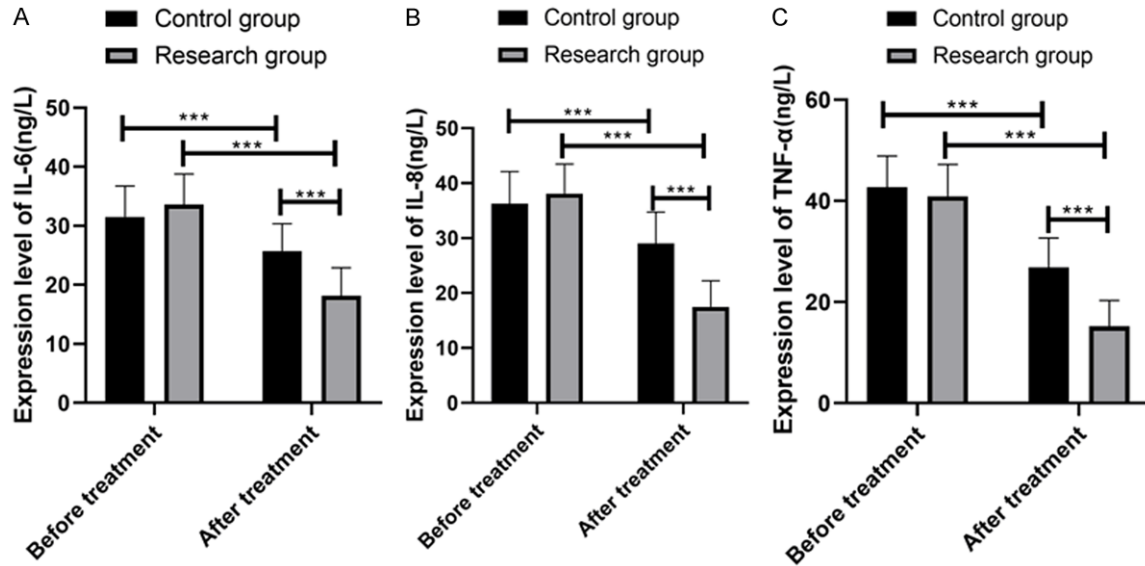
Figure 2. Changes in the serum inflammatory factors. A-C. There was no significant difference in the IL-6/IL-8/TNF-α levels between the two groups before the therapy, but the IL-6/IL-8/TNF-α levels in the two groups after the treatment were lower than they were before the therapy, and the IL-6/IL-8/TNF-α levels in the RG were significantly lower than they were in the CG. ***$P < 0.001$.

We believe that ABH can relieve dyspnea by diluting sputum and alleviating bronchial blockages, and it helps to relax the smooth muscle of the respiratory tract and achieve good spasmolysis and antiasthmatic effects. 6MWT and CAT are commonly-used clinical tools for evaluating the athletic abilities and conditions of patients with COPD [28, 29]. After the therapy, it was found that the 6MWT scores of the patients in the RG were significantly higher than they were in the CG, while the CAT scores were significantly lower than they were in the CG, indicating that compared with the conventional treatment, ABH adjuvant therapy can significantly improve the athletic abilities of patients and ameliorate their conditions.

COPD mainly causes respiratory obstructions and is related to chronic inflammation of the respiratory tract. The main symptoms are lung rales, fever, and cough [30, 31]. Ventilation obstructions are caused by a thickening of the respiratory membrane and the obstruction of the lower respiratory tract due to lung inflammation. In this study, the serum inflammatory cytokine levels in both groups were tested after the therapy. The results revealed that the serum inflammatory cytokine levels in the RG were significantly lower than they were in the CG, which indicated that ABH can significantly

improve patients' inflammatory responses. Biofilm is a key factor in the development of respiratory tract infections, and microorganisms are resistant to many drugs. Ambroxol can inhibit the activity of neutrophils and play an anti-inflammatory role, and it interferes with the activity of the ion channels and transporters in the respiratory epithelia to improve the mucociliary clearance and ameliorate biofilm-dependent respiratory tract infections [32]. COPD is caused by the long-term inhalation of toxic particles and gases, which leads to persistent congenital and adaptive immune responses in the lungs, and it participates in abnormal tissue repair and remodeling, leading to chronic inflammation, an excessive production of mucus in the respiratory tract, and the disruption of gas exchange [33]. In this study, the patients' cellular immune function indexes were tested in both groups. The findings revealed that the immune function of the patients in the RG was significantly ameliorated after the therapy, indicating that ABH combined with conventional treatment such as antibiotics can effectively improve patients' immune function. Inflammation plays a vital role in the control of pathogens and the formation of the subsequent adaptive immunology responses. The combination of an inflammatory response regulated by memory and effector
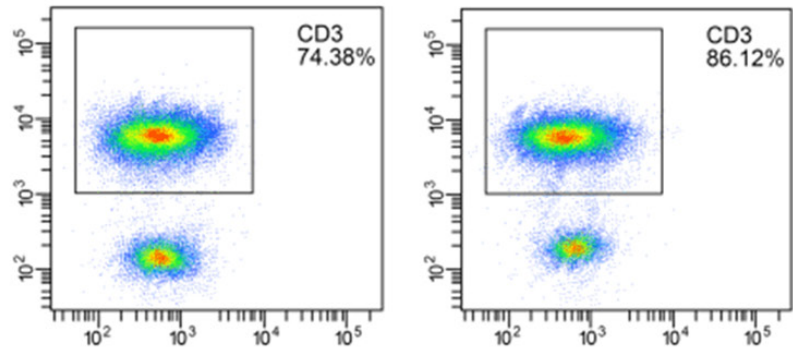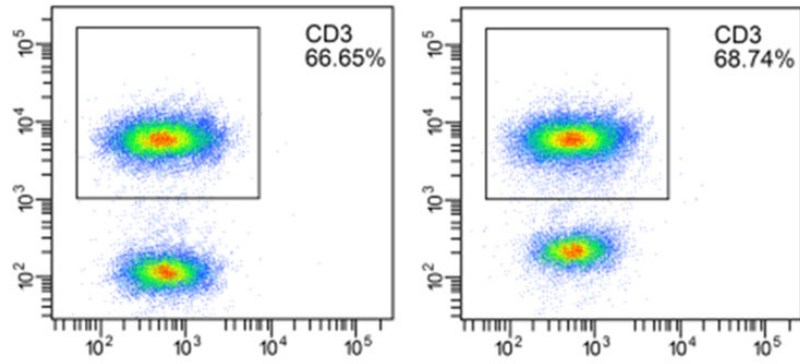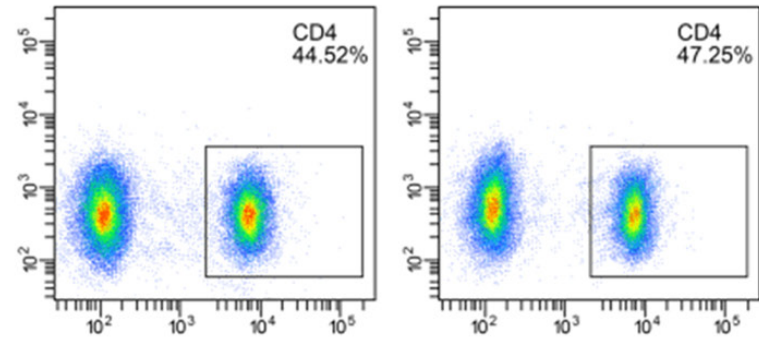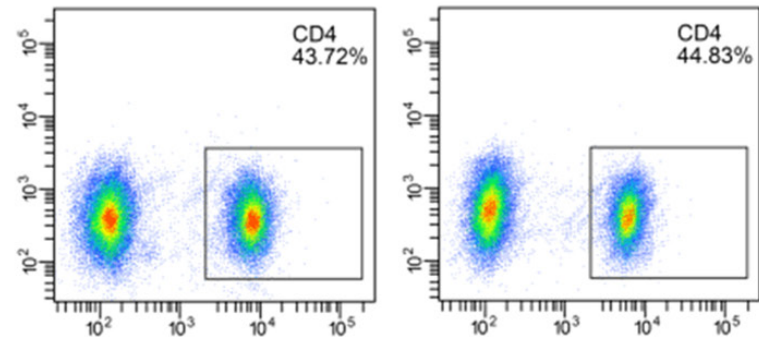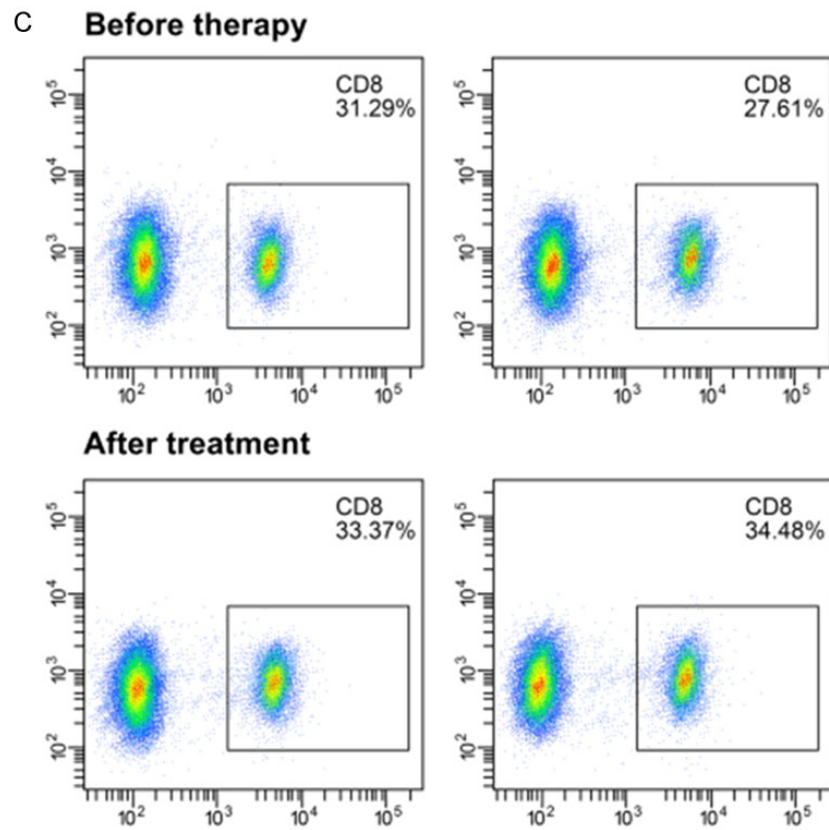
Figure 3. Flow cytometry.

Table 6. Changes in the pulmonary function indexes

PEF (L/S)		FEV1 (L)		FVC (L)	
Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
1.77±0.41	1.98±0.44*	0.87±0.29	1.65±0.33*	2.02±0.42	2.28±0.51*
1.75±0.45	2.51±0.47*	0.85±0.31	1.91±0.38*	2.14±0.43	2.54±0.55*
0.276	6.927	0.397	4.343	1.681	2.917
0.783	<0.001	0.692	<0.001	0.095	0.004

Note: *indicates $P < 0.05$.
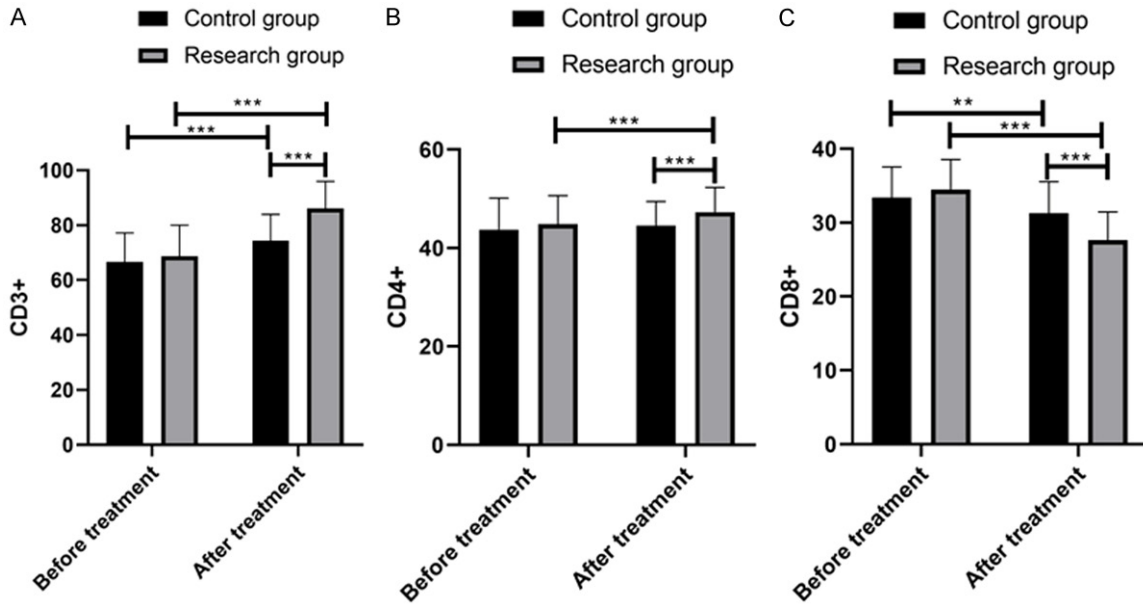
Figure 4. Changes in the immune function indexes. A. Before the therapy, there was no significant difference in the serum CD3+ levels between the two groups. After the therapy, the CD3+ levels in both groups were higher than they were before the therapy, and the CD3+ levels in the RG were significantly higher than they were in the CG. B. Before the therapy, there was no significant difference in the serum CD4+ levels between the two groups. After the therapy, the CD4+ levels in the RG were higher than they were before the therapy, and the CD4+ levels in the RG were significantly higher than they were in the CG. C. Before the therapy, there was no significant difference in the serum CD8+ levels between the two groups. After the therapy, the CD8+ levels in both groups were lower than they were before the therapy, and the CD8+ levels in the RG were significantly lower than they were in the CG. **$P<0.01$, ***$P<0.001$.

Table 7. Comparison of the incidences of adverse reactions

Grouping	Gastrointestinal reaction	Dizziness	Nausea and vomiting	Total
CG (n=69)	2 (2.90)	3 (4.35)	1 (1.45)	6 (8.70)
RG (n=73)	4 (5.48)	3 (4.11)	2 (2.74)	9 (12.33)
X^2				0496
P				0.481

T cell function can better control infections [34, 35]. Therefore, we believe that ABH combined with antibacterial drugs has a better anti-inflammatory effect, thus improving the immune function. The long-term use of ambroxol, a bronchial expectorant, can prevent the acute exacerbation of COPD [36]. Our study has revealed that the short-term use of ABH is effective. At the completion of the study, the incidence of adverse effects was analyzed in both groups. The findings revealed that there was no significant difference in the incidence of adverse effects between the two groups, indicating that the application of ABH in elderly patients with COPD is safe and worthy of clinical promotion.

This study has revealed that ABH has a high clinical effectiveness in elderly patients with COPD, but there are still some shortcomings in

this research. We did not evaluate the patients' treatment compliance. Compliance is affected by many factors, and it may affect the therapeutic effect [37]. Therefore, in future research, we will address this shortcoming.

In conclusion, this study found that ABH can effectively relieve the clinical symptoms, reduce the inflammation, and improve the lung function of elderly patients with COPD, and it has a significant clinical effectiveness and is very safe, so it is worthy of promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Zheng Li, Department of Respiratory Medicine, Affiliated Hospital of Hebei University, No. 212 Yuhua East Road, Baoding 071000, Hebei Province, China. Tel: +86-13643120598; E-mail: lizheng19781120@163.com

References

[1] Corlateanu A, Mendez Y, Wang Y, Garnica RJA, Botnaru V and Siafakas N. Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art. Pulmonology 2020; 26: 95-100.

[2] Dean E. Chronic obstructive pulmonary disease. Nurs Older People 2017; 29: 12.

[3] Ruvuna L and Sood A. Epidemiology of chronic obstructive pulmonary disease. Clin Chest Med 2020; 41: 315-327.

[4] López-Campos JL, Tan W and Soriano JB. Global burden of COPD. Respirology 2016; 21: 14-23.

[5] Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, Cong S, Juan J, Fan J, Lu K, Wang N, Hu Y and Wang L. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med 2018; 6: 421-430.

[6] GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet Respir Med 2017; 5: 691-706.

[7] Hanania NA and O'Donnell DE. Activity-related dyspnea in chronic obstructive pulmonary disease: physical and psychological consequences, unmet needs, and future directions. Int J Chron Obstruct Pulmon Dis 2019; 14: 1127-1138.

[8] Gentry S and Gentry B. Chronic obstructive pulmonary disease: diagnosis and management. Am Fam Physician 2017; 95: 433-441.

[9] Matera MG, Page CP, Calzetta L, Rogliani P and Cazzola M. Pharmacology and therapeutics of bronchodilators revisited. Pharmacol Rev 2020; 72: 218-252.

[10] Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DMG, Han M, López Varela MV, Martinez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA and Vogelmeier C. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J 2019; 53: 1900164.

[11] Kaminsky DA, Guntupalli KK, Lippmann J, Burns SM, Brock MA, Skelly J, DeSarno M, Pecott-Grimm H, Mohsin A, LaRock-McMahon C, Warren P, Whitney MC and Hanania NA. Effect of yoga breathing (pranayama) on exercise tolerance in patients with chronic obstructive pulmonary disease: a randomized, controlled trial. J Altern Complement Med 2017; 23: 696-704.

[12] Wang MT, Liou JT, Lin CW, Tsai CL, Wang YH, Hsu YJ and Lai JH. Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: a nested case-control study. JAMA Intern Med 2018; 178: 229-238.

[13] Xiang J and Wang P. Efficacy of pulmonary surfactant combined with high-dose ambroxol hydrochloride in the treatment of neonatal respiratory distress syndrome. Exp Ther Med 2019; 18: 654-658.

[14] Baranwal AK, Murthy AS and Singhi SC. High-dose oral ambroxol for early treatment of pulmonary acute respiratory distress syndrome: an exploratory, randomized, controlled pilot trial. J Trop Pediatr 2015; 61: 339-350.

[15] Gonzalez Garay AG, Reveiz L, Velasco Hidalgo L and Solis Galicia C. Ambroxol for women at risk of preterm birth for preventing neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2014; CD009708.

[16] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA and Agustí A. 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: 557-582.

[17] Mänttäri A, Suni J, Sievänen H, Husu P, Vähä-Ypyä H, Valkeinen H, Tokola K and Vasankari T.

Six-minute walk test: a tool for predicting maximal aerobic power (VO2 max) in healthy adults. Clin Physiol Funct Imaging 2018; [Epub ahead of print].

[18] Zhou Z, Zhou A, Zhao Y and Chen P. Evaluating the clinical COPD questionnaire: a systematic review. Respirology 2017; 22: 251-262.

[19] Rabe KF and Watz H. Chronic obstructive pulmonary disease. Lancet 2017; 389: 1931-1940.

[20] Ritchie AI and Wedzicha JA. Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. Clin Chest Med 2020; 41: 421-438.

[21] Matera MG, Rinaldi B, Page C, Rogliani P and Cazzola M. Pharmacokinetic considerations concerning the use of bronchodilators in the treatment of chronic obstructive pulmonary disease. Expert Opin Drug Metab Toxicol 2018; 14: 1101-1111.

[22] Stern A, Skalsky K, Avni T, Carrara E, Leibovici L and Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev 2017; 12: CD007720.

[23] Agusti A, Fabbri LM, Singh D, Vestbo J, Celli B, Franssen FME, Rabe KF and Papi A. Inhaled corticosteroids in COPD: friend or foe? Eur Respir J 2018; 52: 1801219.

[24] Wang Y, Li X, Wang D, Sun S and Lu C. In vitro interactions of ambroxol hydrochloride or amlodipine in combination with antibacterial agents against carbapenem-resistant acinetobacter baumannii. Lett Appl Microbiol 2020; 70: 189-195.

[25] Khoury T, Ishay Y, Rotnemer-Golinkin D, Zolotarovya L, Arkadir D, Zimran A and Ilan Y. A synergistic effect of ambroxol and beta-glucosylceramide in alleviating immune-mediated hepatitis: a novel immunomodulatory non-immunosuppressive formulation for treatment of immune-mediated disorders. Biomed Pharmacother 2020; 132: 110890.

[26] Zhang ZQ, Huang XM and Lu H. Ambroxol for the prevention of respiratory distress syndrome in preterm infants: a meta analysis. Zhongguo Dang Dai Er Ke Za Zhi 2010; 12: 858-863.

[27] Zhang H, Liu J, Liu T, Wang Y and Dai W. Antenatal maternal medication administration in preventing respiratory distress syndrome of premature infants: a network meta-analysis. Clin Respir J 2018; 12: 2480-2490.

[28] Frade MC, Dos Reis IM, Basso-Vanelli RP, Brandão AF and Jamami M. Reproducibility and validity of the 6-minute stationary walk test associated with virtual reality in subjects with COPD. Respir Care 2019; 64: 425-433.

[29] Miravitlles M, Koblizek V, Esquinas C, Milenkovic B, Barczyk A, Tkacova R, Somfay A, Zykov K, Tudoric N, Kostov K, Zbozinkova Z, Svoboda M, Sorli J, Krams A and Valipour A. Determinants of CAT (COPD assessment test) scores in a population of patients with COPD in central and Eastern Europe: the POPE study. Respir Med 2019; 150: 141-148.

[30] Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. Clin Sci (Lond) 2017; 131: 1541-1558.

[31] Chang CC, Cheng AC and Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev 2014; CD006088.

[32] Cataldi M, Sblendorio V, Leo A and Piazza O. Biofilm-dependent airway infections: a role for ambroxol? Pulm Pharmacol Ther 2014; 28: 98-108.

[33] van Eeden SF and Hogg JC. Immune-modulation in chronic obstructive pulmonary disease: current concepts and future strategies. Respiration 2020; 99: 550-565.

[34] Cronkite DA and Strutt TM. The regulation of inflammation by innate and adaptive lymphocytes. J Immunol Res 2018; 2018: 1467538.

[35] Caramori G, Ruggeri P, Di Stefano A, Mumby S, Girbino G, Adcock IM and Kirkham P. Autoimmunity and COPD: clinical implications. Chest 2018; 153: 1424-1431.

[36] Huang J, Xu J, Tian L and Zhong L. A thioredoxin reductase and/or thioredoxin system-based mechanism for antioxidant effects of ambroxol. Biochimie 2014; 97: 92-103.

[37] Shakshuki A and Agu RU. Improving the efficiency of respiratory drug delivery: a review of current treatment trends and future strategies for asthma and chronic obstructive pulmonary disease. Pulm Ther 2017; 3: 267-281.