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Original Article

Effect of terbutaline plus doxofylline on chronic obstructive pulmonary disease

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Abstract: Objectives: This study focused on patients with chronic obstructive pulmonary disease (COPD) and aimed at investigating the effect of terbutaline plus doxofylline on their pulmonary function and quality of life. Methods: Ninety COPD patients were divided by using a random number table into a control group (administration of doxofylline) and experimental group (administration of terbutaline combined with doxofylline), with 45 patients in each group. The therapeutic efficacy, pre- and post-treatment pulmonary function and the quality of life were compared between the control and experimental groups. Results: After treatment, patients in the experimental group had lower levels of interleukin-8, tumor necrosis factor α and C-reactive protein (all $P<0.001$), higher forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEVl/FVC (all $P<0.001$), and lower total score of COPD assessment test ($P<0.05$) compared with the control group. Conclusion: Terbutaline combined with doxofylline for the treatment of COPD patients can efficiently decrease inflammatory factor levels, and bring them better pulmonary function and quality of life.

Keywords: Chronic obstructive pulmonary disease, terbutaline, doxofylline, inflammatory, pulmonary function

Introduction

Chronic obstructive pulmonary disease (COPD) is common, with an incidence rate of 10.1% worldwide, and its mortality ranks fourth among all causes of death. COPD patients usually present withsymptoms, such as irreversible airway obstruction, dyspnea, cough and expectoration, and even repeated outbreaks, which severely decrease quality of life [1, 2]. A clinical study has shown that the occurrence of COPD is closely related to the inflammatory response [3]. COPD patients generally have a systemic inflammatory response that is characterized by the elevation of inflammatory factor levels, causing inflammatory damage to the lung tissue and resulting in pulmonary function decline. Various drugs such as terbutaline and doxofylline have been used to treat COPD in clinical practice. However, terbutaline and doxofylline are often used alone or combined with other drugs in the treatment regimen, with few reports on the combination of the two drugs. In recent years, we used terbutaline together with doxofylline to treat COPD patients and achieved a good outcome. In this randomized controlled study, we further explored the efficacy of combination of the two drugs.

Materials and methods

Patients

Ninety COPD patients admitted to our hospital from December 2017 to December 2018 were selected. The subjects were divided by using a random number table into a control group and experimental group, with 45 patients per group. All patients provided informed consent, and the study was approved by the Ethics Committee of our hospital.

Inclusion criteria: Patients were diagnosed with COPD according to the Guidelines for the Diagnosis and Treatment of COPD published by the European Respiratory Society [4]; patients

Table 1. Comparison of baseline data ($\bar{x}$ ± sd; n, %)

Indicator	Experimental group (n=45)	Control group (n=45)	χ^2/t	P
Gender (n, %)			0.062	0.772
Male	26 (57.78)	25 (56.56)		
Female	19 (42.22)	20 (44.44)		
Age (years)	57.7±4.6	58.1±4.8	0.125	0.883
Duration of disease (years)	3.9±0.3	3.1±0.4	0.131	0.976
Smoking history (n)			0.074	0.796
Yes	29	28		
No	16	17		
GOLD grade (n)			0.075	0.801
Grade 1	23	22		
Grade 2	22	23		

Note: GOLD: Global initiative for chronic obstructive lung disease.

did not need mechanical ventilation; patients were at grade 1 or 2 by GOLD classification.

Exclusion criteria: Patients had bronchial asthma, tuberculosis, lung tumor, bronchiectasis, or other diseases that might affect pulmonary function or ventilation function; patients had acute exacerbation of COPD; patients had major organ or systemic dysfunction; patients had malignant tumors; patients were allergic to drugs used in this study.

Methods

Patients in the control group were intravenously infused with doxofylline (Zhejiang Beisheng Pharmaceutical Co., Ltd., China) at 0.2 g/day, which was dissolved in 250 mL 5% glucose injection (Sichuan Kelun Pharmaceutical Co., Ltd., China), for 10 days.

Patients in the experimental group were treated with terbutaline (AstraZeneca AB, Sweden) combined with doxofylline. Terbutaline at 1.3 mL (18 min/time) was inhaled twice a day, for 10 days. The dosage and methods of doxofylline were consistent with those of the control group.

Outcome measures

Inflammatory factors: Before and at the end of the treatment, fasting venous blood samples of 4 mL were drawn at 8 a.m. The enzyme-linked immunosorbent assay was used to determine levels of CRP, TNF-α, and IL-8.

Pulmonary function: Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEVI/FVC before and at the end of the treatment were detected with a spirometer.

Quality of life: COPD assessment test (CAT) was used to assess the quality of life before and at the end of the treatment [5]. The CAT has 8 items including cough, expectoration, chest tightness, sleeplessness, energy, confidence leaving home, breathlessness and limited activities, with a total score of 40 points. Each item is scored from 0 to 5 points. The higher score indicated the poorer thequality of life.

Statistical analysis

The SPSS 22.0 software was employed to analyze the data in this study. The measurement data are presented as mean ± standard deviation ($\bar{x}$ ± sd), and t-test was used to compare differences between groups. Enumerated data are presented as number/percentage (n/%) and compared by χ^2 test. $P<0.05$ indicated that a significant difference existed.

Results

Comparison of baseline data

Gender, age, and duration of disease did not differ between the control group and experimental group ($P>0.05$), shown in **Table 1**.

Comparison of inflammatory factor levels

Inflammatory factor levels before treatment between the control group and experimental group showed no significant differences (all $P>0.05$). Inflammatory factor levels after treatment decreased in both groups, and patients in the experimental group had lower inflammatory factor levels compared to the control group (all $P<0.001$). See **Table 2** and **Figure 1**.

Comparison of pulmonary function

Patients in the control group and experimental group had no significant differences in pulmo-

Table 2. Comparison of CRP, TNF-α, and IL-8 levels ($\bar{x}$ ± sd)

Indicator	Experimental group (n=45)	Control group (n=45)	t	P
CRP (mg/L)				
Before treatment	67.85±1.34	67.86±1.35	0.013	0.127
After treatment	32.52±1.12***	51.21±1.24***	28.972	<0.001
TNF-α (ng/L)				
Before treatment	178.48±2.31	178.49±2.32	0.011	0.201
After treatment	87.34±2.12***	124.39±2.11***	29.587	<0.001
IL-8 (pg/mL)				
Before treatment	268.48±2.01	268.49±2.02	0.014	0.203
After treatment	218.34±2.11***	235.39±2.31***	20.065	<0.001

Note: Compared with before treatment, ***P<0.001. CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-8: interleukin-8.

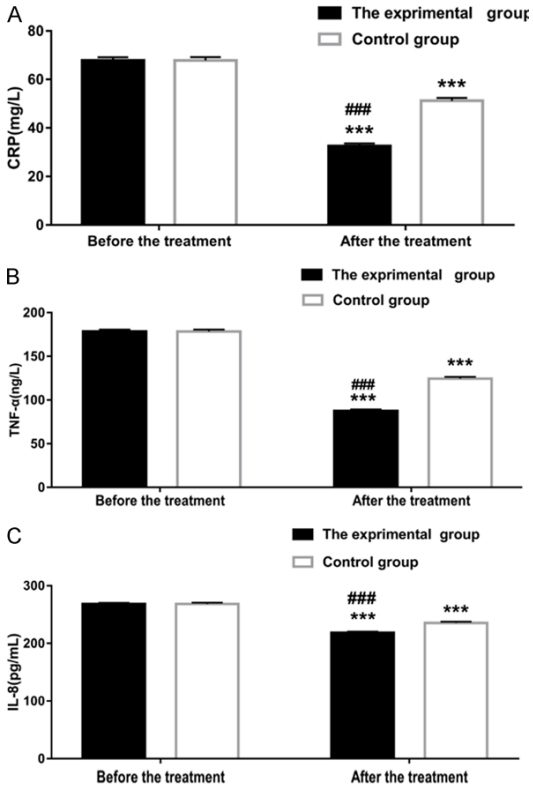

Figure 1. Comparison of CRP, TNF-α, and IL-8 levels. A: CRP; B: TNF-α; C: IL-8. Compared with before treatment, ***P<0.001; compared with the control group, ###P<0.001. CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-8: interleukin-8.

nary function indicators (FVC, FEV1, and FEV1/FVC) before treatment (all P>0.05). Pulmonary function indicators in both groups increased after treatment, and patients in the experimental group had higher pulmonary function indicators compared with the control group (all P<0.001). See **Table 3** and **Figure 2**.

Comparison of quality of life

Before treatment, no significant difference was found in CAT score between the control group and experimental group (P>0.05). CAT score in both groups decreased after treatment, and patients in the experimental group had lower CAT score compared with the control group (P<0.05). See **Table 4**.

Discussion

COPD is a common inflammatory disease of the respiratory system. Clinical manifestations mainly include cough, expectoration,, and dyspnea. At present, the pathogenesis of COPD is still unclear. Previous studies showed that COPD could be associated with pulmonary and systemic inflammatory reactions, as well as protease-antiprotease imbalance. When the body is affected by smoking or environmental pollution, inflammatory cells increase and aggregate, which cause a rapid release of inflammatory factors, aggravating the patient's condition and leading to pulmonary function decline [6, 7]. Moreover, COPD patients experience long-term recurrent symptoms such as cough, expectoration, dyspnea, and even respiratory failure if the condition is not controlled. The recurrent symptoms lead to continuous decline of pulmonary function and poor quality of life [8, 9]. At present, the treatment strategy of COPD is mainly to control infection, alleviate asthma, and dilate the bronchi by drugs. The main drugs include antibiotics, bronchodilators, and glucocorticoids [10, 11].

Terbutaline is an adrenergic agonist that produces selective agonistic effects on smooth muscle receptors. It relaxes bronchial smooth muscle and increases mucociliary clearance, thereby improving the symptoms associated with COPD [12]. Gueho et al. treated COPD patients with terbutaline and found that symptoms and pulmonary function were significantly improved after treatment [13]. Doxofylline is a new type of methylxanthine derivative, that can

Table 3. Comparison of FVC, FEV1 and FEV1/FVC ($\bar{x}$ ± sd)

Indicator	Experimental group (n=45)	Control group (n=45)	t	P
FVC (L)				
Before treatment	2.21±0.14	2.23±0.10	0.780	0.788
After treatment	3.31±0.13***	2.86±0.12***	17.063	<0.001
FEV1 (L)				
Before treatment	1.15±0.13	1.17±0.10	0.818	0.996
After treatment	2.26±0.12***	1.82±0.13***	16.683	<0.001
FEV1/FVC (%)				
Before treatment	52.52±1.22	52.46±1.31	0.225	0.543
After treatment	68.28±1.36***	63.61±1.41***	15.991	<0.001

Note: Compared with before treatment, ***P<0.001. FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second.

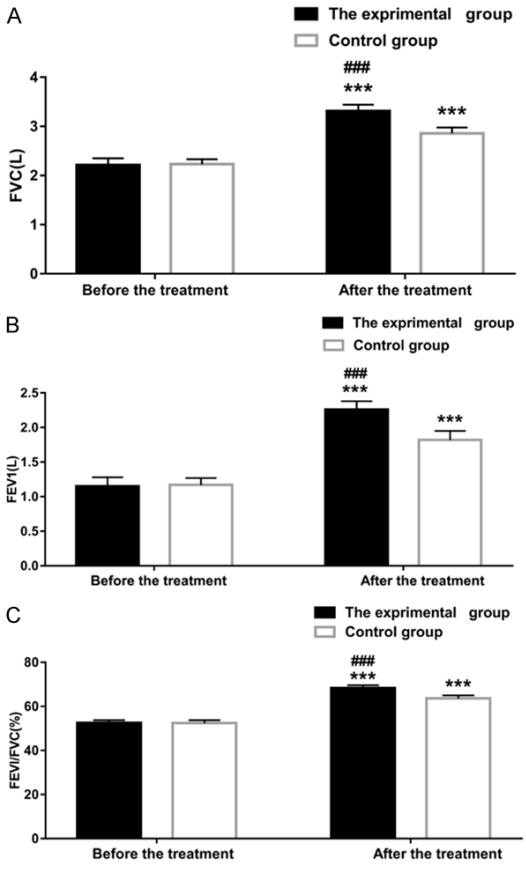

Figure 2. Comparison of FVC, FEV1, and FEVI/FVC. A: FVC; B: FEV1; C: FEVI/FVC. Compared with before treatment, ***P<0.001; compared with the control group, ###P<0.001. FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second.

inhibit phosphodiesterase, activate protease A and proteinase G, reduce the destruction of cyclic adenosine monophosphate, and thus improve symptoms and pulmonary function in COPD patients [14]. Wang et al. used doxofylline in the treatment of COPD patients and found that patients had relieved symptoms, improved pulmonary function, and better quality of life after treatment [15]. In this study, terbutaline combined with doxofylline was more effective than doxofylline alone in the treatment of COPD.

The combination of terbutaline and doxofylline effectively reduced the levels of inflammatory factors. In this study, CRP, TNF-α and IL-8 levels after treatment in the experimental group were 32.52±1.12 mg/L, 87.34±2.12 ng/L, and 218.34±2.11 pg/mL, respectively, while patients in the control group showed higher inflammatory factor levels: (CRP: 51.21±1.24 mg/L, TNF-α: 124.39±2.11 ng/L, and IL-8: 235.39±2.31 pg/mL). The results demonstrated a greater effectiveness of the combination of terbutaline and doxofylline in reducing CRP, TNF-α, and IL-8 levels than doxofylline alone. Terbutaline bound to the β-2 receptor with high selectivity, which activated adenylate cyclase, reduced the release of endogenous mediators, and relieved tissue edema. Doxofylline could inhibit airway inflammatory cytokines, which was conducive to the alleviation of airway and lung tissue damage caused by inflammatory factors [16, 17]. The combination of the two drugs synergistically consolidated the therapeutic efficacy, controlled the development of inflammation, and reduced CRP, TNF-α, and IL-8 levels.

The combination of terbutaline and doxofylline effectively improved pulmonary function. In this study, after treatment FVC, FEV1, and FEVI/FVC in the experimental group were 3.31±0.13 L, 2.26±0.12 L, and 68.28±1.36%, respectively, while patients in the control group showed lower pulmonary function indicators (FVC: 2.86±0.12 L, FEV1: 1.82±0.13 L, and FEVI/FVC: 63.61±1.41%). The results suggested that terbutaline plus doxofylline in treating COPD had a better effect on the improvement of pulmonary function as well as the increase of FVC, FEV1, and FEVI/FVC. Terbutaline could inhibit the tissue edema caused by pro-inflammatory substances, improve bronchial mucociliary clearance, and effectively relax the spasm of bron-

Table 4. Comparison of CAT score ($\bar{x}$ ± sd)

Indicator	Experimental group (n=45)	Control group (n=45)	t	P
CAT				
Before treatment	18.76±4.33	18.75±4.32	0.135	0.657
After treatment	10.67±1.35*	13.53±1.54*	9.368	<0.05

Note: Compared with before treatment, *P<0.05. CAT: chronic obstructive pulmonary disease assessment test.

chial smooth muscle. As a result, COPD-related symptoms such as cough and expectoration could be relieved. Doxofylline can inhibit phosphodiesterase in airway smooth muscle cells, reduce calcium concentration, and relax smooth muscle to alleviate symptoms [18, 19]. The combination of the two drugs could further reduce the impact of COPD symptoms, thereby effectively improving pulmonary function in COPD patients.

The combination of terbutaline and doxofylline effectively improved patients' quality of life. After treatment, the total score of CAT in the experimental group was 10.67±1.35 score, while patients in the control group showed a higher total score of CAT (13.53±1.54 score). The results suggested that the combination of terbutaline and doxofylline contributed to the improvement of the quality of life and CAT scores in COPD patients. Terbutaline improved airway function and relaxed the bronchial smooth muscle. Doxofylline plays a role in relieving respiratory spasm and inhibiting inflammatory response. The synergistic effect of the two drugs can reduce inflammation, alleviate related symptoms, and improve pulmonary function, thus reducing the impact of COPD symptoms and effectively improving quality of life [20, 21].

In summary, compared with doxofylline alone, terbutaline plus doxofylline for the treatment of COPD can efficiently decrease inflammatory factor levels, enhance pulmonary function, and further improve quality of life. However, this study had some limitations, such as small sample size and short-term follow-up. A further study with expanded sample size and extended follow-up is required to verify the clinical value of terbutaline combined with doxofylline in the treatment of COPD.

Disclosure of conflict of interest

None.

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