

Comparison of the efficacy of aerosol inhalation between the ipratropium bromide and terbutaline on the patients with AECOPD

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Abstract: To observe the clinical efficacy of aerosol inhalation of ipratropium bromide and terbutaline on the patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). A total of 136 COPD patients with acute exacerbation were divided into the ipratropium bromide group (n=69) and the terbutaline group (n=67). Patients in the ipratropium bromide group were required to take ipratropium bromide, while those in the terbutaline group took terbutaline for 3 days. Then, changes in symptoms, vital signs, blood-gas indicators and pulmonary functions were compared and analyzed between two groups. In ipratropium bromide group, patients with amelioration in vital signs and symptoms, especially for the symptom of coughing ($P<0.01$), were more than those in the terbutaline group, with statistically significant difference ($P<0.05$). In addition, following medication, analysis showed that the improvement in the blood-gas indicators and pulmonary functions in the ipratropium bromide was excellent in comparison with the terbutaline group, especially the improvement in the pulmonary ventilation function ($P<0.01$). Comparison over the incidence rates of adverse events in the ipratropium bromide group and terbutaline group showed an evident difference ($P<0.05$). For treatment of patients with acute exacerbation of COPD, aerosol inhalation of ipratropium bromide is a safe but effective method.

Keywords: Aerosol inhalation, ipratropium bromide, terbutaline, COPD, acute phase.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a kind of pulmonary disease with incomplete irreversible airway limitation as the major feature and is associated with the abnormal inflammatory responses of lung to the harmful substance or gas (Plant *et al.*, 2000; Jones 2015). For COPD patients, symptoms like persistent exacerbation of symptoms, like aggravation of cough, expectoration, dyspnea and/or tensed breathe, increased secretion of purulent or adhesive purulent sputum, concomitant with the fever or any other inflammations, suggest that COPD has evolved into the acute exacerbation of COPD (AECOPD) and the regular medication for COPD should be accordingly varied (Pauwels *et al.*, 2003; Pleasants *et al.*, 2016). AECOPD frequently occurs in autumn or winter, and the acute increase in the number of patients, plus the recurrent acute exacerbation, results in the significant increase in the mortality rate. Thus, AECOPD has become a key issue regarding to the public health (Malerba *et al.*, 2004). In this study, we collected the data from a total of 136 AECOPD patients in this hospital for treatment between June 2016 and December 2017 undertaking the treatment through the aerosol inhalation of ambroxol or α -chymotrypsin, with promising clinical outcome.

MATERIALS AND METHODS

Subjects

A total of 112 COPD patients who were admitted to this hospital between June 2016 and December 2017 and conformed to the diagnostic criteria of AECOPD (Weiser 2006) were enrolled into this study, and all patients were confirmed with no pulmonary heart disease or right heart failure. Patients were randomized in two groups, i.e. the ipratropium bromide group (n=69) and the terbutaline group (n=67). In the ipratropium bromide group, there were 44 males and 25 females aged between 54 and 78 years old, with an average age of (60.4±4.7) years old. In the terbutaline group, there were 38 males and 29 females aged between 52 and 79 years old, with an average age of (61.1±4.3) years old. Before admission, femoral arterial blood of patients was subjected to the analysis of the blood-gas indicators to measure the partial pressure of oxygen (PaO₂) and partial pressure of carbon dioxide (PaCO₂), and the forced vital capacity (FVC), ratio of forced expiratory volume in 1 second (FEV1) to FVC (FEV1/FVC) and the peak expiratory flow (PEF) were determined using the Spirometry. In addition, we also compared the general data of patients, including gender, age distribution and disease condition, between two groups, and the differences had no statistical significance ($P>0.05$), suggesting that the data were comparable.

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Methods

Following admission, all patients underwent the regular treatment, including the oxygen inhalation, anti-infection therapy, spasmolysis and asthma-relief, and the aerosol inhalation of drugs for 3 days. Then, patients in the ipratropium bromide group were required to take ipratropium bromide three times a day (10 min/time) by aerosol inhalation of 2mL ipratropium bromide in 2mL normal saline, while those in the terbutaline group took terbutaline twice per day (5mg/time).

Observation indexes

At the admission and 4th day after treatment, patients in two groups were subjected to extract the femoral arterial blood for analysis of blood-gas indicators and the measurement of pulmonary functions. In addition, the expectoration amounts were determined at different time points, from the admission to the first time of aerosol inhalation, and at 2 h after each aerosol inhalation using a disposable graduated cylinder. Questionnaire was also prepared for data analysis, in which cough times, expectoration amount and asthma were divided into the significant improvement, improvement and no response.

Ethical approval

This protocol had been approved by the Ethic Committee of the Mianyang Central Hospital of Sichuan Province, and all subjects had agreed to participate in the study

STATISTICAL ANALYSIS

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was utilized for data analysis. Enumeration data were compared between two groups using chi-square test, while measurement data in form of means \pm standard deviation ($\bar{x} \pm s$) using the t test. $P < 0.05$ suggested that the difference had statistical significance.

RESULTS

Comparisons of the symptoms and vital signs between two groups (table 1)

In ipratropium bromide group, patients with amelioration in vital signs and symptoms, especially for the symptom of coughing, were more than those in the terbutaline group, with statistically significant difference ($P < 0.01$). Following treatment, the expectoration amount in the ipratropium bromide group outran that in the terbutaline group ($P < 0.01$) (table 2). Comparison of the blood-gas indicators and the pulmonary function between two groups after the medication (table 3)

In addition, following medication, the improvement in the blood-gas indicators and pulmonary functions in the ipratropium bromide was better in comparison with the terbutaline group, especially the pulmonary ventilation function ($P < 0.01$).

Safety evaluation

In the ipratropium bromide group and the terbutaline group, there were 4 patients and 11 patients reporting the adverse events, with an incidence rate of 5.60% (4/69) and 16.42% (11/67) ($P < 0.05$). In the ipratropium bromide group, there were 2 patients with nausea, 1 with discomfort in pharynx and 1 with dizziness, and all adverse events were mitigated after suspension of aerosol inhalation, with no severe adverse reactions. In the terbutaline group, there were 3 with nausea, 5 with aggravated asthma, 2 with palpitation and 1 with headache and all adverse reactions were alleviated after suspension of aerosol inhalation. Aggravation in asthma and increases in the wheezing of lungs were identified in 2 patients during the aerosol inhalation, and due to the intravenous administration of spasmolytic for alleviation, these patients had to quit the study.

DISCUSSION

The pathogenesis of COPD is associated with a variety of inflammatory cells, including the neutrophils, lymphocytes, platelets, mastocytes and eosinophilic granulocyte, as well as the inflammatory mediators. Previous studies have shown that mild or moderate AECOPD is always concomitant with the increases in the sputum secretion and the quantity of neutrophils in airway wall, as well as the augment in eosinophilic granulocytes, and the levels of relevant inflammatory mediators (like TNF- α , LTB4 or IL-8) are also elevated with enhanced oxidative stress responses. In severe AECOPD, the quantity of airway neutrophils is increased, with up-regulation of chemotactic factors (Kido *et al.*, 2004; Singh *et al.*, 2016; Vestbo *et al.*, 2017; Jang *et al.*, 2003).

As the most common aspiration quaternary amine anticholinergic agents in clinical practice, ipratropium bromide acts as a short-acting β_2 receptor agonist with no selective to the subgroup of M receptor, and can bind to β_2 receptors in the membrane to abolish the increase in the guanosine monophosphate, thereby facilitating the diastole of bronchial smooth muscle (Feldman *et al.*, 2016; Su *et al.*, 2004; Wedzicha *et al.*, 2016). Following aerosol inhalation, ipratropium bromide is rapidly absorbed and mainly targets the lung, thereby blocking the cholinergic M1 and M3 receptors to inhibit the secretion of airway mucus, eradicate the bronchial spasm, suppress the vagus nerve activity and reduce the release of active substances, thus facilitating the diastole of bronchial smooth muscle (Confalonieri *et al.*, 2005; Singh *et al.*, 2016; Singh *et al.*, 2016). Furthermore, ipratropium bromide can also trigger the diastole of the large and moderate airways and decrease the secretion of airway (Venkatasamy *et al.*, 2016); it acts within 5 min after inhalation, and the peak level is attained between 30 and 60 min. Accumulating evidence has shown that ipratropium bromide can improve the pulmonary functions and exercise tolerance

Table 1. Improvement of the symptoms and the vital signs of patients in two groups after medication

Symptoms	Ipratropium bromide group				Terbutaline group				P value
	Excellence	Improvement	Failure	Total effectiveness rate (%)	Excellence	Improvement	Failure	Total effectiveness rate (%)	
Cough	24	31	14	79.71	16	27	24	64.18	<0.05
Expectoration	25	34	10	85.51	17	26	24	64.18	<0.01
Asthma	25	33	11	84.06	17	28	22	67.16	<0.05
Moist crackles	17	30	22	68.12	9	24	34	49.25	<0.05

Table 2. Comparison of the expectoration amounts of the ipratropium bromide group and the terbutaline group before and after medication ($\bar{x} \pm s$)

Group	n	Before aerosol inhalation (mL/2h)	After aerosol inhalation (mL/2h)	Increase
Ipratropium bromide group	69	8.25±1.51*	13.86±3.43	6.03±1.99
Terbutaline group	67	7.59±2.04	9.57±3.97	4.76±1.03

Table 3. Comparison of the blood-gas indicators and pulmonary functions of the ipratropium bromide group and the terbutaline group before and after medication ($\bar{x} \pm s$)

Group	n	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	FVC (L)	FEV ₁ /FVC (%)	FEV ₁ (%)
Ipratropium bromide group	69	70.18±4.60	54.16±3.22	1.74±0.87	53.75±12.65	54.82±9.38*
Terbutaline group	67	64.80±3.42	58.83±4.13	1.17±0.38	42.32±11.15	50.44±10.87

Note: P < 0.01, *P > 0.05 for comparison between ipratropium bromide group and terbutaline group.

of COPD patients, so as to alleviate the dyspnea of COPD patients (Watz, *et al.*, 2016; Beeh, *et al.*, 2016; Hamelmann, *et al.*, 2016).

Terbutaline is a kind of selective β_2 receptor agonist that can activate the β_2 receptor of airway and the adenylate cyclase to increase the intracellular level of cAMP and decrease the level of free calcium; consequently, bronchial smooth muscle is relaxed, with decreases in release of allergic mediators, and vascular permeability, hereby contributing to the relief in asthma (Schulz *et al.*, 2006; Rabe *et al.*, 2007). In addition, alterations of chemical features of terbutaline after administration endows itself the ability to avoid the inactivation by COMT or monoamine oxidase, hence prolonging the action time, which has become one of its prominent features (Singh *et al.*, 2016; Homson *et al.*, 2004).

Data of this study showed that for AECOPD patients, direct aerosol inhalation of ipratropium bromide, in comparison with the terbutaline, worked better in ameliorating the symptoms and vital signs of patients ($P < .05$), especially for the symptom of coughing ($P < 0.01$), and following treatment, the expectoration amount in the ipratropium bromide group outran that in the terbutaline group ($P < 0.01$). In addition, following medication, analysis showed that the improvement in the blood-gas indicators and pulmonary functions in the ipratropium bromide was excellent in comparison with the terbutaline group, especially the improvement in the pulmonary ventilation function ($P < 0.01$). The incidence rates of adverse events in the ipratropium bromide group and terbutaline group were 5.60% (4/69) and 16.42% (11/67), respectively ($P < 0.05$). Results above showed that aerosol inhalation of ipratropium bromide was effective in improving the symptoms and vital signs of patients, especially in clearing the airway and facilitating the expectoration, thus ameliorating the pulmonary function of patients and the ipratropium bromide is superior to the terbutaline. Thus, it is a safe and effective method with few adverse reactions.

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