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Original Research Article

Effect of montelukast/budesonide formoterol powder inhalation in chronic obstructive pulmonary disease

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Abstract

Purpose: *To investigate the clinical efficacy of montelukast/budesonide formoterol powder inhalation in treating chronic obstructive pulmonary disease (COPD) and its impact on serum high-sensitivity C-reactive protein (hs-CRP), cancer antigen 125 (CA-125), and interleukin (IL)-6 levels.*
Methods: *In total, 86 COPD patients treated in the clinic of Department of Respiratory Medicine in Yichun People's Hospital between December 2019 and December 2020 were recruited and randomly assigned to group A and group B alternately at the point of admission. Group B received conventional treatment, while group A was treated with conventional treatment plus montelukast/budesonide formoterol powder inhalation.*
Results: *Patients receiving montelukast/budesonide formoterol powder inhalation showed lower scores for cough, sputum, and shortness of breath, compared conventional treatment ($p < 0.001$). Patients in group A showed lower serum levels of hs-CRP, CA-125, and IL-6 after treatment than those in group B ($p < 0.05$). Pulmonary function and arterial blood gas indices were significantly different between the two groups after treatment ($p < 0.05$). Montelukast/budesonide formoterol powder inhalation resulted in higher Generic Quality Of Life Inventory-74 (GQOLI-74) scores and 6-min walking distance (6MWD) scores in patients than conventional treatment ($p < 0.001$). Also, Group A had a lower incidence of adverse reactions than group B ($p < 0.05$).*
Conclusion: *Montelukast/budesonide formoterol powder inhalation has a better therapeutic effect versus conventional treatment, and improves patients' lung function and exercise tolerance. Further clinical trials are, however, required prior to general use in clinical practice.*

Keywords: *Montelukast, Budesonide formoterol powder inhaler, Chronic resistance lung, Clinical efficacy, High-sensitivity; C-reactive protein; Cancer antigen 125; Interleukin -6*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease [1]. Its etiology is not yet clear, and the pathogenesis is usually related to exposure to toxic particles and gases. After disease progression, it causes severe lung damage, heart failure, or respiratory failure, seriously compromising the prognosis [2,3]. COPD ranks the fifth-largest economic burden caused by chronic disease, which necessitates exploration of effective therapeutic drugs for the disease. In COPD episodes, the respiratory symptoms of the patient are significantly

aggravated, and the clinical manifestations include increased sputum volume, coughing, and wheezing. Thus, the treatment of COPD is to achieve timely alleviation of the patient's clinical symptoms and improvement of ventilation function [4]. Montelukast is a leukotriene receptor anti-caking agent that selectively inhibits the smooth muscles in the airway, relieves smooth muscle spasms, and mitigates clinical symptoms. Budesonide formoterol powder inhalation is a compound drug that effectively inhibits the inflammatory response and enhances the stability of smooth muscle cells [5,6]. However, the combination of the two in the treatment of COPD and the improvement of patients' lung function has been marginally explored. This study was undertaken to further explore the efficacy of montelukast/budesonide formoterol powder inhalation on COPD and its effects on the levels of serum inflammatory factors.

METHODS

General patient information

Totally 86 COPD patients treated in the clinic of the Department of Respiratory Medicine in Yichun People's Hospital between December 2019 and December 2020 were recruited and assigned to group A and group B alternately at the point of admission.

Inclusion criteria

Patients who met the diagnostic criteria for COPD in *Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2013 ed)* [7], aged >18 years, with clear consciousness, good cognitive function, and who were able to cooperate with medical staff to complete the corresponding scale assessment were included.

Exclusion criteria

Patients with other respiratory diseases; with severe blood, liver, kidney, and immune system diseases; with similar treatment before randomization were excluded.

Ethical approval

This study was approved by the ethics committee of Yichun People's Hospital, and undersigned informed consent forms have been obtained from all patients. The study protocol was in line with the guidelines of Helsinki Declaration [8].

Treatments

Group B received conventional treatment, such as cough and asthma relief, correction of water electrolysis disorders and pH imbalance, and antibiotics treatment based on the patient's drug sensitivity [9]. The patients received one dose of Tiotropium Bromide Powder Inhalation daily (Spiriva®, Registration Number H20140954, Boehringer Ingelheim Pharma GmbH & Co.KG), and each dose contains 18 μg Tiotropium Bromide. A conventional treatment protocol with a similar prescription regimen was introduced to the patients in group A.

In addition, group A received 2 doses of budesonide formoterol powder inhalation daily (Registration Number H20140458, AstraZeneca AB), and each dose contains 160 μg budesonide and 4.5 μg formoterol. Group A also received one montelukast tablet daily (Registration Number J20130054, Merck Sharp & Dohme Italia SPA (Italy) Hangzhou Merck Pharmaceutical Co. Ltd), with one tablet containing 4mg of montelukast. The duration of treatment for the two groups of patients was a fortnight.

Evaluation parameters/indices

(1) ***Clinical symptoms***

The severity of cough, sputum expectoration, and shortness of breath was scored. The scoring criteria are shown in Table 1.

Table 1: Evaluation criteria for clinical symptoms

Symptom	0 points	1 point	2 points	3 points
Cough	No cough	Mild intermittent cough that does not interfere with normal life	Between mild and severe	Frequent coughing day and night, which has affected normal life
Expectoration	No expectoration	10-15 mL of sputum daily	50-100 mL of sputum	Over 100 mL sputum daily
Shortness of breath	No shortness of breath	Shortness of breath after activities	Shortness of breath after walking on the flat ground	Shortness of breath after light activities, unable to lie down, mostly in semi-sitting and lying position

(2) ***Serum high-sensitivity C-reaction protein (hs-CRP), interleukin-6 (IL-6), and cancer antigen 125 (CA-125)***

Five milliliters of fasting venous blood were collected from the patients before treatment and 3, 5, 7, and 14 days after treatment. The blood samples were centrifuged to isolate the serum, and the serum hs-CRP and IL-6 levels were determined using an enzyme-linked immunosorbent assay. The chemiluminescence method was used to determine serum cancer antigen 125 (CA-125) levels. The above time points (before treatment and 3, 5, 7, and 14 days after treatment) were set as T0, T1, T2, and T3. All assay kits were purchased from Shanghai Hengyuan Biotechnology Co. Ltd and operated according to the kit instructions. Color Doppler ultrasound diagnostic equipment (Xuzhou Bells Electronic Technology Co. Ltd) was used to determine the lung function indicators, including pulmonary artery systolic pressure (PASP), mean pulmonary artery pressure (MPAP), and pulmonary artery diastolic pressure (PADP). A blood gas analyzer (Wuhan Mingde Biotechnology Co. Ltd) was used to determine the arterial blood gas indices of the patients before and after treatment, including arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2).

(3) ***Quality of life***

The *Generic Quality of Life Inventory—74* (GQOLI-74) [10] was used to evaluate the quality of life of the patients. The full score was 100 points. A higher score indicates better quality of life. The 6-min walking distance test (6MWD) [11] was used to measure the exercise tolerance of patients.

(4) ***Adverse reactions***

The occurrence of adverse reactions in the two groups was recorded.

Statistical analysis

All data analysis was done using SPSS 21.0 software, while graphics were plotted with GraphPad Prism 7 (GraphPad Software, San Diego, USA). The enumeration data are expressed as [n (%)] and determined by chi-square test, while measurement data are expressed as (mean ± SD) and analyzed by t-test. Statistical differences were set at $p < 0.05$.

RESULTS

Baseline data

The two groups showed similar baseline characteristics including sex ratio, mean age, mean BMI value, mean disease duration, lung function classification before enrollment, education level, and place of residence *(p* > 0.05). (Table 2).

Table 2: Comparison of baseline data between the two groups

Variable	Group A (n=43)	Group B (n=43)	χ^2/t	*P*-value
Sex			0.047	0.828
Male	25 (58.14%)	24 (55.81%)		
Female	18 (41.86%)	19 (44.19%)		
Age (year)	62.61 ± 5.62	62.73 ± 5.74	0.098	0.922
Mean BMI (kg/m^2)	21.33 ± 0.86	21.38 ± 0.79	0.281	0.780
Mean disease course (year)	3.42 ± 0.56	3.47 ± 0.49	0.441	0.661
Pulmonary function classification before enrollment				
I	14 (32.56%)	12 (27.91%)	0.221	0.639
II	24 (55.81%)	23 (53.49%)	0.047	0.829
III	5 (11.63%)	8 (18.60%)	0.816	0.366
Place of residence			0.047	0.829
Township	20 (46.51%)	21 (48.84%)		
Rural area	23 (53.49%)	22 (51.16%)		
Educational background				
College	13 (30.23%)	15 (34.88%)	0.212	0.645
Middle school	19 (44.19%)	16 (37.21%)	0.434	0.510
Primary school	11 (25.58%)	12 (27.91%)	0.059	0.808

Table 3: Comparison of clinical symptom scores before and after treatment between the two groups (mean ± SD, n = 43)

Groups	n	Cough		Expectoration		Shortness of breath	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A	43	1.84 ± 0.47	0.89 ± 0.16	1.96 ± 0.42	0.93 ± 0.33	2.14 ± 0.46	0.76 ± 0.22
B	43	1.86 ± 0.52	1.19 ± 0.23	1.93 ± 0.38	1.25 ± 0.28	2.16 ± 0.42	1.26 ± 0.19
T		0.187	7.021	0.347	4.849	0.211	11.279
P-value		0.852	0.000	0.729	0.000	0.834	0.000

Clinical symptom scores

The two groups did not differ in the scores of various clinical symptoms before treatment *(p* > 0.05). The scores for cough, sputum, and shortness of breath after treatment in group A were lower than those in group B *(p* < 0.05). (Table 3).

Serum hs-CRP levels

The hs-CRP levels of group A patients at T0, T1, T2, and T3 were 84.54 ± 17.62 mg/mL, 53.35 ± 12.47 mg/mL, 35.48 ± 9.63 mg/mL, and 26.98 ± 8.32 mg/mL, respectively, and those of patients in group B at T0, T1, T2, and T3 were 84.67 ± 16.94 mg/mL, 67.14 ± 11.92 mg/mL, 40.62 ± 9.21 mg/mL, and 37.21 ± 8.69 mg/mL, respectively. The statistics at T1 were t = 5.242 and *p* = 0.000, at T2 were t = 2.529 and *p* = 0.013, and at T3 were t = 5.576 and *p* = 0.000. Patients in group A showed lower serum hs-CRP levels after treatment than group B *(p* < 0.05, Figure 1).

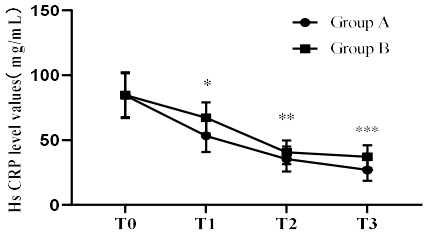

Figure 1: Comparison of changes in serum hs-CRP levels between the two groups of patients at different times (mean ± SD)

Changes in serum CA-125 levels

The CA-125 levels of patients in group A at T0, T1, T2, and T3 were 78.43 ± 12.07 u/mL, 57.82 ± 10.34 u/mL, 36.17 ± 9.26 u/mL, and 27.38 ± 8.35 u/mL, respectively, and those of patients in group B at T0, T1, T2, and T3 were 78.56 ± 11.98 u/mL, 63.38 ± 10.26 u/mL, 42.46 ± 9.14 u/mL, and 34.76 ± 8.59 u/mL, respectively. The statistics at T1 were t = 2.503 and *p* = 0.000, at T2 were t = 3.170 and *p* = 0.002, and at T3 were t = 4.040 and *p* = 0.000. Patients in group A showed lower serum CA-125 levels after treatment versus group B (*p* < 0.05). (Figure 2).

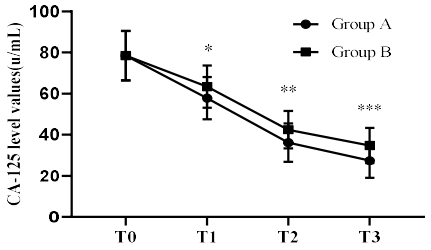

Figure 2: Comparison of changes in serum CA-125 levels between the two groups of patients at different times (mean ± SD)

Serum IL-6 levels

The IL-6 levels of group A patients at T0, T1, T2, and T3 were 94.36 ± 13.27 pg/mL, 70.34 ± 11.93 pg/mL, 57.44 ± 9.25 pg/mL, and 34.23 ± 7.16 pg/mL, respectively, and those of patients in group B at T0, T1, T2, and T3 were 94.47 ± 13.19 pg/mL, 76.87 ± 11.32 pg/mL, 63.04 ± 8.92 pg/mL, and 46.12 ± 7.24 pg/mL, respectively. The statistics at T1 were t = 2.604 and *p* = 0.011, at T2 were t = 2.858 and *p* = 0.005, and at T3 were t = 7.657 and *p* = 0.000. Patients in group A showed lower serum IL-6 levels after treatment versus group B *(p* < 0.05). (Figure 3).

Pulmonary function indices

Montelukast/budesonide formoterol powder inhalation resulted in lower levels of MPAP, PADP, and PASP versus conventional treatment *(p* < 0.05). (Table 4).

Arterial blood gas indices

The PaO_2 and $PaCO_2$ values of the two groups before treatment were comparable (P>0.05), and group A had a higher PaO_2 value and a lower $PaCO_2$ value than group B after treatment (P<0.05). (Table 5).

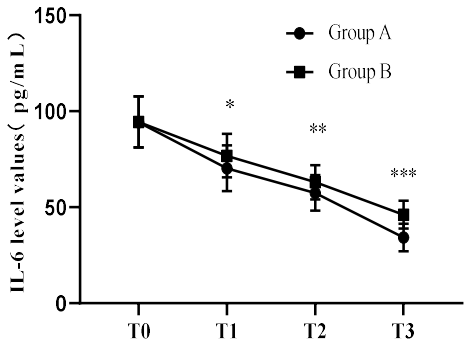

Figure 3: Comparison of serum IL-6 levels in the two groups of patients at different times (mean ± SD)

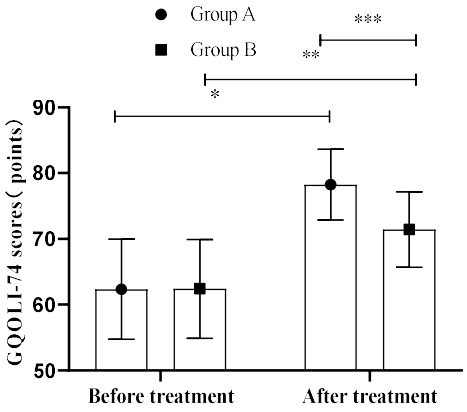

Figure 4: Comparison of GQOLI-74 scores between the two groups before and after treatment (mean ± SD)

GQOLI-74 and 6MWD scores

The GQOLI-74 scores of group A patients before and after treatment were 62.33 ± 7.62 and 78.25 ± 5.38, respectively, and those of patients in group B before and after treatment were 62.41 ± 7.52 and 71.42 ± 5.73, respectively. The statistics at T1 were t = 11.192 and p = 0.000, at T2 were t = 6.249 and p = 0.000, and at T3 were t = 5.698 and p = 0.000. The 6MWD scores of group A patients before and after treatment were 233.56 ± 37.63 m and 289.17 ± 42.31 m, respectively, and those of patients in group B before and after treatment were 233.49 ± 38.04 m and 264.51 ± 43.12 m, respectively. The statistics at T1 were t = 6.440 and p = 0.000, at T2 were t = 3.538 and p = 0.000, and at T3 were t = 2.677 and p = 0.000. Montelukast/budesonide formoterol powder inhalation resulted in higher GQOLI-74 and 6MWD scores of patients versus conventional treatment (p < 0.05). (Figure 4 and Figure 5).

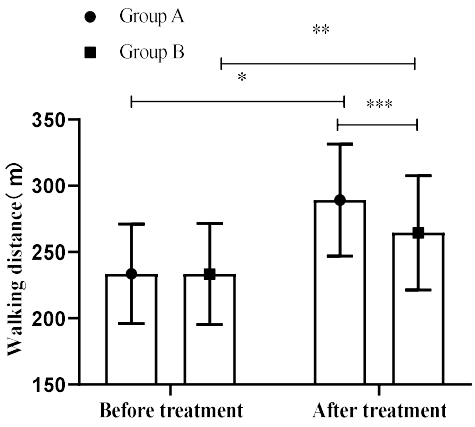

Figure 5: Comparison of 6MWD before and after treatment between the two groups (mean ± SD)

Table 4: Comparison of pulmonary function indices of the two groups of patients after treatment (mean ± SD, mmHg)

Group	MPAP	PADP	PASP
A	27.36 ± 6.70	18.36 ± 6.71	42.58 ± 9.82
B	34.51 ± 7.03	28.94 ± 7.11	58.26 ± 8.77
T	5.503	7.097	7.810
P-value	0.000	0.000	0.000

Table 5: Comparison of arterial blood gas indexes before and after treatment in the two groups ($\bar{}$mean ± SD, mmHg)

Group	n	PaO_2		$PaCO_2$	
		Before treatment	***After treatment***	***Before treatment***	***After treatment***
A	43	53.71 ± 9.72	73.44 ± 9.82	53.18 ± 12.64	42.06 ± 7.18
B	43	54.04 ± 9.84	66.83 ± 9.16	53.25 ± 12.52	47.92 ± 8.72
T		0.156	3.228	0.026	3.402
P-value		0.876	0.002	0.980	0.001

Table 6: Comparison of the incidence of adverse reactions between the two groups [n(%)]

Group	n	Dizziness	Heart palpitations	Difficulty in breathing	Rash	Total incidence
A	43	2(4.65)	1(2.33)	1(2.33)	2(4.65)	13.95 % (6/43)
B	43	4(9.30)	5(11.63)	2(4.65)	5(11.63)	37.21 % (16/43)
χ^2						6.108
P-value						0.013

Incidence of adverse reactions

Group A had a lower incidence of adverse reactions than group B ($p < 0.05$). (Table 6).

DISCUSSION

The main characteristics of COPD are irreversible airflow limitation and chronic inflammation of lung parenchyma, airway, and pulmonary blood vessels. The pathogenesis of the disease involves multiple biological processes such as inflammation, the release of metalloproteinases, oxidative stress, and cell proliferation [12]. During the acute onset of COPD, apoptotic cells and invading bacteria in the patient's body fail to be timely removed by macrophages, causing inflammatory responses and the release of inflammatory mediators such as IL-6. The entry of inflammatory mediators into the blood destroys the structure of the lungs and promotes inflammatory response of neutrophils, which triggers a cascade of complications and accelerates the progress of COPD [13].

Currently, the combination of different treatment methods is preferred for the treatment of COPD [14]. The treatment for COPD includes the use of bronchodilators and anti-inflammatory drugs to relieve the symptoms of airway obstruction and inhibit airway inflammation [15]. Clinically, the commonly used drugs are inhaled corticosteroids, which effectively relieve the clinical symptoms of COPD patients. Budesonide formoterol powder inhalation is a highly effective anti-inflammatory drug that acts on the airway epithelial cells of patients to inhibit the thickening of basement membranes and the exudation of inflammatory cells, thereby enhancing the role of β2 receptor agonists and reducing the inflammatory response [16].

Montelukast is a cysteinyl leukotriene (CysLTs) receptor-specific anti-caking agent, which significantly inhibits the release of inflammatory mediators and cytokines and alleviates airway allergies [17]. In the present study, group A had lower levels of serum inflammatory factors than group B after treatment. Romem *et al* [18] demonstrated in an animal study that montelukast inhibited the release of IL-6 in sensitized asthmatic rats and reduced the accumulation of bronchial inflammatory cells in asthmatic rats, which relieved airway inflammation and prevented airway immune damage. It indicates that montelukast may inhibit the inflammatory response of patients with pulmonary or bronchial diseases and alleviate clinical symptoms. Due to the impairment of respiratory function, COPD severely compromises the quality of life of patients [19]. In the present study, the GQOLI-74 scores and 6MWD results of group A were higher than those of group B, which was consistent with the research results by Clark *et al* [20], who stated that after treatment of azithromycin/montelukast for elderly patients with asthma, the 6MWD was 269.28 ± 32.72 m, which was significantly longer than that of 208.71±24.37 m before treatment, indicating that montelukast improves exercise tolerance and the prognosis of patients. The limitations of this study are the small sample size without consideration of regional differences and the absence of long-term follow-up. Hence, future investigation with an expanded sample size and long-term follow-up is required.

CONCLUSION

Montelukast/budesonide formoterol powder inhalation improves the lung function of patients with COPD, reduces inflammation in the body, improves exercise tolerance, and lowers the incidence of adverse drug reactions.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. The authors contributed equally to this research.

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