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Observation on the Efficacy and Safety of Riociguat in Patients with Chronic Obstructive Pulmonary Disease (COPD) Complicated by Pulmonary Arterial Hypertension (PAH)

Ying Peng*

Zhongxiang People's Hospital, Zhongxiang 431900, Hubei, China

***Corresponding author*:** Ying Peng, 18772703605@163.com

Abstract: *Objective*: To investigate the efficacy and safety of riociguat in patients with chronic obstructive pulmonary disease (COPD) complicated by pulmonary arterial hypertension (PAH). *Methods*: A total of 98 patients with COPD and PAH admitted to Zhongxiang People's Hospital from January 2023 to December 2024 were selected and randomly divided into a control group and an observation group using a random number table method, with 49 patients in each group. The control group received conventional treatment, while the observation group received riociguat in addition to the conventional treatment. Clinical efficacy, pulmonary function indicators, pulmonary artery pressure indicators, blood gas indicators, and 6-minute walking distance were compared between the two groups, and adverse reactions during treatment were recorded. *Results*: After treatment, the total effective rate in the observation group was 93.88%, higher than that in the control group (79.59%). The pulmonary function indicators, pulmonary artery pressure indicators, blood gas indicators, and 6-minute walking distance in the observation group were superior to those in the control group, with statistically significant differences ($p < 0.05$). There was no significant difference in the total incidence of adverse reactions between the two groups ($p > 0.05$). *Conclusion*: Riociguat treatment can improve pulmonary function, pulmonary artery pressure, and blood gas status in patients with COPD complicated by PAH, enhance exercise tolerance and clinical efficacy, and is safe without increasing the risk of adverse reactions.

Keywords: Chronic obstructive pulmonary disease; Pulmonary arterial hypertension; Riociguat; Efficacy; Safety

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1. Introduction

Pulmonary arterial hypertension (PAH), as a frequent and serious complication of chronic obstructive pulmonary disease (COPD), cannot be ignored. As COPD progresses, chronic hypoxemia, pulmonary

inflammation, endothelial dysfunction, and other factors collectively lead to pulmonary vascular remodeling and constriction, causing PAH, which in turn leads to right heart dysfunction and even death [1,2]. The incidence of COPD complicated by PAH increases with disease severity and is particularly common in patients with severe COPD, affecting their quality of life, exercise tolerance, and prognosis [3]. Epidemiological data show that the incidence of PAH in COPD patients is 20–50%, and both the incidence and severity of PAH increase with the progression of COPD [4]. Therefore, finding a safe and effective treatment regimen to improve the condition of patients with COPD complicated by PAH has become a key focus of clinical research. Currently, the primary and core strategy for treating PAH is to optimize the treatment of the underlying pulmonary disease, including long-term oxygen therapy, bronchodilators, smoking cessation, pulmonary rehabilitation, etc. However, some patients still have severe PAH and progressive right heart dysfunction, with limited effects on reducing pulmonary artery pressure and difficulty in effectively delaying disease progression. Riociguat activates soluble guanylate cyclase (sGC) through a dual mechanism, enhancing the NO-cyclic guanosine monophosphate (cGMP) signaling pathway without relying on nitric oxide (NO), thereby dilating pulmonary vessels, reducing pulmonary artery pressure, and improving pulmonary circulation [5]. However, there are currently few studies on its application in patients with COPD complicated by PAH. Based on this, this study aimed to investigate the efficacy and safety of riociguat in patients with COPD complicated by PAH.

2. Materials and methods

2.1. General information

From January 2023 to December 2024, this study admitted and treated 98 patients with COPD complicated by PAH. They were randomly divided into a control group and an observation group using a random number table method, with 49 patients in each group. This study was approved by the Medical Ethics Committee of our hospital, and all patients participating in the study signed informed consent forms.

2.1.1. Inclusion criteria

(1) Met the diagnostic criteria for COPD [6];
(2) Diagnosed with PAH [7];
(3) Age > 18 years;
(4) Normal cognitive and communication abilities and clear consciousness.

2.1.2. Exclusion criteria

(1) Combined with important organ dysfunction such as liver and kidney dysfunction or malignancy;
(2) Presence of mental disorders;
(3) Combined with hematological diseases;
(4) Combined with other serious pulmonary diseases such as tuberculosis;
(5) Combined with severe left heart dysfunction or arrhythmia;
(6) Allergic to the study drugs.

2.2. Methods

2.2.1. Control group

Conventional treatment regimen:

(1) Bronchodilators

Salbutamol aerosol [produced by GlaxoSmithKline Pharmaceuticals (UK) Co., Ltd., National Medical Products Administration Approval Number H20150673, specification: 100 μg/puff], 100 μg each time, with a maximum daily dose not exceeding 8 times;

(2) Anti-inflammatory treatment

For patients with repeated acute exacerbations, budesonide formoterol powder for inhalation (AstraZeneca, Approval Number H20140458, specification: 2 mL:1 mg) was given, 1 inhalation each time, twice a day;

(3) Oxygen therapy

For patients with resting oxygen saturation < 88%, oxygen was administered at a flow rate of 1–2 L/min for at least 15 hours per day;

(4) Symptomatic treatment

Diuretic, anticoagulant, cough-relieving, and expectorant treatments were given according to the patient's condition.

2.2.2. Observation group

The observation group received oral riociguat tablets (Bayer AG, National Medical Products Administration Approval Number H20200015, specification: 1 mg/tablet) in addition to the conventional treatment in the control group. The initial dose was 1 mg each time, three times a day; after 1 week of treatment, if the patient tolerated it well without obvious adverse reactions such as headache, dizziness, or hypotension, the dose was adjusted to 1.5 mg each time, three times a day; after another week of observation, if the patient still tolerated it well, the dose could be further adjusted to 2 mg each time, three times a day; the maximum dose did not exceed 2.5 mg each time, three times a day. If the patient developed obvious adverse reactions during dose adjustment, the current dose was maintained or appropriately reduced.

Both groups received continuous treatment for 8 weeks.

2.3. Observation indicators

2.3.1. Clinical efficacy evaluation

After treatment, clinical efficacy was evaluated based on the improvement in cardiac function classification, symptom relief, and changes in exercise tolerance, divided into three grades: markedly effective, effective, and ineffective:

(1) Markedly effective

Cardiac function classification improved by ≥ 2 grades, symptoms significantly relieved, and 6-minute walking test (6MWT) increased by ≥ 100 m;

(2) Effective

Cardiac function classification improved by 1 grade, symptoms relieved to some extent, and 6MWD increased by 50–99 m;

(3) Ineffective

Did not meet the above criteria or the condition worsened [8]. The total effective rate was the sum of the proportions of markedly effective and effective cases.

2.3.2. Pulmonary function parameter measurement

Using pulmonary function testing equipment, the forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) of the subjects were measured, and the ratio of FEV1/FVC was calculated simultaneously.

2.3.3. Pulmonary artery pressure indicator detection

Pulmonary artery pressure (mPAP) and pulmonary artery systolic pressure (PASP) were detected using a cardiac ultrasound diagnostic instrument (Philips EPIQ7C), operated by experienced ultrasound physicians.

2.3.4. Blood gas indicator detection

2 mL of arterial blood was drawn from the patient in a fasting state (anticoagulated with heparin), and an Abbott i-STAT blood gas analyzer (USA) was used to detect the partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (PaCO2) in the arterial blood. The entire detection process must strictly follow aseptic operation specifications to prevent air from mixing in.

2.3.5. 6-minute walking distance detection

Using the 6-minute walking test, the patient walked as fast as possible in a straight, obstacle-free corridor for 6 minutes, and the walking distance was recorded. The patient received routine oxygen inhalation for 10 minutes before the test to avoid the influence of strenuous exercise on the results. During the detection process, the patient was closely observed for any discomfort, and the test was immediately stopped if chest pain or worsening dyspnea occurred.

2.3.6. Adverse reaction monitoring

During the continuous treatment period, the occurrence of adverse reactions was observed and recorded daily, including symptoms such as headache, dizziness, chest tightness, gastrointestinal discomfort, and fatigue. Statistical Methods Data were processed using SPSS 27.0. Measurement data conforming to a normal distribution were expressed as ($\overline{x} \pm s$), and a *t*-test was used; count data were expressed as [n(%)], and a χ^2 test was used. $p < 0.05$ indicated a statistically significant difference.

3. Results

3.1. Comparison of baseline data between the two groups

The comparison of baseline data between the two groups showed no statistically significant differences ($p > 0.05$), as shown in **Table 1**.

Table 1. Comparison of baseline data between the two groups [n(%)/ $\overline{x} \pm s$]

Group	Number of cases (n)	Gender		Age (years)	COPD duration (years)
		Female	Male		
Observation group	49	21 (42.86)	28 (57.14)	63.80 ± 5.84	8.52 ± 2.16
Control group	49	24 (48.98)	25 (51.02)	63.40 ± 5.60	8.86 ± 2.20
χ^2/t value		0.370		0.346	0.772
p value		0.543		0.730	0.442

3.2. Comparison of clinical efficacy between the two groups

The overall effective rate in the observation group was significantly superior to that in the control group, with a statistically significant difference ($p < 0.05$), as shown in **Table 2**.

Table 2. Comparison of clinical efficacy between the two groups [n(%)]

Group	Number of cases (n)	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	49	25 (51.02)	21 (42.86)	3 (6.12)	46 (93.88)
Control group	49	19 (38.77)	20 (40.82)	10 (20.41)	39 (79.59)
χ^2 value					4.346
p value					0.037

3.3. Comparison of pulmonary function indicators between the two groups

Before treatment, there were no significant differences in various pulmonary function parameters between the two groups of subjects ($p > 0.05$). After intervention, all pulmonary function indicators in the observation group showed a tendency to be higher than those in the control group, and the differences were statistically significant ($p < 0.05$). See **Table 3**.

Table 3. Comparison of pulmonary function between the two groups ($\overline{x} \pm s$)

Group	Number of cases (n)	FEV_1 (L)		FVC (L)		FEV_1/FVC (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	49	0.88 ± 0.23	1.53 ± 0.35*	1.43 ± 0.39	2.05 ± 0.53*	54.51 ± 5.65	65.45 ± 6.02*
Control group	49	0.85 ± 0.26	1.12 ± 0.40*	1.49 ± 0.37	1.67 ± 0.54*	55.30 ± 5.53	58.14 ± 6.21*
t value		0.605	5.400	0.781	3.516	0.700	5.916
p value		0.547	< 0.001	0.437	< 0.001	0.486	< 0.001

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

3.4. Comparison of pulmonary artery pressure indicators and blood gas indicators between the two groups

Before treatment, there were no statistically significant differences in these indicators between the two groups ($p > 0.05$). After treatment, the values of $PaCO_2$, mPAP, and PASP in the observation group were all lower than those in the control group, while the value of PaO_2 was higher than that in the control group, with statistically significant differences ($p < 0.05$). See **Table 4**.

Table 4. Comparison of pulmonary artery pressure indicators and blood gas indicators between the two groups ($\overline{x} \pm s$)

Group	Number of cases (n)	PaO_2 (mmHg)		$PaCO_2$ (mmHg)		mPAP (mmHg)		PASP (mmHg)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	49	43.58 ± 5.14	76.54 ± 5.64*	58.79 ± 4.33	39.78 ± 3.56*	50.12 ± 4.56	32.63 ± 3.21*	52.44 ± 4.63	41.62 ± 3.85*

Control group	49	44.10 ± 5.20	68.58 ± 5.28*	58.25 ± 4.39	45.58 ± 3.88*	49.67 ± 4.27	39.48 ± 3.69*	51.79 ± 4.28	47.85 ± 4.20*
t value		0.498	7.212	0.613	7.710	0.504	9.804	0.722	7.654
p value		0.620	< 0.001	0.541	< 0.001	0.615	< 0.001	0.472	< 0.001

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

3.5. Comparison of 6-minute walk distance between the two groups

Before treatment, there was no statistically significant difference in the 6-Minute Walk Distance (6MWD) between the two groups ($p > 0.05$). After treatment, the 6MWD in the observation group was longer than that in the control group, with a statistically significant difference ($p < 0.05$), as shown in **Table 5**.

Table 5. Comparison of 6-minute walk distance between the two groups ($\overline{x} \pm s$)

Group	Number of cases (n)	6MWD (m)	
		Before treatment	After treatment
Observation group	49	326.18 ± 22.27	432.24 ± 28.68*
Control group	49	328.06 ± 22.11	386.46 ± 25.66*
t value		0.676	8.327
p value		0.419	< 0.001

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

3.6. Comparison of incidence rates of adverse reactions between the two groups

There was no statistically significant difference in the overall incidence rate of adverse reactions between the two groups ($p > 0.05$), as shown in **Table 6**.

Table 6. Comparison of incidence rates of adverse reactions between the two groups [n(%)]

Group	Number of cases (n)	Headache	Dizziness	Chest tightness	Gastrointestinal discomfort	Fatigue	Total incidence rate
Observation group	49	1 (2.04)	0 (0.00)	1 (2.04)	1 (2.04)	2 (4.08)	5 (10.20)
Control group	49	1 (2.04)	2 (4.08)	0 (0.00)	1 (2.04)	3 (6.12)	7 (14.28)
χ^2 value							0.380
p value							0.538

4. Discussion

Pulmonary arterial hypertension (PAH) is a severe complication of chronic obstructive pulmonary disease (COPD). Its core pathological mechanisms include pulmonary vasoconstriction triggered by long-term hypoxia, pulmonary vascular remodeling, and vascular endothelial injury mediated by inflammatory factors, ultimately leading to elevated pulmonary artery pressure [9]. Currently, the conventional treatment for COPD complicated by PAH primarily focuses on controlling the underlying disease and providing symptomatic support, but its effectiveness in improving PAH is limited. Riociguat, as a soluble guanylate cyclase (sGC) stimulator, can directly dilate pulmonary vessels and improve vascular remodeling.

The results of this study indicate that the total effective rate in the observation group after treatment was higher than that in the control group, while mean pulmonary artery pressure (mPAP) and pulmonary artery

systolic pressure (PASP) were lower in the observation group ($p < 0.05$), consistent with the findings of Ke Yijun et al. [10]. From the perspective of disease pathology, the development of COPD complicated by PAH is closely related to chronic hypoxemia, pulmonary inflammation, and endothelial dysfunction. Long-term hypoxic conditions stimulate pulmonary vasoconstriction, triggering pulmonary vascular remodeling, while pulmonary inflammatory responses further exacerbate vascular damage. Endothelial dysfunction leads to a decrease in nitric oxide (NO) production and reduced activity of the cyclic guanosine monophosphate (cGMP) signaling pathway, ultimately resulting in elevated pulmonary artery pressure and increased right ventricular load [11]. Although conventional treatment improves COPD symptoms and alleviates hypoxic conditions through bronchodilators, anti-inflammatory agents, and oxygen therapy, its ability to repair established pulmonary vascular lesions and restore the impaired NO-cGMP pathway is limited, making it difficult to effectively reduce pulmonary artery pressure. This often leads to persistent disease progression and suboptimal treatment outcomes in some patients. Unlike traditional drugs that rely on NO to activate sGC, riociguat can directly bind to the active site of sGC, activating the enzyme even in the presence of insufficient NO production, thereby effectively enhancing the activity of the NO-cGMP signaling pathway. Elevated cGMP levels promote relaxation of pulmonary vascular smooth muscle, reduce pulmonary vasoconstriction, and delay the process of pulmonary vascular remodeling through dual inhibition, fundamentally improving pulmonary circulation and reducing pulmonary artery pressure [12]. The reduction in pulmonary artery pressure effectively alleviates the right ventricular afterload, improves right ventricular systolic function, and increases cardiac output, thereby relieving core symptoms such as fatigue and chest tightness after activity in patients. Simultaneously, the decrease in pulmonary vascular resistance facilitates the resolution of pulmonary congestion, reduces airway secretion retention, improves the coordination of pulmonary ventilation and gas exchange, and further alleviates COPD-related symptoms such as cough and wheezing. Ultimately, this leads to an improvement in cardiac function classification, symptom relief, and exercise tolerance, thereby enhancing the overall treatment effectiveness. In the meta-analysis by Zhang Qianqian on riociguat for the treatment of pulmonary hypertension, it was also proposed that this drug can effectively increase patients' exercise tolerance and improve cardiac function [13].

The results of this study show that all pulmonary function parameters in the observation group were higher than those in the control group ($p < 0.05$), demonstrating the role of riociguat in improving pulmonary function. By reducing pulmonary artery pressure, riociguat decreases pulmonary vascular resistance, improves pulmonary tissue perfusion, alleviates pulmonary congestion, and provides more adequate oxygen and nutrient supply to pulmonary tissues, thereby reducing pulmonary tissue damage and improving pulmonary ventilation function [14]. Additionally, after the reduction in pulmonary artery pressure, the right ventricular load decreases, and right ventricular function improves, reducing the further impact of pulmonary circulation congestion caused by right ventricular dysfunction on pulmonary ventilation and creating a virtuous cycle, ultimately leading to improved pulmonary function [15]. Furthermore, the observation group also showed superior improvement in blood gas parameters compared to the control group ($p < 0.05$). On one hand, riociguat improves pulmonary circulation, increases the alveolar ventilation-perfusion ratio, and enhances gas exchange efficiency. On the other hand, improved pulmonary function strengthens the lungs' ventilatory capacity, further optimizing the gas exchange process, alleviating hypoxemia and hypercapnia, providing a favorable internal environment for the patient's metabolic processes, and helping to reduce multi-organ damage and improve overall health status.

This study also revealed that the 6-minute walk distance (6MWD) in the observation group was longer than that in the control group after treatment ($p < 0.05$), indicating a significant improvement in patients' exercise tolerance. The possible reasons are that the reduction in pulmonary artery pressure, improvement in pulmonary function, and optimization of blood gas status alleviate symptoms such as dyspnea and chest tightness during exercise in patients, reduce cardiopulmonary load during exercise, enabling patients to tolerate longer and more intense exercise, thereby improving exercise tolerance. In terms of safety, there was no statistically significant difference in the total incidence of adverse reactions between the two groups ($p > 0.05$), and no serious adverse reactions occurred in the observation group. Although riociguat may cause mild discomfort such as headache and dizziness, these are mostly related to the initial vasodilatory effect of the drug and can be effectively reduced by adjusting the dosage gradient, with most patients tolerating it well [16]. This result indicates that adding riociguat to conventional treatment does not increase the burden of adverse reactions in patients and ensures drug safety.

5. Conclusion

In conclusion, riociguat is effective in improving pulmonary function, reducing pulmonary artery pressure, optimizing blood gas status, and enhancing exercise tolerance in patients with COPD complicated by PAH, with good safety. However, this study has certain limitations, including a small sample size, a single-center design, a short observation period, and no long-term follow-up of patients, which prevented the assessment of the long-term efficacy and safety of riociguat. Future research should involve larger-sample, multicenter, randomized controlled long-term follow-up studies to further validate the efficacy and safety of riociguat in this population and explore in-depth the mechanisms of its effects on pulmonary vascular remodeling and right ventricular function, aiming to provide more sufficient evidence for individualized treatment.

Disclosure statement

The author declares no conflict of interest.

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