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Effects of Salmeterol-Fluticasone Combined with Treprostinil on Blood Gas Indices and Inflammatory Factors in Patients with COPD Complicated with Severe Pulmonary Hypertension

Xiangchao Kong [1], Hengchao Zhang [1,*]

[1.] The Third People's Hospital of Deqing, No. 1 Jimin Road, Xinshi Town, Deqing County, 313201 Huzhou, Zhejiang, China

Keywords

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* **Correspondence**

Hengchao Zhang

The Third People's Hospital of Deqing, No. 1 Jimin Road, Xinshi Town, Deqing County, 313201 Huzhou, Zhejiang, China

E-mail: 740109209@qq.com

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Abstract

Background: To analyze the effects of Salmeterol-Fluticasone combined with treprostol on blood gas indexes and inflammatory factors in patients with chronic obstructive pulmonary disease (COPD) complicated with severe pulmonary hypertension. **Methods:** A total of 108 patients with COPD complicated with severe pulmonary hypertension admitted to our hospital from May 2019 to April 2022 were selected and divided into control group and study group by random number table method, with 54 cases in each group. Both groups were given low flow oxygen therapy, the control group was given treprostinil, and the observation group was given Salmeterol-Fluticasone and treprostinil. The clinical efficacy, blood gas index, serum factor level and incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total clinical effective rate of observation group was significantly higher than that of control group. Compared with those before treatment, arterial partial pressure of oxygen (PaO_2) and blood oxygen saturation (SaO_2) levels in two groups after treatment were significantly increased, and the levels of PaO_2 and SaO_2 in observation group were significantly higher than those in the control group ($p < 0.05$). Compared with those before treatment, the levels of arterial blood partial pressure of carbon dioxide ($PaCO_2$), serum matrix metalloproteinase-9 (MMP-9), C-reactive protein (CRP) and tumor necrosis factor (TNF-α) in two groups after treatment were significantly decreased, and the levels in the observation group were significantly lower than those in the control group ($p < 0.05$). There was no significant difference in the incidence of adverse reactions between two groups ($p > 0.05$). **Conclusion:** Salmeterol-Fluticasone combined with treprostinil has excellent efficacy in the treatment of COPD patients with severe pulmonary hypertension, which can not only effectively improve the hypoxia of patients, but also help to relieve the inflammatory response of the body, and has a high safety.

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disease caused by recurrent attacks of chronic bronchitis. Due to the long-term hypoxic condition of the body, the fibromuscular endothelium of COPD patients is thickened and the smooth muscle of small pulmonary arteries and arterial mesothelium is continuously increased, which leads to a continuous increase in pulmonary artery pressure, and patients often show symptoms such as exertional dyspnea, palpitations, shortness of breath and weakness [1]. To improve the clinical symptoms of patients with COPD complicated with severe pulmonary hypertension, long-term oxygen therapy, pulmonary vasodilators, endothelin receptor antagonists and other drugs are often used for clinical treatment [2]. Treprostinil is a common vasodilator, which not only can relax the systemic arterial blood vessels, but also has the effect of inhibiting the proliferation of smooth muscle cells. However, occasionally, patients suffer from headache, nausea, diarrhea, abdominal pain and other adverse effects after taking this drug [3]. Salmeterol-Fluticasone has the dual effect of relieving bronchospasm and anti-inflammation, and is commonly used clinically to relieve some symptoms such as coughing, phlegm, dyspnea, and oppression in chest [4]. At present, there are relatively few clinical studies on the use of Salmeterol-Fluticasone combined with treprostinil in COPD patients with severe pulmonary hypertension. Therefore, this study explores the clinical efficacy of Salmeterol-Fluticasone in combination with treprostinil in the treatment of COPD patients with severe pulmonary hypertension, thus looking for a reliable method to improve the clinical outcome of patients with this disease. Now, the results of the study are reported as follows.

2 Data and methods

2.1 General data

108 COPD patients complicated with severe pulmonary hypertension admitted to our hospital from May 2019 to April 2022 were selected and randomly divided into control group and observation group, with 54 cases in each group. The study was approved by Ethics Committee of our hospital and the written informed consent was taken from all the patients. There was no statistical significance in general data between the two groups ($p > 0.05$), which were comparable, as shown in Table 1.

Table 1 Comparison of general data between observation group and control group.

Groups	Cases	Sex (M/F)	Age (year)	Course of disease (year)	mPAP (mmHg)
Observation	54	28/26	66.58 ± 5.55	8.32 ± 2.23	48.69 ± 7.36
Control	54	27/27	67.08 ± 5.38	8.36 ± 2.34	48.15 ± 7.19
Statistical values		0.037	0.475	0.090	0.386
p		0.847	0.636	0.923	0.701

2.2 Inclusion criteria

(1) Patients who met the diagnostic criteria for COPD in *Guideline for Primary Care of Chronic Obstructive Pulmonary Disease: Practice Version (2018)* [5]. (2) Patients who met the diagnostic criteria for severe pulmonary hypertension in *Expert Consensus on the Screening, Diagnosis and Treatment of Pulmonary Hypertension* [6].

2.3 Exclusion criteria

(1) Patients with other respiratory system diseases. (2) Patients with other diseases causing severe pulmonary hypertension. (3) Patients allergic to Salmeterol-Fluticasone and treprostinil. (4) Patients in pregnancy or lactation.

2.4 Therapeutic methods

Two groups of patients were treated with administration of low flow oxygen. Additionally, the control group was given treprostinil injection (Specification: 20 mL; 20 mg; National Medicine Permit No. H20203101; Manufacturer: Zhaoke Pharmaceutical (Hefei) Co., Ltd.) by subcutaneous infusion pump, at an initial dose of 0.625 $ng \cdot kg^{-1} \cdot min^{-1}$ per day according to the patient's weight, which was adjusted according to the patient's condition. The maximum dose was 8.75 $ng \cdot kg^{-1} \cdot min^{-1}$, and the minimum dose was 0.3 $ng \cdot kg^{-1} \cdot min^{-1}$. In addition to the treatment as the control group, the observation group was given Salmeterol-Fluticasone powder (Package specification: 50 μg/250 μg × 60 Discus; Registration Certificate No.: H20150324; Manufacturer: Glaxo Wellcome Production, France), taking 1 inhalation 2 times a day. Besides, the treatment course of both groups was 20 days.

2.5 Observation indexes

(1) Clinical efficacy [4]: Markedly effective: Degree of respiratory symptom relief ≥ 2 levels; Effective: Degree of respiratory symptom relief ≤ 1 level; Ineffective: No sign of improvement. Overall effective clinical efficacy = (Markedly effective + Effective) Cases/Total cases × 100%.

(2) Blood gas index: Before and after treatment, arterial partial pressure of oxygen (PaO_2), arterial oxygen saturation (SaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$) were measured by blood-gas analyzer (ABL700, Radiometer, Denmark) in both groups.

(3) Level of serum factor: Before and after treatment, fasting venous blood was collected from both groups in the morning. The levels of serum matrix metalloproteinase-9 (MMP-9) and tumor necrosis factor (TNF-α) were detected by enzyme-linked immunosorbent assay, and the level of C-reactive protein (CRP) was measured by immunoturbidimetry assay using a Roche automatic biochemical analyzer.

(4) Adverse reaction: The occurrence of adverse reactions such as facial flushing and skin itching in both groups were observed and recorded.

2.6 Statistical methods

SPSS 20.0 was used for statistical analysis, count data were compared using the X^2 test, and measurement data were expressed by mean ± standard deviation. *t*-test for independent samples was used for comparison between both groups, and *t*-test for paired samples was used for comparison before and after treatment. Differences were considered statistically significant at $p < 0.05$.

3 Results

3.1 Comparison between two groups of patients in clinical symptoms

After treatment, the total clinical effective rate of the observation group was 92.59% and that of the control group was 64.81%. Significantly, the total clinical effective rate of the observation group was higher than that of the control group ($p < 0.05$), as shown in Table 2.

Table 2 Comparison between two groups of patients in clinical symptoms [cases (%)].

Groups	Cases	Markedly effective	Effective	Ineffective	Overall effective
Observation	54	30 (55.56)	20 (37.04)	4 (7.41)	50 (92.59)
Control	54	14 (46.67)	21 (38.89)	19 (35.19)	35 (64.81)
X^2					3.825
p					<0.001

3.2 Comparison of blood gas index levels between two groups of patients before and after treatment

Before treatment, there was no significant difference in the levels of PaO_2, SaO_2 and $PaCO_2$ between both groups ($p > 0.05$). However, compared with those before the treatment, the levels of PaO_2 and SaO_2 in both groups increased obviously after the treatment ($p < 0.05$), and the level of $PaCO_2$ decreased obviously ($p < 0.05$). Besides, the levels of PaO_2 and SaO_2 in the observation group were obviously higher than those in the control group ($p < 0.05$), and the level of $PaCO_2$ was obviously lower than that in the control group ($p < 0.05$), as shown in Table 3.

3.3 Comparison of serum factor in two groups of patients before and after treatment

Before treatment, there was no significant difference in the levels of MMP-9, CRP and TNF-α between the two groups ($p > 0.05$). However, compared with those before the treatment, the levels of MMP-9, CRP and TNF-α were patently lower in both groups after the treatment ($p < 0.05$), and these levels in the observation group were significantly lower than those in the control group ($p < 0.05$), as shown in Table 4.

3.4 Comparison of adverse reaction in two groups of patients

There was no significant difference in the incidence of adverse reactions between both groups ($p > 0.05$), as shown in Table 5.

Table 3 Comparison of blood gas indexes in two groups of patients (mean ± standard deviation).

Groups	Cases	PaO_2 (kPa)		SaO_2 (%)		$PaCO_2$ (kPa)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	54	7.56 ± 2.71	14.16 ± 2.96 *	77.56 ± 8.25	96.32 ± 5.47 *	7.16 ± 2.01	3.16 ± 1.08 *
Control	54	7.68 ± 2.82	12.34 ± 3.14 *	77.69 ± 8.21	90.18 ± 4.96 *	7.18 ± 2.11	3.96 ± 1.21 *
t		0.226	3.099	0.082	6.111	0.050	3.625
p		0.822	0.003	0.935	<0.001	0.960	<0.001

Compared with the same group before treatment: * $p < 0.05$.

Table 4 Comparison of serum factor in two groups of patients (mean ± standard deviation).

Groups	Cases	MMP-9 (μg/L)		CRP (mg/L)		TNF-α (mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	54	518.25 ± 71.37	354.74 ± 30.91 *	40.29 ± 16.83	7.68 ± 0.96 *	36.29 ± 5.36	22.36 ± 4.11 *
Control	54	517.69 ± 72.54	417.48 ± 39.21 *	39.58 ± 15.28	8.94 ± 1.17 *	36.93 ± 5.84	30.73 ± 4.56 *
t		0.040	9.234	0.230	6.118	0.593	10.02
p		0.968	<0.001	0.819	<0.001	0.554	<0.001

Compared with the same group before treatment: * $p < 0.05$.

Table 5 Comparison of adverse reaction in two groups of patients.

Groups	Cases	Facial flush	Skin itching	Dry mouth	Constipation	Adverse reaction total
Observation	54	0 (0.00)	2 (3.70)	2 (3.70)	1 (1.85)	5 (9.26)
Control	54	1 (1.85)	0 (0.00)	2 (3.70)	1 (1.85)	4 (7.41)
X^2						0.129
p						0.897

4 Discussions

With the deterioration of the disease, the right heart afterload of COPD patients with pulmonary hypertension will be increased constantly, and the exercise ability of the patients will be declined significantly, eventually leading to right ventricular failure, and even death in severe cases [7]. Currently, there is still no effective method to treat COPD patients with pulmonary hypertension. Therefore, this study explored the clinical efficacy of treprostinil combined with Salmeterol-Fluticasone in the treatment of COPD patients with severe pulmonary hypertension. The results showed that this method could not only effectively improve the lung function of patients, but also significantly alleviate the body's inflammatory response.

The long-term hypoxia of the body could damage the pulmonary vessels of COPD patients with pulmonary hypertension, leading to the remodeling of the pulmonary vessels and the deterioration of the patient's condition. Clinically, patients' pulmonary function is often assessed by determining changes in PaO_2, SaO_2 and $PaCO_2$ indicators. Specifically, PaO_2 refers to the pressure generated by oxygen molecules dissolved in blood, with a normal value of 95-100 mmHg; SaO_2 is an estimated value of oxygen content in blood, and if SaO_2 is lower than 95%, it may indicate poor blood oxygenation; The reference value of $PaCO_2$ is 35~45 mmHg, which can be used to measure alveolar ventilation [8]. The results showed that after treatment, the total clinical effective rate of the observation group was significantly higher than that of the control group. Compared with those before treatment, the levels of PaO_2 and SaO_2 in the observation group were significantly higher than those in the control group after treatment. Compared with that before treatment, $PaCO_2$ level in the two groups decreased significantly after treatment, and that in the observation group was significantly lower than that in the control group. The results indicated that Salmeterol-Fluticasone combined with treprostinil is effective in treating COPD patients with severe pulmonary hypertension and can effectively improve the patients' pulmonary function. Treprostinil has similar effects to prostacyclin, promoting the production of cyclic adenosine monophosphate (cAMP) after combining with prostacyclin receptors, opening Ca^+-K^+ channels, hyperpolarizing cell membranes, and promoting pulmonary vasodilation to improve patients' lung function [8]. Salmeterol in Salmeterol-Fluticasone is a long-acting β 2 agonist that can quickly activate adenylyl cyclase in the cell membrane, and under the action of Mg^{2+} or Ca^{2+}, convert adenosine triphosphate (ATP) to cAMP in cells, increase the cAMP/cCMP ratio, and open calcium-activated potassium channels. As a result, the intracellular calcium concentration and calcium sensitivity to stimulants are reduced, thereby calming bronchial smooth muscle, and further improving the patient's lung function [9].

Inflammation not only destroys the wall elastic fibers of the pulmonary bronchi in COPD patients with pulmonary hypertension, but also causes chronic mucus hypersecretion in the lung lumen and progressive destruction of the lung parenchyma. Moreover, chronic damage to the lungs and airways and impaired cilia function contribute to bacterial colonization of the lungs in COPD combined with pulmonary hypertension, which further aggravates the patient's condition. CRP and TNF-α are common clinical indicators of inflammation, and MMP-9 is often used to assess patients' quality of life. The results of this study showed that MMP-9, CRP and TNF-α levels in both groups after treatment were significantly higher than those before treatment, and these levels were significantly lower in the observation group than those in the control group. It indicated that Salmeterol-Fluticasone in combination with treprostinil is effective in treating COPD patients with

severe pulmonary hypertension and is beneficial in relieving the inflammatory response of the organism. Treprostinil inhibits the production of thromboxane A_2 (TXA_2) by prostaglandin H_2, which reduces the concentration of TXA_2, promotes pulmonary vasodilation, continuously reduces pulmonary artery pressure and pulmonary vascular resistance, and effectively improves the patient's pulmonary function, in order to alleviate the inflammatory response of the body [10]. Fluticasone propionate in salmeterol, a glucocorticoid (GC), can be embedded in cell membranes at high GC concentrations to alter the activity of its membrane-associated proteins, resulting in abnormal ion transport across membranes, thereby inhibiting immune cell function and reducing the inflammatory response of the body. Meanwhile, GC could also dephosphorylate p38MAPK and weaken its activity by promoting the expression of mitogen activated protein kinase phosphatase-1 (MKP-1), and further inhibit p38MAPK signaling pathway, so as to alleviate the inflammatory response of the body [11].

In addition, our study also showed that there was no significant difference in the incidence of adverse reactions between both groups, indicating that Salmeterol-Fluticasone combined with treprostinil has a high safety in the treatment of COPD patients with severe pulmonary arterial hypertension.

In conclusion, Salmeterol-Fluticasone combined with treprostinil has excellent efficacy in treating COPD patients with severe pulmonary hypertension, which can not only improve the patient's hypoxic condition, but also effectively relieve the body's inflammatory response, and has a high safety profile.

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Conflicts of Interest

All authors declare that the research was conducted in the absence of any commercial or fnancial relationships that could be construed as a potential confict of interest.

Author Contributions

X.K. and H.Z. conceptualized the trial, participated in creating the study design and the statistical analysis plan. H.Z. made the first draft of the manuscript. All authors reviewed and revised the manuscript critically for important intellectual content. All authors reviewed the final manuscript as submitted. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by Ethics Committee of our hospital and the written informed consent was taken from all the patients.

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Availability of Data and Materials

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Supplementary Materials

Not applicable.

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