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Original Research Article

Efficacy of triple therapy inhalers in acute exacerbations of chronic obstructive pulmonary disease

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Abstract

Purpose: *To evaluate the efficacy of triple inhaled therapy, a combination of inhaled glucocorticoids, long-acting muscarinic antagonists, and long-acting β2 agonists in managing acute exacerbations of chronic obstructive pulmonary disease (COPD).*
Methods: *Medical data of 100 patients with acute exacerbation of COPD admitted to Shaoxing Second Hospital, Shaoxing, China between January 2020 to December 2022 was collected and retrospectively analyzed. The patients were randomized into control (n = 50) and study groups (n = 50). Control group received budesonide/formoterol inhalers while the study group received triple inhaled therapy (budesonide/glycopyrronium/formoterol inhalers). Arterial blood gas, pulmonary function, immune function, adverse effects, and efficacy were evaluated.*
Results: *The study group exhibited significantly higher pH, partial pressure of arterial oxygen (PaO_2), and lower partial pressure of carbon dioxide ($PaCO_2$) compared to control group ($p < 0.001$). Furthermore, the study group showed significantly higher levels of pulmonary function and immune function indices compared to control group ($p < 0.001$). There was no significant difference in incidence of adverse reactions between the two groups ($p > 0.05$). The study group was associated with higher clinical efficacy compared to the control group ($p < 0.05$).*
Conclusion: *Triple inhaled therapy significantly alleviates the clinical symptoms of patients with COPD and enhances pulmonary and immune functions. Future studies should cover a larger and more diverse group of participants for broader validity.*

Keywords: *Triple inhaled therapy, COPD, Acute exacerbation, Budesonide, Glycopyrronium bromide, Formoterol inhaler*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common clinical condition with the third highest mortality worldwide. This disease increases pulmonary airway resistance and disrupts gas exchange, resulting in long-term chronic hypoxia. The underlying etiology of COPD remains poorly understood, and currently, there are no highly effective targeted drugs available for clinical use, posing an extremely serious threat to life and health [1-3]. The standard pharmacological treatment for COPD typically involves a combination of inhaled glucocorticoids and long-acting β2 agonists [4].

Several studies have shown that budesonide and formoterol inhalers can enhance respiratory function, reduce the release of inflammatory mediators, and improve lung function in patients with COPD within a short time [5]. Previous studies have demonstrated that triple-inhaled therapy with glucocorticoids, long-acting muscarinic antagonists (LAMA) and long-acting β2 agonists (LABA) reduces the risk of acute exacerbations of COPD [6]. Thus, this present study was aimed at evaluating the efficacy of triple inhaled therapy (budesonide/glycopyrronium bromide/formoterol inhalers) in managing acute exacerbation of COPD.

METHODS

Patient characteristics

Medical data of 100 patients with acute exacerbations of COPD admitted to Shaoxing Second Hospital, Shaoxing, China between January 2020 to December 2022 were collected and retrospectively analyzed. The patients were randomized equally into study and control groups. Study group received triple inhaled therapy comprising of budesonide/glycopyrronium bromide/formoterol while control group received a combination of budesonide and formoterol inhalers. This study was approved by the ethics committee of Shaoxing Second Hospital Medical Community General Hospital (approval no. 2024-028) and complied with the Declaration of Helsinki [7].

Inclusion criteria

Patients who met the diagnostic criteria in the 2001 Guidelines for the Diagnosis and Management of COPD developed by Barber *et al* [8], history of at least one acute exacerbation of COPD in the previous year, and who were fully informed about the study procedures and signed the informed consent form.

Exclusion criteria

Patients with other serious organ diseases, psychiatric problems that interfere with normal communication, patients at risk of inhalation, diagnosed with asthma, patients with poor compliance, and contraindications or allergies to the study medications.

Treatments

After admission, patients in both groups were treated with anti-infective treatment, expectorants oxygen support, and nebulized terbutaline hydrochloride solution (1 mL twice daily). During this period, routine physiological data, such as blood pressure, heart rate, pulse rate, and oxygen saturation, were closely monitored. Adverse symptoms were resolved promptly, and oxygen saturation was maintained at > 90 %. Control group received 2 mg budesonide/formoterol inhalers (2 puffs) twice daily while study group received budesonide/glycopyrronium /formoterol inhalers (2 puffs) twice daily. The drug was administered solely via transoral inhalation. In case of a missed dose, it was important to replenish it as soon as possible and follow the regular medication schedule for the next dose. Double doses were not allowed to compensate for missed doses. Patients in both groups were treated for 20 days.

Evaluation of parameters/indices

Arterial blood gas indices

The pH, arterial oxygen partial pressure (PaO_2), and carbon dioxide partial pressure ($PaCO_2$) were measured using a GEM3000 blood gas analyzer (Beckman, USA, Food & Drug Administration, 2008, No. 2401894), and values were compared before and after treatment in both groups.

Pulmonary function

Forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC were measured using an FGC-A+ pulmonary function tester (Anhui Institute of Electronic Science, Anhui Machinery Note approval no. 20172210164), and values compared before and after treatment in both groups.

Immune function

The T-lymphocyte (CD3+, CD4+, CD4+/CD8+) were compared before and after treatment using a flow cytometer (Eisen Bio Hangzhou Co., Ltd., Zhejiang Food and Drug Administration Arms Quorum 2014 no. 2400581).

Adverse effects

Adverse reactions including dry and bitter throat, dry nose and diarrhea, were observed. The number of patients experiencing adverse reactions was recorded to calculate the ARR.

Overall efficacy

Efficacy was classified as markedly effective (clinical symptoms and coughing frequency were

significantly reduced, as well as dyspnea and other phenomena); effective (clinical symptoms, coughing frequency and dyspnea were reduced); ineffective (a state that did not meet the above criteria).

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS version 20.0, IBM, Armonk, NY, USA), and Graph Pad Prism 7 (GraphPad Software, San Diego, USA) was employed to generate the required visualizations. Measurement data were expressed as mean ± standard deviation (SD) and compared using t-test. Count data were expressed as frequency and percentages (%) and compared using the chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

There were no significant differences in baseline characteristics of the patients in both groups ($p > 0.05$; Table 1).

Arterial blood gas

Study group exhibited significantly higher pH values and PaO_2 and lower $PaCO_2$ compared to control group ($p < 0.001$; Table 2).

Pulmonary function

Patients with triple therapy inhalers had significantly higher levels of pulmonary function compared to control group ($p < 0.001$; Table 3).

Table 1: Baseline characteristics (n = 50 in each group)

Group	Study group	Control group	X^2/t	*P*-value
Sex			0.034	0.855
Male	33	22		
Female	17	18		
Age (years)				
Range	44-74	43-74		
Mean age	65.21±12.24	65.22±12.58	0.004	0.997
Heart rate	124.20±15.21	124.52±15.89	0.113	0.911
Diabetes	32	30	0.223	0.637
Hypertension	11	12	0.086	0.769
Coronary heart disease	7	8	0.076	0.783
Duration of disease (years)				
Range	3-21	3-20		
Mean duration of disease	7.25±0.89	7.32±0.57	0.513	0.609

Some values are expressed as mean ± standard deviation

Table 2: Arterial blood gas (n = 50)

Parameter	Group			
	Study		***Control***	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*
pH	7.20±0.21	7.42±0.12*	7.21±0.20	7.29±0.13**
PaO_2 (mmHg)	53.12±14.23	83.88±15.41*	53.22±14.56	70.21±14.23**
$PaCO_2$ (mmHg)	80.12±11.24	55.24±9.80*	80.13±11.25	65.12±9.82**

*$P < 0.05$ vs before treatment, **$p < 0.05$ vs study group. Values are presented as mean ± SD

Table 3: Pulmonary function (n = 50)

Parameter	Group			
	Study		***Control***	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*
FEV_1 (L)	1.11±0.12	1.81±0.15*	1.12±0.13	1.65±0.14**
FVC (L)	2.01±0.15	2.41±0.12*	2.02±0.12	2.19±0.14**
FEV_1/FVC (%)	55.45±3.59	79.12±5.32*	55.46±3.60	72.56±5.46**

*$P < 0.05$ vs before treatment, **$p < 0.05$ vs study group. Values are presented as mean ± SD. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC)

Immune function

Study group showed significantly higher levels of CD4+/CD8+, CD3+ and CD4+ compared to control group ($p < 0.001$; Figure 1).

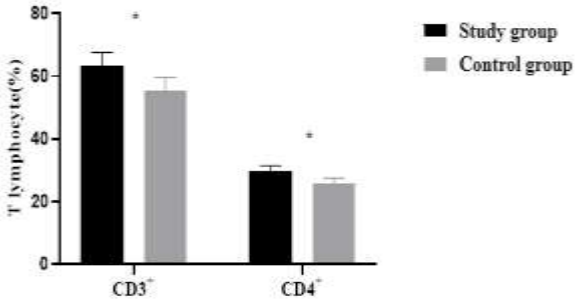

Figure 1: Immune function Note: *$P < 0.001$ vs study group

Adverse effects

In the study group, there was 1 case (1.7 %) of dry and bitter throat, 1 case (1.7 %) of dry nose, and 2 cases (3.3 %) of diarrhea, with an ARR of 6.7 %. In the control group, there were 3 cases of dry and bitter throat (5.0 %), 1 case of dry nose (1.7 %), and 2 cases of diarrhea (3.3 %), with an ARR of 10 %. There was no significant difference in adverse reaction rate (ARR) between study and control groups ($P = 0.509$, Figure 2).

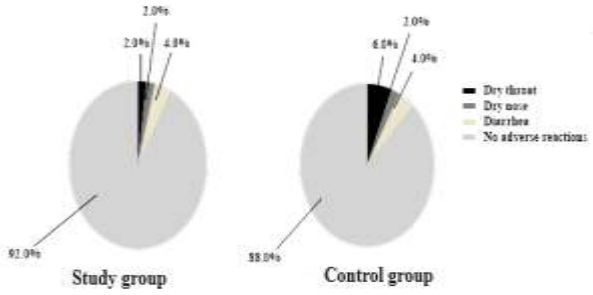

Figure 2: Adverse reaction rate n (%)

Clinical efficacy

Study group was associated with a higher clinical efficacy compared to control group ($p < 0.05$; Table 4).

DISCUSSION

Patients with COPD frequently experience symptoms of hypoxia, malnutrition, and immune deficiency, with severe diaphragmatic fatigue, further worsening pulmonary dysfunction. Therefore, symptom management, risk reduction, and improvement of body function are paramount in managing patients with acute exacerbations of COPD [9-12]. Dual therapy with LABA and glucocorticoids are conventional drugs for COPD treatment with antispasmodic and broncho-dilating effects, which enhance short-term respiratory function. However, long-term maintenance therapy leads to poor disease control, mild deterioration, and poor patient compliance. Long-acting muscarinic antagonist (LAMA), such as inhaled glycopyrronium bromide, binds to muscarinic receptors with high affinity and features an extended dissociation curve. This agent brings about long-term bronchial dilation in patients with COPD, further enhancing immune capacity and tolerance to hypoxia. The efficiency of triple inhaled therapy outperforms the two-drug combination [13-16].

In this study, improvement in pulmonary function indices (FEV1, FVC, and FEV1/FVC) in study group was significantly higher after treatment compared to control group. It therefore indicates that budesonide, glycopyrronium and formoterol effectively improve lung function and circulation capacity. As a result, hypoxia and carbon dioxide retention were more effectively reduced, leading to significantly better arterial blood gas in study group compared to control group after treatment. Clinical trials have shown that budesonide/glycopyrronium/formoterol triple therapy reduced the incidence of acute exacerbations in moderate and even severe COPD, prolonged duration of exacerbations, improved lung function, symptom relief, and quality of life [5,16]. These findings were consistent with the results of the present study. In addition, COPD is associated with an increase in the frequency of anaerobic enzymes in T-lymphocytes, leading to immune dysfunction and increased risk of infection.

Table 4: Clinical efficacy n (%)

Group	Markedly effective	Effective	Ineffective	Total efficacy
Study	23(46.0)	25(50.0)	2(4.0)	48(96.0)
Control	13(26.0)	27(54.0)	10(20.0)	40(80.0)
χ^2	3.525	0.134	5.926	5.926
P-value	0.060	0.715	0.015	0.015

Therefore, enhancement of immune function may provide prognostic benefits for patients [17-19]. In this study, immune function in study group was significantly higher compared to control group ($p < 0.001$). This suggested that triple-inhaled therapy enhances immune function in patients with COPD, prevents further disease deterioration, inhibits aggregation of inflammatory cells, and exerts anti-inflammatory effects. Previous studies have revealed that the combination of these three drugs enhances immune function [20], which is in tandem with this study. In addition, studies have shown that more than 70 % of COPD patients treated with a combination of budesonide, glycopyrronium and formoterol inhalers experienced no acute exacerbations within 1 year. Hence, the Global Initiative for COPD has recommended maintenance therapy with triple inhaled therapy for severe and extremely severe COPD. However, given the complexity of COPD management, which often involves frequent episodes, the choice of treatment should be based on the patient's clinical symptoms, habits, preferences, and inhaler characteristics. Rational selection of triple-inhaled therapy improves clinical efficacy while ensuring drug safety and patient tolerability.

Limitations of this study

Limitations of this study include a potentially limited sample size and the absence of long-term follow-up, which significantly impact the validity of the findings. It is crucial to conduct longitudinal studies over extended periods to evaluate the long-term efficacy and safety of triple inhaled therapy in COPD management.

CONCLUSION

Triple-inhaled therapy comprising budesonide, glycopyrronium and formoterol enhances pulmonary function, and improves immune responses, with lower incidence of adverse effects and higher efficacy. These findings provide valuable insights into the potential of triple-inhaled therapy as a comprehensive treatment approach that addresses both respiratory symptoms and underlying immune challenges in COPD patients. Future studies should cover a larger and more diverse group of participants, to ensure that the findings are more representative.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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. WW conceived and designed the study, and drafted the manuscript. HT collected, analyzed and interpreted the experimental data. Both authors revised the manuscript for important intellectual content. Both authors read and approved the final manuscript for publication.

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