

## Original Research Article

# Effect of a combination of low-dose aminophylline and budesonide on lung function, serum inflammatory factors and quality of life of patients with chronic obstructive pulmonary disease

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Sent for review: 23 March 2021

Revised accepted: 26 May 2021

### Abstract

**Purpose:** To investigate the effect of a combination of low-dose aminophylline and budesonide on lung function, serum inflammatory factors and quality of life of patients with chronic obstructive pulmonary disease (COPD).

**Methods:** A total of 120 COPD patients admitted to Jiaozhou Central Hospital of Qingdao from January 2018 to January 2019 were the subjects for this study. They were divided into two groups based on the order of admission, with 60 patients in each group. The two groups of patients were treated with conventional COPD therapy. In addition, patients in group B were treated with budesonide, while those in group A were treated with a combination of low-dose aminophylline and budesonide. Lung function indices, serum levels of inflammatory factors, quality of life (QOL), 6-min walking distance (6MWD), and overall treatment effectiveness in the two groups were compared.

**Results:** Lung function indices were significantly higher in group A than in group B, while patients in group A had significantly lower serum levels of inflammatory factors than patients in group B ( $p < 0.001$ ). There was markedly higher QOL in group A patients than in patients of group B, but patients in group A achieved longer 6MWD than group B patients ( $p < 0.001$ ). More patients showed treatment effectiveness in group A than in group B ( $p < 0.05$ ).

**Conclusion:** Treatment with a combination of low-dose aminophylline and budesonide effectively improves lung function indices in COPD patients, reduces serum levels of inflammatory factors, but enhances their QOL. Thus, the combination treatment may be clinically beneficial to COPD patients.

**Keywords:** Aminophylline, Budesonide, Chronic obstructive pulmonary disease (COPD), Lung function

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is seen frequently in clinics. Glucocorticoid

therapy is often used in clinical practice to optimize lung function indices in COPD patients so as to reduce the likelihood of deterioration of their conditions. However, the effects of

glucocorticoids last only for a short duration, and their anti-inflammatory effects are unsatisfactory. Therefore, glucocorticoids are used in combination with other drugs so as to improve the treatment outcome of COPD patients [1-3].

It is stated in COPD treatment guidelines that bronchodilators are effective in relieving COPD symptoms, and their combination with glucocorticoids decreases inflammatory reactions in patients, thereby further enhancing their lung function. Moreover, the combined treatment has been reported to be more beneficial for long-term therapy of patients than the use of a single drug [4-7]. One of the bronchodilators used in the combined-drug treatment of COPD patients is aminophylline. This study was carried out to investigate the clinical efficacy of a combination of low-dose aminophylline and budesonide in COPD patients.

## METHODS

### Profile of patients

A total of 120 COPD patients admitted to our hospital from January 2018 to January 2019 were selected as the study subjects. They were assigned to two groups: A and B, according to the order of admission. As shown in Table 1, there were no significant differences in general data between patients in the two groups ( $p > 0.05$ ). This study was approved by the Institutional Review Board of Jiaozhou Central Hospital of Qingdao (approval no.: JCHQ-2017965). This study was performed in accordance with the institutional guidelines of Jiaozhou Central Hospital of Qingdao.

### Inclusion/exclusion criteria

#### Inclusion criteria

The following categories of patients were included in this study: (a) patients who signed informed consent to participate in the study, fully aware of the processes involved, or patients for whom family members signed informed consent; (b) patients whose COPD status was diagnosed and confirmed in accordance with the diagnostic criteria for COPD, and (c) patients with negative bronchodilator test results.

#### Exclusion criteria

Patients in the following categories were excluded from the study: (a) patients who had other organ diseases, including respiratory diseases; (b) patients who had mental health problems, or who were unable to communicate; (c) patients who had received or were receiving glucocorticoid treatments; (4) patients who had medication contraindications, and (c) pregnant or lactating patients.

### Treatments

All patients were administered conventional treatments such as expectorant and oxygen inhalation. Patients in group B were treated with 200 µg of budesonide (AstraZeneca AB, H20140458) and 1 inhalation twice daily, while patients in group A were orally administered aminophylline (Shanxi Taiyuan Pharmaceutical Co. Ltd, GYZZ H14020283) at a low dose of 100 mg *b.i.d.* after addition of budesonide [8-11]. The treatments lasted 24 weeks for all patients.

**Table 1:** Baseline patient information

Group	Group A (n=60)	Group B (n=60)	$\chi^2/t$	P-value
<b>Gender</b>			0.038	0.845
<b>Male</b>	41	40		
<b>Female</b>	19	20		
<b>Age (years)</b>	67.10±10.11	67.21±11.20	0.056	0.955
<b>COPD disease Course (years)</b>	9.11±5.21	9.20±5.41	0.093	0.926
<b>Clinical symptoms</b>				
<b>Chest distress</b>	55	56	0.120	0.729
<b>Cough</b>	35	34	0.034	0.853
<b>Breathe difficulty</b>	32	33	0.034	0.855
<b>Lung function</b>			0.036	0.850
<b>II</b>	38	37		
<b>III</b>	22	23		
<b>History of smoking</b>	24	25	0.035	0.853
<b>History of drinking</b>	27	26	0.034	0.854

## Determination of COPD parameters in patients

The lung function indices measured included forced respiratory volume in 1 second (FEV1), forced vital capacity ratio (FEV1/FVC), and FEV1 as percentage of predicted value (FEV1 %). Other parameters were serum levels of inflammatory factors, i.e., C-reactive protein (CRP), adiponectin (APN), interleukin-6 (IL-6) and QOL. For QOL, two scores for respiratory symptoms and activity limitation in St. George's Respiratory Questionnaire (SGRQ) were selected as rationale for the evaluation of QOL for patients in this study [12-15]. The scores ranged from 0 to 100, with higher scores signifying lower QOL. The other lung function used was 6MWD: the 6MWD before and after treatment were compared between the two groups. The overall treatment efficacy was rated as follows: if all the symptoms of COPD disappeared, the treatment outcome was classified as *significantly effective*. If the symptoms of COPD were significantly reduced, the outcome was deemed *effective*. However, if the condition of the patient remained unchanged or became worse, the treatment outcome was classified as *ineffective*.

## Statistical analysis

The data processing software used in this study was SPSS 20.0, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for drawing pictures. Measurement data are presented as mean  $\pm$  standard deviation (SD). Enumeration data are expressed as number (%). Chi squared ( $\chi^2$ ) test and *t*-test were used for

statistical analysis.  $P < 0.05$  was considered indicative of statistically significant difference.

## RESULTS

### Lung function indices

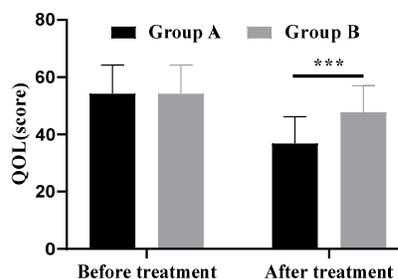
After treatment, lung function indices were markedly higher in group A patients than in group B patients ( $p < 0.001$ , as shown in Table 2).

### Serum levels of inflammatory factors

As shown in Table 3, after treatment, patients in group A had significantly lower serum levels of inflammatory factors than those in group B ( $p < 0.001$ ).

### Quality of life (QOL)

The SGRQ score was much lower in group A patients, but group A patients had markedly higher QOL than group B patients ( $p < 0.001$ ; Figure 1).



**Figure 1:** Comparison of QOL between the two groups of patients before and after treatment; \* $p < 0.001$

**Table 2:** Comparison of lung function indices of patients (mean  $\pm$  SD)

Parameter	Group A	Group B	t	P-value		
FEV1 (L)	Before treatment	1.12 $\pm$ 0.20	Before treatment	1.11 $\pm$ 0.21	0.267	0.790
	After treatment	1.80 $\pm$ 0.41	After treatment	1.42 $\pm$ 0.35	5.460	0.000
	T	11.546	T	5.883		
	P-value	0.000	P-value	0.000		
FEV1 / FVC (%)	Before treatment	49.50 $\pm$ 4.11	Before treatment	49.51 $\pm$ 4.10	0.013	0.989
	After treatment	64.10 $\pm$ 5.11	After treatment	55.40 $\pm$ 4.15	10.237	0.000
	T	17.245	T	7.821		
	P-value	0.000	P-value	0.000		
FEV1%	Before treatment	51.10 $\pm$ 4.20	Before treatment	51.12 $\pm$ 4.32	0.026	0.980
	After treatment	78.21 $\pm$ 3.52	After treatment	65.20 $\pm$ 4.21	18.364	0.000
	T	38.320	T	18.080		
	P-value	0.000	P-value	0.000		

**Table 3:** Comparison of serum inflammatory factor levels in patients ( $\bar{x} \pm s$ )

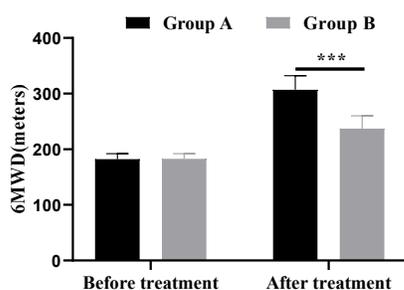
Item	Group A	Group B	t	P-value		
IL-6 (ng/L)	Before treatment	6.31±1.05	Before treatment	6.30±1.20	0.049	0.961
	After treatment	4.11±1.10	After treatment	5.10±1.05	5.043	0.000
	t	11.206	t	5.829		
	P-value	0.000	P-value	0.000		
CRP (mg/L)	Before treatment	6.94±0.95	Before treatment	6.93±0.56	0.070	0.944
	After treatment	3.55±0.80	After treatment	4.45±0.65	6.763	0.000
	t	21.143	t	22.390		
	P-value	0.000	P-value	0.000		
APN (mg/L)	Before treatment	9.81±0.52	Before treatment	9.80±0.54	0.103	0.918
	After treatment	7.80±1.11	After treatment	8.52±1.02	3.700	0.000
	t	12.702	t	8.591		
	P-value	0.000	P-value	0.000		

**Table 4:** Comparison of overall efficacy between the two groups (n, %)

Variable	Markedly effective	Effective	Invalid	Overall efficacy
Group A	21	37	2	58 (96.67)
Group B	12	38	10	50 (83.33)
$\chi^2$				5.926
P-value				0.015

### MWD values for the patients

As shown in Figure 2, after treatment, patients in group A had significantly longer 6MWD than those in group B ( $p < 0.001$ ).

**Figure 2:** Comparison of 6MWD between the two groups of patients before and after treatment; \*\*\* $P < 0.001$ 

### Overall treatment efficacy

Higher number of patients presented with overall treatment effectiveness in group A than in group B ( $\chi^2 = 5.926$ ,  $p = 0.015$ ), as shown in Table 4.

## DISCUSSION

At present, the pathogenesis of COPD has not been fully elucidated. However, it is thought that physiological and environmental factors are

involved in the development of the disease. In clinical practice, COPD patients are treated using strategies that reduce airway inflammation and mitigate obstruction of airflow, so as to optimize pulmonary function. These treatments rely mostly on glucocorticoids. However, recent studies have shown that the anti-inflammatory effect of glucocorticoid monotherapy is too unsatisfactory to reduce the levels of inflammation in COPD patients: other drugs are needed as adjunctive therapy [16-19].

Aminophylline is a third-line drug used in the treatment of COPD. In this study, low-dose aminophylline was administered in combination with budesonide to patients in group A. Furthermore, after treatment, FEV1 was  $1.80 \pm 0.41$ L; FEV1/FVC was  $64.10 \pm 5.11$  % and FEV1 % was  $78.21 \pm 3.52$  in group A. Lung function indices were markedly higher in group A than in group B. Moreover, patients in group A had significantly lower serum levels of inflammatory factors than those in group B. Thus, aminophylline effectively increased the levels of intracellular cyclic adenosine monophosphate in patients, allowing its anti-inflammatory effect to be exerted while reducing bronchial hypersensitivity, thereby decreasing clinical symptoms of COPD.

In a study that classified COPD patients treated with combination of low-dose aminophylline and budesonide as study group, and those treated

with budesonide alone as control group, it was found that FEV1 and FEV1/FVC of patients in the study group were  $1.85 \pm 0.39$  L and  $64.50 \pm 5.02$  %, respectively, post-treatment, whereas FEV1 and FEV1/FVC of patients in the control group were  $1.40 \pm 0.35$  L and  $54.99 \pm 4.15$  %, respectively. Moreover, lung function indices were markedly higher in the study group than in the control group. It has been shown that combination of low-dose aminophylline and budesonide was effective in improving pulmonary function of COPD patients [20]. Similar results were obtained in the present study.

Reduced exercise tolerance is one of the most distinct features of COPD patients. In this study, after treatment, patients in group A had markedly longer 6MWD than those in group B, indicating that aminophylline effectively enhanced their skeletal muscular activity, improved contractility of their heart muscles, and raised their capacity for exercise. In light of treatment outcomes such as significant improvement in pulmonary function and substantial increase in capacity for physical exercise, group A patients showed markedly higher QOL than those in group B, suggesting a better overall QOL.

### Limitations of the study

Despite the positive results this study yielded, it still has several limitations with respect to the interpretation of the results. First, the sample size was small, only 120 patients were included; Second, the follow-up time was short; Third, no blind method was used. Multi-center, double-blind, large-sample clinical research is needed to further verify the conclusions of this study.

### CONCLUSION

Given the above findings, we recommend low-dose aminophylline combined with budesonide a promising option for COPD patients. It is assumed that aminophylline can enhance the anti-inflammatory effect of glucocorticoids and significantly reduce serum inflammatory factor levels, providing new ideas for the treatment of COPD patients. In the meantime, whether other drugs that reduce inflammatory factors can also play a role in the treatment of COPD remains to be determined in future research.

### DECLARATIONS

#### Conflict of interest

No conflict of interest is associated with this work.

### Contribution of authors

We 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 the authors. Shuli Zhang, Qingfeng Liu and Zhaojun Chu conducted the experiments and collected the data; Shuli Zhang, Lili Wang, Qingfeng Liu designed the experiments and wrote the paper. Shuli Zhang and Fangchao Jiang analyzed the data. All authors reviewed and approved the final version of the manuscript for publication.

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