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Clinical Observation of Ambroxol Combined with Naloxone in the Treatment of AECOPD with Respiratory Failure

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Keywords

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Abstract

Objective: This study aims to analyze the effects of ambroxol combined with naloxone in the treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients with respiratory failure. **Methods:** 100 patients with AECOPD complicated with respiratory failure admitted to our hospital from January 2020 to February 2021 were divided into a control group and an observation group by random number table method. Patients in both groups received conventional treatment combined with low-flow oxygen therapy. Control group patients were given naloxone on this basis, while observation group patients were additionally given ambroxol combined with naloxone. Lung function, blood gas index levels, immune function, inflammatory factor levels and adverse reactions were compared between the two groups. **Results:** After treatment, levels of forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), peak expiratory flow rate (PEF), arterial partial pressure of oxygen (PaO_2), $CD4^+$ and $CD4^+/CD8^+$ of patients in two groups were increased while partial pressure ($PaCO_2$) and $CD8^+$ levels were declined. Additionally, changes in these indexes were more apparent in the observation group than in the control group. C-reactive protein (CRP), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels of patients in both groups were sharply abated after treatment, and these levels in the observation group were lower than those in the control group. Adverse reactions of patients in both groups showed no significant difference. **Conclusion:** Ambroxol combined with naloxone and low-flow oxygen therapy safely improves lung function and immune function, regulates blood gas index levels and reduces the inflammatory response in AECOPD patients with respiratory failure.

1 Introduction

Studies have shown that chronic obstructive pulmonary disease (COPD) is susceptible to the influences of respiratory infections, respiratory muscle fatigue and airway obstruction and accordingly develops into acute exacerbation of COPD (AECOPD) [1]. AECOPD is commonly accompanied by respiratory failure and enjoys high mortality and morbidity rates [2]. Low-flow oxygen therapy is frequently adopted in the clinical treatment of AECOPD with respiratory failure and is important for hypoxia and dyspnoea relief [3]. However, the efficacy of this therapy is limited as long-term oxygen therapy will have negative impacts on the pharynx [3,4]. Therefore, it is necessary to improve oxygen therapy for the treatment and prognosis of patients. Naloxone plays a key role in correcting drug intoxication and respiratory depression and ambroxol, a sputum chemotherapeutic agent, is capable of regulating immune function and attenuating lung oxidative damage [5]. In this case, this study adopted ambroxol combined with naloxone for the treatment of AECOPD patients with respiratory failure and observed its clinical effects to provide insight into the clinical treatment of AECOPD patients combined with respiratory failure.

2 Materials and methods

2.1 Diagnosis criteria

A total of 100 AECOPD patients complicated with respiratory failure admitted to our hospital from January 2020 to February 2021 were divided into a control group (n = 50 cases) and an observation group (n = 50 cases). There was no significant difference between the general data of patients in the two groups (Table 1, $p > 0.05$). The study was approved by the Medical Ethics Committee and the written informed consent was signed by all study participants. Inclusion criteria: Patients meet the diagnostic criteria for AECOPD and respiratory failure in *Respiratory Medicine* [6]; Patients that can tolerate low-flow oxygen therapy; Patients with complete clinical data. Exclusion criteria: Patients with unstable hemodynamically; Patients that are allergic or intolerant to the medicines used in this study; Patients who need invasive mechanical ventilation.

Table 1 Comparison of general data between patients in the two groups.

Group	Cases	Gender (cases)		Age (years old)	Course of disease (years)	COPD classification (cases)	
		Male	Female			Moderate	Severe
Observation group	50	27	23	56.14 ± 7.57	3.48 ± 0.82	34	16
Control group	50	29	21	55.91 ± 7.62	3.53 ± 0.84	32	18
X^2/t		0.162		0.151	-0.302	0.178	
p		0.687		0.880	0.767	0.673	

2.2 Methods

Patients in both groups received conventional treatment including expectoration, asthma, anti-infection and correction of acid-base balance. Control group patients were additionally given low-flow oxygen inhalation treatment for consecutive 5 days (d) with the following settings: flow: 30 L/min, temperature: 34 ℃, oxygen flow: 1 L/min, oxygen concentration: 25%. On this basis, patients in the control group were given intravenous injection twice/d with 250 mL 0.9% sodium chloride solution containing 2 mg naloxone (specification: 1 mL : 1 mg, Beijing Yongkang Pharmaceutical Co., Ltd, State medical permitment number: H20059406). On the basis of treatment in the control group, observation group patients were given 250 mL 0.9% sodium chloride solution with 30 mg ambroxol intravenously, twice/d. Both groups were treated continuously for 5 d.

2.3 Observational indexes

2.3.1 Pulmonary function and blood gas indexes

Before and after treatment, an FMJ-10000 spirometer (Yuejian, Jiangsu, China) was used to assess the pulmonary function indexes (forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), peak expiratory flow rate (PEF) of patients in both groups. The arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2) of patients in two groups were detected by a BG-800 automatic blood gas analyzer (EFG, Shenzhen, China).

2.3.2 Immune function

The levels of $CD4^+$ and $CD8^+$ of patients in both groups were measured before and after treatment using a CytoFLEX flow cytometer (Beckman Coulter, Brea, CA, USA).

2.3.3 Inflammatory cytokines

Before and after treatment, 3 mL of fasting inferior venous blood from patients in both groups was collected in the early morning and levels of C-reactive protein (CRP), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were analyzed by enzyme-linked immunosorbent assay (ELISA).

2.3.4 Adverse reactions

Adverse reactions of patients in both groups were recorded.

2.4 Statistical analysis

The statistical analysis was performed using the SPSS 20.0. software, count data were compared using the x^2 test and measurement data were processed as the mean ± standard deviation. Differences between the two groups were assessed with an independent sample *t*-test and pre- and post-treatment comparisons were conducted using the paired sample *t*-test. Statistical significance was established at $p < 0.05$.

3 Results

3.1 Comparison of pulmonary function and blood gas indexes between patients in two groups

Before treatment, there was no significant difference between FVC, FEV_1, PEF, PaO_2 and $PaCO_2$ levels of patients in both groups ($p > 0.05$). After treatment, the levels of FVC, FEV_1, PEF and PaO_2 were notably upregulated while $PaCO_2$ level was downregulated in patients in two groups, and greater changes in these indexes were observed in the observation group, as compared with those in the control group (Table 2, $p < 0.05$).

3.2 Comparison of immune function between patients in two groups

Before treatment, no significant difference was observed in the levels of $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ between patients in two groups ($p > 0.05$). After treatment, the levels of $CD4^+$ and $CD4^+/CD8^+$ of patients in two groups all soared while $CD8^+$ level was declined, and changes in these indexes were more significant in the observation group than in the control group (Table 3, $p < 0.05$).

3.3 Comparison of inflammatory cytokine levels between patients in two groups

There was no significant difference in the levels of CRP, TNF-α and IL-6 of untreated patients between the two groups ($p > 0.05$). After treatment, the levels of CRP, TNF-α and IL-6 of two group patients were sharply abated, with those in the observation group lower than those in the control group (Table 4, $p < 0.05$).

3.4 Comparison of adverse reactions between patients in two groups

There was no significant difference in adverse reactions between patients in both groups (Table 5, $p > 0.05$).

Table 2 Comparison of pulmonary function and blood gas indexes between patients in two groups (mean ± standard deviation).

Observational indexes		Observation group (n = 50)	Control group (n = 50)	*t*	*p*
FVC (L)	Before treatment	2.64 ± 0.36	2.59 ± 0.38	0.675	0.501
	After treatment	3.34 ± 0.47 *	2.96 ± 0.41 *	4.308	0.000
FEV_1 (L)	Before treatment	1.81 ± 0.33	1.84 ± 0.35	-0.441	0.660
	After treatment	3.19 ± 0.56 *	2.72 ± 0.48 *	4.506	0.000
PEF (L/s)	Before treatment	3.62 ± 0.54	3.67 ± 0.59	-0.442	0.659
	After treatment	5.14 ± 0.66 *	4.58 ± 0.53 *	4.678	0.000
PaO_2 (mmHg)	Before treatment	53.93 ± 6.10	54.12 ± 6.86	-0.146	0.884
	After treatment	83.25 ± 7.35 *	76.62 ± 7.90 *	4.345	0.000
$PaCO_2$ (mmHg)	Before treatment	71.98 ± 8.42	71.65 ± 8.36	0.197	0.845
	After treatment	48.14 ± 6.39 *	52.66 ± 7.27 *	-3.302	0.001

* vs. pre-treatment: * $p < 0.05$.

Table 3 Comparison of immune function between patients in two groups (mean ± standard deviation).

Group	Cases	$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	50	30.51 ± 3.94	41.25 ± 4.71 *	33.89 ± 4.36	28.23 ± 3.14 *	0.98 ± 0.16	1.46 ± 0.37 *
Control group	50	30.67 ± 3.88	38.04 ± 4.64 *	33.48 ± 4.29	31.10 ± 3.53 *	0.96 ± 0.19	1.22 ± 0.32 *
t		-0.205	3.433	0.474	-4.296	0.569	3.469
p		0.838	0.001	0.637	0.000	0.570	0.001

* vs. pre-treatment: * $p < 0.05$.

Table 4 Comparison of inflammatory cytokine levels between patients in two groups (mean ± standard deviation).

Group	Cases	CRP (mg/L)		TNF-α (ng/L)		IL-6 (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	50	21.23 ± 6.17	9.57 ± 2.35 *	82.74 ± 12.59	41.89 ± 8.55 *	29.42 ± 7.07	14.36 ± 3.51 *
Control group	50	21.48 ± 6.52	14.44 ± 3.21 *	82.62 ± 13.82	56.62 ± 8.73 *	29.13 ± 7.11	18.43 ± 3.72 *
t		-0.197	-8.656	0.045	-8.524	0.205	-5.627
p		0.844	0.000	0.964	0.000	0.838	0.000

* vs. pre-treatment: * $p < 0.05$.

Table 5 Comparison of adverse reactions between patients in two groups [Cases (%)].

Group	Cases	Nauseating	Vomiting	Burning in the stomach	Indigestion	Restlessness	Incidence of adverse reactions
Observation group	50	1 (2.00)	2 (4.00)	1 (2.00)	2 (4.00)	0 (0.00)	6 (12.00)
Control group	50	2 (4.00)	2 (4.00)	0 (0.00)	1 (2.00)	2 (4.00)	7 (14.00)
X^2							0.088
p							0.766

4 Discussion

AECOPD is a severe and recurrent disease and untimely clinical intervention of it can lead to deteriorated lung function, CO_2 retention, and increased airway limitation, eventually causing respiratory failure as well as endangering the life and health of patients [7-9]. Naloxone is an opioid receptor antagonist that competitively antagonises β -endorphin-induced central respiratory depression, stimulates the central respiratory, promotes breathing and ventilation as well as relieves CO_2 retention and tissue hypoxia, so as to improve lung function [10]. Ambroxol is a respiratory chemotherapeutic drug that can improve lung function and regulate blood gas index levels by regulating secretory glandular mucus and plasma, increasing lung surface-active substance synthesis, reducing lung surface tension, and finally diluting or dissolving sputum [11,12]. In this study, patients in the control group were treated with naloxone and low-flow oxygen therapy, while patients in the observation group were given naloxone combined with ambroxol and low-flow oxygen treatment. The results revealed that the levels of FVC, FEV_1, PEF and PaO_2 in both groups were elevated after treatment while that of $PaCO_2$ was decreased. Moreover, changes in these indexes were more significant in the observation group than in the control group, indicating that ambroxol combined with naloxone and low-flow oxygen therapy can effectively improve lung function and regulate blood gas indexes in AECOPD patients with respiratory failure.

Clinical studies demonstrated that patients with AECOPD combined with respiratory failure have a low immune function, which is mainly due to reduced lung function and inflammatory infiltration of cells [13]. CRP, TNF-α and IL-6 are common inflammatory cytokines [13,14]. Of them, CRP is an acute-phase protein that reflects the systemic inflammatory response, TNF-α is secreted by macrophages, and IL-6 is produced by mast cells and neutrophils [13,14]. When tissue trauma or infection occurs in the body, TNF-α and IL-6 levels will increase abnormally, which aggravates the body's inflammatory response [13,14]. In this study, increased levels of $CD4^+$ T lymphocytes, and $CD4^+/CD8^+$ as well as decreased levels of $CD8^+$, CRP, TNF-α and IL-6 were observed in patients in both groups after treatment. In addition, more obvious changes in these indexes were found in the observation group as compared to the control group. This suggests that ambroxol combined with naloxone and low-flow oxygen therapy can effectively improve the immune function and alleviate the inflammatory response in AECOPD patients with respiratory failure. Ambroxol can attenuate the inflammatory response of the body by inhibiting the activation of nuclear transcription factor (NF- κ B) and the release of inflammatory factors such as IL-6 as well as antagonizing neutrophil activation [15]. Furthermore, ambroxol combined with naloxone exhibits synergistic effects on reducing the content of pro-inflammatory factors and enhancing the defence and immune function of the body. Besides, no significant difference in the adverse reactions between patients in the two groups was observed in this study, indicating the safety of ambroxol combined with naloxone as the adjuvant treatment for AECOPD patients with respiratory failure.

In conclusion, ambroxol combined with naloxone and low-flow oxygen therapy can safely improve lung function and immune function, regulate blood gas index levels and reduce the inflammatory response in AECOPD patients with respiratory failure.

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Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, J.G.; Data curation, J.Z.; Formal analysis, J.G.; Methodology, J.Z.; Writing-original draft, J.G.; Writing-review and editing, J.Z. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee and the written informed consent was signed by all study participants.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Materials

Not applicable.

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