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Original Research Article

Effect of non-invasive ventilator in combination with tiotropium bromide on pulmonary function and sleep quality of patients with chronic obstructive pulmonary disease complicated with obstructive sleep apnea-hypopnea syndrome

Dongli Liu[1], Xiaolong He[2], Jianquan Gao[1], Qiangqiang Luan[1], Yanling Du[1]*
[1]Department of Respiratory and Critical Medicine, [2]Department of ICU Medicine, Yan'an Traditional Chinese Medicine Hospital, Yan'an 716000, Shanxi Province, China

For correspondence: **Email: djhb77@163.com; **Tel:** +86 13892163668*

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Abstract

Purpose: *To study the influence of non-invasive ventilator and tiotropium bromide on pulmonary function and sleep quality of patients with chronic obstructive pulmonary disease (COPD) combined with obstructive sleep apnea-hypopnea syndrome (OSAHS).*
Methods: *One hundred and twenty patients with COPD-OSAHS were selected and randomly assigned to control group (CG) and treatment group (TG), with 60 subjects in each group. Non-invasive ventilator therapy was used in both groups, based on conventional therapy, while tiotropium bromide was added in TG. Treatment effectiveness in the two groups was evaluated and compared.*
Results: *Total effectiveness was significantly higher in TG than in CG. Post-therapy arterial oxygen saturation (SaO_2) and oxygen partial pressure (PaO_2) were increased, while partial pressure of carbon dioxide ($PaCO_2$) and lactic acid (Lac) were decreased in both groups ($p < 0.05$). Post-treatment values of indices of lung function, viz, forced expiratory volume (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were higher than the corresponding pre-treatment levels, and also values were significantly higher in TG than in CG ($p < 0.05$). Average sleep time, apnea and hypopnea index (AHI) and mechanical ventilation time of TG were less than those of CG. There were lower levels of C-reactive protein (CRP), procalcitonin (PCT) and interleukin-17 (IL-17) in TG than in CG. During the treatment, no obvious adverse reaction was seen in both groups.*
Conclusion: *Non-invasive ventilator, in combination with tiotropium bromide, is more effective in the treatment of COPD-OSAHS than the use of non-invasive ventilator alone. However, further clinical trials are required before its adoption in clinical practice.*

Keywords: *Chronic obstructive pulmonary disease (COPD), Obstructive sleep apnea-hypopnea syndrome (OSAHS), Tiotropium bromide, Noninvasive ventilator*

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INTRODUCTION

It has been reported that chronic obstructive pulmonary disease (COPD) occurs in about 200 million people worldwide, with incidence as high as 9-10 % in people over 40 years old [1-4]. It is a chronic respiratory inflammatory disease that seriously endangers human health. If poorly controlled, COPD easily deteriorates into COPD complicated with obstructive sleep apnea-hypopnea syndrome, that is, COPD-OSAHS overlap syndrome. Currently, the conventional treatment approaches mostly involve low flow oxygen inhalation, respiratory function exercise and asthma relief. However, the effects of these treatments on some patients remain unsatisfactory. Although non-invasive ventilator produces some benefits in the treatment of COPD-OSAHS, the use of non-invasive ventilator alone is not enough, especially with increase in the incidence of the disease. Therefore, there is need to explore new ways to treat this disease [5-7]. Tiotropium bromide is a new type of long-acting anticholinergic drug which produces effects such as dilation of the airway, inhibition of tension of cholinergic nerve, inhibition of airway mucosal secretion, and anti-inflammation. Therefore, it is recommended as a top treatment choice in the multi-national COPD guidelines. However, there is still a deficiency of clinical studies regarding the effect of tiotropium bromide in COPD-OSAHS patients. Therefore, in this study, the effect of tiotropium bromide on COPD-OSAHS patients was investigated in order to improve the treatment effectiveness of the disease.

METHODS

Patient profile

The chosen research subjects were COPD-OSAHS patients treated in our hospital from December, 2019 to December, 2020.

Ethical approval

This research received approval from the ethical committee of Yan'an Traditional Chinese Medicine Hospital (approval no. 20191004), and was carried out in line with the guidelines of Helsinki Declaration of Helsinki [8]. Patients and their families knew about the details of the research, and signed informed consent form.

Inclusion criteria

The included subjects were patients who satisfied the diagnostic criteria of COPD-OSAHS formulated by the Chinese Society of Respiratory Diseases, patients with high treatment compliance and good cooperation with regular follow-up, and patients with no contraindications to non-invasive ventilator.

Exclusion criteria

Subjects who were allergic to tiotropium bromide, patients with complications of cardiomyopathy or liver disease, patients suffering from tuberculosis, lung tumor, asthma and other lung diseases, patients with liver and kidney dysfunction, patients with a history of respiratory tract infection within six weeks before enrollment, and those with pregnancy or lactation, were not included.

Through pulmonary function examination, COPD may be diagnosed when the ratio of FEV1 to FVC is less than 70% following inhalation of bronchodilator. In 2014, the World Health Organization (WHO) classified GOLD grades according to the degree of airflow limitation, that is, grade I (FEV1≥ 80 % of the expected value), grade II (50 % ≤ FEV1 < 80 % of the expected value), grade III (30%≤ FEV1 < 50 % of the expected value), and grade IV (FEV1< 30%). Based on *Guidelines for Diagnosis and Treatment of OSAHS (Draft)* issued by the Chinese Society of Respiratory Diseases [9], OSAHS was confirmed when apnea hypopnea index (AHI) was more than 5 times/h: 5 ≤ AHI ≤ 20 was mild, 20 ≤ AHI ≤ 40 was moderate, and AHI ≥ 40 was severe.

Based on inclusion and exclusion criteria, 120 patients were equally and randomly assigned to CG and TG using the digital table method. Non-invasive ventilator therapy was used in both groups, based on conventional therapy, while tiotropium bromide was added in TG. There were no significant differences in baseline data such as gender, age and GOLD grades between the two groups ($p > 0.05$).

Treatments

All patients received conventional treatment including diet control, weight loss, low-flow oxygen inhalation, functional exercise, asthma treatment, and antibiotics. If necessary, glucocorticoids were inhaled to replace the use of expectorants, antitussive drugs and immunomodulatory drugs [10,11]. The control group received bi-level positive airway pressure (BiPAP) ventilation with ResMed ventilator for conventional treatment.

Table 1: Comparison of baseline data (n = 60)

Index	CG	TG	t/ χ^2	*P*-value
Gender(male/female)	36/24	38/22	0.1410	0.707
Age (years)	56.84±7.14	58.37±7.52	1.1429	0.2554
BMI （kg/m^2）	23.89±2.14	24.35±2.38	1.1133	0.2679
Disease course (years)	8.12±2.36	8.43±2.44	0.7074	0.4807
Smoking history	43 （71.67）	39 （65）	0.6162	0.432
GOLD grade**s**			0.0333	0.855
Ⅱ	30 （50）	29 （48.33）		
Ⅲ	23 （38.33）	23 （38.33）		
Ⅳ	7 （11.67）	8 （13.33）		
Comorbidities			0.3419	0.559
Diabetes	21 （35）	18 （30）		
Hypertension	21 （35）	24 （40）		
Coronary heart disease (CHD**)**	18 （30）	18 （30）		

In addition to the treatment in CG, the TG daily inhaled 18 μg of tiotropium bromide (specification: 18 μg; manufacturer: Boehringer Ingelheim, Germany; approval No. H20140954). Both groups received treatment for 12 weeks.

Assessment of clinical indices

Treatment effectiveness (TE)

Clinical efficacy was evaluated based on results of lung function indicator FEV1. If the FEV1 level was increased by more than 20 %, the treatment was markedly effective. Treatment was effective if the FEV1 level increased by 10 - 20 %, and ineffective if the FEV1 level increased by less than 10% or if FEV1 actually decreased. TE was calculated as in Eq 1.

TE (%) = [(ME + E)/T] x 100 .....(1)

where *TE* = Total effectiveness; *ME* = number of markedly effective cases; *E* = number of effective cases, and *T* = total number of cases.

Blood gas

Before and after treatment, fasting arterial blood was obtained in the morning, and a blood gas analyzer (model: GEM Premier3000) was used to measure indicators such as arterial oxygen saturation (SaO_2), partial pressure of carbon dioxide ($PaCO_2$), oxygen partial pressure (PaO_2) and lactic acid (Lac), with normal reference values of blood gas indicators as references: SaO_2 (95-98 %), $PaCO_2$ (35-45 mmHg); $PaCO_2$ (80-110 mmHg), and Lac (0.5-1.5 mmol/L).

Pulmonary function

An automatic pulmonary function detector was used to measure FEV1, FVC and FEV1/FVC ratio, before and after treatment. The reference range of FEV1/FVC was > 70%. If FEV1/FVC was < 70% after bronchodilators were used, persistent airflow limitation occurred.

Inflammatory factors

Five (5) ml of peripheral vein blood from each subject was centrifuged at 3000 rpm for 10 min. The supernatant was kept frozen at -80 °C prior to analysis. C-Reactive protein (CRP) and IL-17 were assayed with ELISA, while procalcitonin (PCT) was measured using double-antibody sandwich immunochemiluminometric assay (ILMA).

Other indicators and adverse reactions

Mean sleep time, AHI index, mechanical ventilation time and adverse reactions during treatment were recorded in both groups.

Statistical analysis

In this study, the data were processed using SPSS20.0, while GraphPad Prism7 was used to draw pictures for the data. Measurement results are presented as mean ± SD, while counted data are expressed as numbers and percentages [n (%)]. Comparison was done using chi squared test and *t*-test. Values of $p < 0.05$ indicated significance.

RESULTS

Clinical efficacy

Table 2 shows that total treatment effectiveness was significantly higher in TG than in CG ($p < 0.05$).

Table 2: Clinical treatment effectiveness in each CG and TG [n (%)]

Group	Ineffective	Effective	Markedly effective	Total effectiveness
CG	9(15)	26(43.33)	25(41.67)	51(85.00)
TG	1(1.67)	24(40.00)	35(58.33)	59(98.33)
t				6.9818
P-value				0.008

Table 3: Levels of blood gas indices (mean ± SD)

Index		CG (n=60)	TG (n=60)	t	*P*-value
SaO_2 (%)	Before treatment	79.21±5.76	79.19±5.82		
	After treatment	90.21±6.19	95.86±5.61	5.238	0.000
$PaCO_2$ (kPa)	Before treatment	10.26±0.80	10.31±0.74		
	After treatment	7.85±0.63	6.33±0.67	12.802	0.000
PaO_2 (kPa)	Before treatment	6.78±0.79	6.64±0.77		
	After treatment	10.02±0.51	11.65±0.63	15.576	0.000
Lac (mmol/L)	Before treatment	4.33±0.71	4.35±0.68		
	After treatment	2.81±0.55	1.33±0.42	16.565	0.000

Table 4: Pulmonary function indexes in Cg and TG (mean ± SD)

Index		CG	TG	*t*	*P*-value
FEV1 (L)	Before treatment	46.49±3.52	46.33±3.48		
	After treatment	66.57±6.41	76.66±5.38	9.3394	0.000
FVC (L)	Before treatment	1.58±0.29	1.62±0.54		
	After treatment	1.95±0.37	2.68±0.46	9.1849	0.000
FEV1/FVC (%)	Before treatment	42.37±3.14	42.47±3.01		
	Before treatment	65.84±5.64	78.06±6.29	11.2041	0.000

Table 5: Comparison of sleep time, AHI index and mechanical ventilation time (mean ± SD, n = 60)

Group	Sleep time (h)	AHI index	Mechanical ventilation time (days)
CG	10.22±4.09	21.25±4.52	8.35±2.15
TG	7.18±3.14	11.37±3.16	5.31±1.36
t	4.5668	13.8766	9.2561
P-value	0.000	0.000	0.000

Blood gas indices

After treatment in both groups, SaO_2 and PaO_2 indices were increased, while $PaCO_2$ and Lac indexes were decreased. There were significant post-treatment differences in the various indexes between the two groups ($p < 0.05$).

Pulmonary function indices

After treatment, FEV1, FVC and FEV1/FVC (pulmonary function indexes) in CG and TG were markedly increased, with significantly higher indexes in TG.

Sleep time, AHI index and mechanical ventilation time

Average sleep time, AHI index and mechanical ventilation time were markedly low, relative to CG.

Comparison of levels of inflammatory factors

After treatment, CRP, PCT and IL-17 in both groups were decreased, but were markedly lower in TG.

Adverse reactions

There were no obvious adverse reactions in both groups during the treatment.

DISCUSSION

Clinical studies show that OSAHS is complicated with COPD in about 10 % of patients, while 50 % of patients with moderate and severe COPD have OSAHS complication [12-15]. In recent years, with advancements in social economy, the incidence of COPD-OSAHS has significantly increased due to environmental pollution, smoking, obesity, and unbalanced diet.

Table 6: Levels of inflammatory factors (mean ± SD)

Index		CG	TG	t	*P*-value
CRP （mg/L）	Before treatment	44.97±9.06	45.34±8.71		
	After treatment	15.62±2.89	9.18±2.11	13.9407	0.000
PCT （ng/ml）	Before treatment	8.95±1.43	8.86±1.35		
	After treatment	3.39±0.91	1.58±0.78	11.6977	0.000
IL-17 （pg/ml）	Before treatment	92.57±24.81	92.48±25.66		
	After treatment	51.40±17.65	36.68±11.34	5.4350	0.000

It has been confirmed that OSAHS is a common and potentially life-threatening disease. When AHI index is above 20, the 10-year mortality may reach 38 %. Without effective treatment, the 5-year mortality may reach 6 – 13 % [16-19]. So far, studies have found that COPD-OSAHS causes higher hypoxia during sleep than single disease (COPD or OSAHS), and severe hypoxia damages pulmonary vascular endothelial function, which further leads to pulmonary hypertension. In addition, continuous hypertension results in pulmonary heart disease, which is more serious in patients with COPD-OSAHS than in those with single disease [20-22].

Non-invasive ventilation, an emerging technique, helps patients relieve pressure on the respiratory muscles, reduces intubation rate, and cuts down the incidence of invasive complications. Although non-invasive ventilation relieves patients' hypoxia, it does not inhibit glandular secretion and expectoration. Therefore, the use of non-invasive ventilation alone does not produce obvious effects. Tiotropium bromide, a long-term anticholinergic drug, is often used in the treatment of COPD to relax airway smooth muscles and reduce resistance during pulmonary ventilation.

Moreover, it has been reported that long-term use of tiotropium bromide markedly reduced frequency of cough, dyspnea and expectoration, decreased the frequency of COPD attack and clinical death, and improved exercise tolerance [23]. Tiotropium bromide has been the first-line medication in the treatment of COPD, but its clinical efficacy in the treatment of OSAHS has not been ascertained.

In this study, 120 COPD-OSAHS patients were selected to investigate the clinical effect of tiotropium bromide. It was found that there was markedly higher total treatment effectiveness in the TG than in CG. This demonstrates that the curative effect of tiotropium bromide on COPD-OSAHS is of high value. Current research has demonstrated that the frequency of hypoxia in COPD-OSAHS patients is much higher than that of any other symptom attributed to airway obstruction, reduced alveolar oxygen reserve and low ventilation in COPD. Furthermore, OSAHS patients present decreased cardiac output, respiratory muscle fatigue and inhibited respiratory central chemoreceptor. At the same time, compared with OSAHS subjects, patients with COPD-OSAHS overlap syndrome are more prone to sleep apnea, which is consistent with the report of Marra *et al* [24].

In this study, tiotropium bromide was added to the treatment in the TG. It was found that the SaO_2 and PaO_2 of both groups were increased, while $PaCO_2$ and Lac were decreased, with significant differences between the two groups after treatment. These results indicate that tiotropium bromide effectively relieved hypoxia and alleviated carbon dioxide retention. Furthermore, this study examined the pulmonary functions of patients before and after treatment. It was found that after treatment, pulmonary function indexes i.e., FEV1, FVC and FEV1/FVC in both groups were higher than those before treatment, with significantly higher values in TG than in CG, indicating that tiotropium bromide effectively optimized pulmonary function.

In addition, the average sleep time, AHI index, mechanical ventilation time, and levels of CRP, PCT and IL-17 were lower in TG than in CG. No obvious adverse reaction was found in both groups during the treatment, showing that tiotropium bromide improved the sleep quality and reduced inflammatory reactions, which may be part of the mechanisms involved in improving the airway function of patients. Moreover, tiotropium bromide is safe.

The cause of apnea and hypopnea is airflow limitation. There are many reasons for airflow limitation in COPD-OSAHS patients, but the main reason is abnormal rise in cholinergic nerve tension. Tiotropium bromide is a long-acting M-cholinoceptor-blocking drug. It acts by competitively binding M_1 choline receptor and M_3 choline receptor on bronchial smooth muscle, thereby exerting an antagonistic effect. Therefore, long-term inhalation of tiotropium bromide significantly dilates the bronchus, improves damaged pulmonary function, and reduced various symptoms.

CONCLUSION

Non-invasive ventilator, in combination with tiotropium bromide, significantly mitigates adverse symptoms in patients with COPD-OSAHS, reduces inflammatory response, improves lung function and respiratory status, and significantly enhances treatment efficacy, thereby boosting the sleep quality of patients. Therefore, the combined therapy may be used as an effective treatment for COPD-OSAHS. However, further clinical trials are required before its adoption in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest 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. Dongli Liu conceived and designed the study, and drafted the manuscript. Xiaolong He and Jianquan Gao collected, analyzed and interpreted the experimental data. Qiangqiang Luan and Yanling Du revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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