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The effect of ventilator mask atomization inhalation of ipratropium bromide and budesonide suspension liquid in the treatment of COPD in acute exacerbation period on circulating levels of inflammation and prognosis

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Abstract. – OBJECTIVE: We investigated the effects of ventilator mask atomization inhalation of ipratropium bromide and budesonide suspension liquid in the treatment of acute exacerbation COPD (AECOPD) on circulating levels of inflammatory factors and prognosis.

PATIENTS AND METHODS: A total of 86 cases of patients on ventilator support were randomly divided into control group and observation group with 43 cases each. The control group was administered routine treatment including basic disease treatment, anti-infection, maintenance of a stable internal environment, nutritional support, oxygen inhalation and so on. All the patients were administered saline through a ventilator mask. The observation group was treated with atomized inhalation of ipratropium bromide and budesonide suspension and oxygen flow 3-5 L/min, 15-20 min/time and twice a day for 1 week. The treatment effects were compared.

RESULTS: Serum TNF-α, IL-6, and CRP levels were decreased in both groups after treatment, but levels in the observation group were significantly lower than those of the control group; differences were statistically significant ($p < 0.05$). Forced vital capacity (FVC), forced expiratory volume (FEV_1), FEV_1/FVC and maximal expiratory flow rate in the observation group were significantly higher than those in the control group after treatment ($p < 0.05$). After treatment, the PaO_2, SpO_2 and respiratory failure index (RFI) of the observation group were significantly higher than those of the control group. The $PaCO_2$ levels of the observation group were lower than those of the control group. The differences were statistically significant ($p < 0.05$). The clinical efficacy of the observation group was better than that of the control group; the ventilation time and total treatment time was significantly shorter and the differences were statistically significant ($p < 0.05$).

CONCLUSIONS: The ventilator mask atomizing inhalation of ipratropium bromide and budesonide suspension liquid in the treatment of AECOPD can significantly improve circulating inflammatory reaction, improve lung function and blood gas levels, increase the treatment efficiency, and shorten the treatment time.

Key Words:
Ventilator, Ipratropium bromide, Budesonide, Acute exacerbation of COPD, Circulating inflammation.

Introduction

Chronic obstructive pulmonary disease (COPD) is often caused by respiratory progressive airflow limitation due to noxious particles or gas. It ranks as the fourth largest cause of death in the world, the incidence rises each year and has become one of the important global public health problems[1]. Acute exacerbation of COPD (AECOPD) is a major factor in the progression of COPD and decreased lung function. Within a short period, respiratory symptoms of patients increase and lung function decreases due to illness, ropy sputum, sputum weakness, and sputum retention in the airway. The infection is aggravated, which aggravates hypoxemia, respiratory failure, and may threaten life[2]. In 2015, for severe and very severe AECOPD patients by ventilator assisted breathing, the COPD Global Initiative (GOLD) recommended a combined glucocorticoid inhalation therapy to improve the lung function in COPD patients and clinical symptoms[3]. Glucocorticoid combined with β_2 receptor agonist in the treatment of AECOPD is a commonly used method of atomizing inhalation. In this study, we investigated the application of

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ventilator mask atomization inhalation of ipratropium bromide and budesonide suspension liquid in the treatment of AECOPD patients and relationship of circulating levels of inflammation and prognosis to provide a reference for the clinical treatment.

Patients and Methods

Patients

We selected a total of 86 cases first diagnosed with AECOPD at our hospital from January 2014 to January 2016 on ventilator therapy. Inclusion criteria: (1) Meet the definition and diagnostic criteria of AECOPD by GOLD, (2) non-invasive effective mechanical ventilation treatment, (3) glucocorticoids or bronchial dilation agents were not used in the previous month, (4) informed consent was obtained.

Exclusion criteria: (1) serious disease of heart, brain, liver, kidney and other important organs disease, bronchial asthma, pulmonary bulla, chronic respiratory failure, primary lung cancer, etc., (2) presence of autoimmune diseases, contraindications to corticosteroids, drug intolerance and (3) Poor compliance, poor clinical data, etc.

Patients were divided according to the order of admission into the control group and the observation group by a random number method; there were 43 cases in each group. In the control group, there were 25 cases of males and 18 females that were aged 45-78 years old with an average age of (68.6±12.5) years old. The COPD course ranged from 3 to 12 years, with an average age of (8.3±3.4) years, body mass index (BMI) of 22.5-23.66 kg/m^2 with an average BMI of (21.5±2.3) kg/m^2. There were 5 cases of hypertension, 3 cases of diabetes mellitus, 4 cases of heart disease, and 10 cases of smoking. The basal dyspnea index (BDI) is 8-12 points, with a mean of (10.5±2.2) points.

In the observation group, there were 23 cases of males and 20 females aged 42-75 years old, with an average age of (66.7±13.4) years old. Age course ranged from 2.5 to 13 years, with an average age of (8.5±3.6) years. The body mass index (BMI) of this cohort was 20.6-23.2 kg/m^2, with an average BMI of (21.6±2.8) kg/m^2. There were 6 cases of hypertension, 2 cases of diabetes mellitus, 3 cases of heart disease, and 8 cases of smoking. The basal dyspnea index (BDI) is 8-12 points, with a mean of (10.5±2.2) points. The BDI is 6-11 points, with a mean of (9.6±2.8) points. The baseline data in the two groups were comparable.

Methods

Two groups of patients all performed noninvasive mechanical ventilation in two levels of positive pressure ventilation mode. Patients in the control group were treated with routine treatment, including basic disease therapy, anti-infection, maintenance of stable internal environment, nutritional support, oxygen inhalation and so on. The control group was treated with a ventilator mask inhalation of saline and the observation group was treated with atomized inhalation of ipratropium bromide and budesonide suspension. Among them, the ipratropium bromide (Atrovent, produced by Laboratoire Unither, Amiens, France) specifications are 2 ml/250 μg each, import drug registration certificate No. H20100681, and budesonide suspension (Pulmicort, produced by Astra-Zeneca, Wilmington, DE, USA), specifications are 2 ml/1 mg each, registration certificate of imported drugs, No. H20140475) were each administered in 2 ml+0.9% sodium chloride injection with adjusted oxygen flow 3-5 L/min, 15-20 min/time, and twice a day for 1 week. During aerosol inhalation, in order to maintain airway patency, the patient must change position timely, promote sputum drainage, pay attention to avoiding spray in the eyes, closely monitor vital signs of consciousness and breath, such as the occurrence of dyspnea, dizziness, nausea and other symptoms, and take timely treatment. After inhalation, water must be used for gargle in order to clean the nose and mouth.

Observation Index and Evaluation Method

We compared circulating blood inflammatory factor levels before and after the treatment, including TNF-α, IL-6 and CRP levels. We collected 3 ml fasting blood in the early morning, centrifuged at 2000 g for 20 min, took the upper serum, and stored at -20 °C. We detected levels by ELISA and the kit was purchased from Jiangsu Biyuntian Technology (Co. Ltd., Jiangsu, China). The enzyme mark instrument was from Beijing Liuyi Factory, and protocol was carried out in strict accordance with the manufacturers instructions.

We compared lung function and blood gas index before and after treatment. We looked at lung function indexes including forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1 FVC, peak expiratory flow rate (PEFR), blood gas indexes include arterial carbon dioxide partial pressure ($PaCO_2$), partial pressure of oxygen (PaO_2), and oxygen saturation (SpO_2). We also calculated the respiratory failu-

Table I. Comparison of serum levels of inflammatory cytokines.

	TNF-α (pg/ml)		IL-6 (pg/ml)		CRP (mg/L)	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	34.5±12.3	15.7±7.8	125.4±23.6	89.6±12.7	12.6±3.2	8.9±2.6
Observation group	36.7±13.6	9.6±4.5	134.9±34.5	65.4±13.3	13.5±3.4	5.7±2.2
t	0.234	4.532	0.326	4.958	0.185	4.432
p	0.745	0.034	0.659	0.030	0.862	0.036

re index (RFI) = PaO_2 / FiO_2 (inspiratory oxygen concentration).

We compared the clinical curative effects; the standard evaluation was divided into 3 levels: excellent, effective and ineffective. We compared the ventilation time and the total course of treatment.

Statistical Analysis

We used the SPSS20.0 (SPSS Inc., Chicago, IL, USA) software for statistical analysis, and measurement data was expressed by mean ± standard deviation. The group comparison was tested by independent sample *t*-test and comparison within the group was tested by paired *t*-test. The count data were expressed by cases or (%), the group comparison was tested by χ^2-test, and ranked data were tested by the rank sum. $p<0.05$ indicated that the difference was statistically significant.

Results

Comparison of Serum Levels of Inflammatory Cytokines

The serum TNF-α, IL-6 and CRP levels were decreased in both groups after treatment, and those of the observation group were significantly lower than those of the control group; differences were statistically significant ($p<0.05$) (Table I).

Comparison of Lung Function Indexes

Forced vital capacity (FVC), forced expiratory volume (FEV_1), FEV_1/FVC and PEFR value in the observation group were significantly higher than those in the control group after treatment ($p<0.05$) (Table II).

Comparison of Blood Gas Indexes

After treatment, the PaO_2, SpO_2 and respiratory failure index (RFI) of the observation group were significantly higher than those of the control group. The $PaCO_2$ was lower than that of the control group, and the differences were statistically significant ($p<0.05$) (Table III).

Clinical Curative Effect Comparison

The clinical efficacy of the observation group was better than that of the control group; the differences were statistically significant ($p<0.05$) (Table IV).

Comparison of Ventilation Time and Total Course of Treatment

The ventilation time and total treatment time were significantly shorter in the observation

Table II. Comparison of lung function indexes.

	FVC (L)		FEV_1 (%)		FEV_1/ FVC (%)		PEFR (L/s)	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	1.3±0.4	1.7±0.6	52.6±8.2	66.8±6.3	54.5±12.3	62.3±14.7	3.1±1.2	3.3±1.1
Observation group	1.4±0.5	2.3±0.7	51.5±8.6	71.6±7.2	53.2±13.6	73.5±12.4	3.0±1.4	4.4±1.3
t	0.065	4.123	0.089	4.436	0.121	4.895	0.048	4.526
p	0.912	0.036	0.865	0.031	0.789	0.022	0.936	0.028

Table III. Comparison of blood gas indexes.

	PaO_2 (mmHg)		$PaCO_2$ (mmHg)		SpO_2 (%)		RFI	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	46.8±12.2	76.5±8.3	65.8±8.9	49.6±5.4	82.3±5.6	94.6±4.5	312.5±42.6	414.6±37.8
Observation group	44.7±13.6	82.4±7.5	67.2±9.2	42.5±6.3	79.6±5.7	97.3±3.4	295.6±45.7	483.5±42.7
t	0.125	5.231	0.163	4.968	0.252	4.752	0.326	5.532
p	0.863	0.018	0.821	0.020	0.765	0.025	0.639	0.014

Table IV. Comparison of clinical effects [cases (%)]

Group	Cases	Excellence	Effective	ineffective
Control group	43	8 (18.6)	22 (51.2)	13 (30.2)
Observation group	43	18 (41.9)	20 (46.5)	5 (11.6)
Z			7.497	
p			0.024	

group and the differences were statistically significant ($p<0.05$) (Table V).

Discussion

The pathogenesis of COPD involves oxidative damage, and the imbalance of protease and anti-protease, immune disorder and airway inflammation, in which airway inflammation plays an important role in the occurrence, development, treatment and prognosis of the disease[4,5]. Under the stimulation of various factors, neutrophils, macrophages and monocytes aggregate, activate and release a large number of IL-6, TNF-α and CRP, as well as others circulating inflammatory factors[5]. In addition, IL-6 can also recruit other positive factors and release inflammatory mediators, which result in a cascade of inflammatory responses, and increased alveolar, interstitial and airway epithelial injury[6]. TNF-α is massively released and can induce the levels of endothelial cell adhesion molecule (ICAM-1) to be increased. This stimulates the white blood cell surface adhesion molecule VIA-4 to be up-regulated, and the interaction between the two makes the white blood cells quickly reach the inflammation target, and initiate an inflammatory reaction[7]. Serum CRP is a kind of acute phase protein in liver cell synthesis and the levels of COPD in acute exacerbation stage is rapidly increasing. Its levels are often closely related to the severity and prognosis of the disease[8]. The results showed that the serum TNF-α, IL-6 and CRP levels are decreased in both groups after treatment, and those of the observation group were significantly lower than those of the control group; the differences were statistically significant. It suggests that the inflammatory response played an important role in AECOPD, and the treatment of the observation group can further reduce the level of the lesion and reduce the extent of the lesion.

In the treatment of COPD, through the aerosol inhalation, the medicine reaches the targeted treatment on the bronchial alveoli and, within a short amount of time, the medicine concentration rose and achieved a quick effect[9]. Ammonium bromide is a type of anti-cholinergic drug, which can produce antagonistic effects on the neurotransmitter acetylcholine, and thus, effectively inhibit vagal reflex[10]. At the same time, the combination of M receptor and acetylcholine in bronchial smooth muscle was blocked, which achieved the antagonism of the contraction of the bronchus, prolonged the relaxation time of the large and middle airways and the effect of treatment was achieved [11]. Bu-

Table V. Comparison of ventilation time and total course of treatment (d)

Group	Ventilation Time	Total Course of treatment
Control group	6.4±1.2	11.2±1.5
Observation group	3.5±0.6	6.8±1.1
t	5.236	5.649
p	0.022	0.016

desonide is a type of glucocorticoid that can be effective in suppression of inflammatory factors such as circulating IL-6 and TNF-α, and achieve a local anti-inflammatory effect[12]. At the same time, the stability of smooth muscle and endothelial cells is enhanced as well as the immune function. The release of allergic media is reduced, and the synthesis and release of bronchial contractile substance is suppressed; the reaction of the smooth muscle's contraction is reduced[13]. The effect of budesonide on human biology is slight, with a relatively good safety profile even with a frequent use. The two drugs combined with atomization inhalation can effectively control circulating inflammatory factors, with airway dilation, rapid onset, longer effective times, and less adverse reactions[14,15].

The study concluded that after treatment, the pulmonary function and blood gas indexes of the observation group were significantly improved, and the clinical effects were better than those of the control group.

Conclusions

The ventilation time and total treatment were significantly shortened, and the differences were statistically significant. In conclusion, the ventilator mask atomizing inhalation of ipratropium bromide and budesonide suspension liquid in the treatment of AECOPD can significantly improve the circulating inflammatory reaction, improve lung function and blood gas levels, increase the treatment efficiency, and shorten the treatment time. Therefore, it is worthy of clinical application and promotion.

Conflict of interest

The authors declare no conflicts of interest.

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