

## Clinical Study of Jianpi Yifei Decoction Combined with Nikethamide in the Treatment of Chronic Obstructive Pulmonary Disease Patients with Respiratory Failure

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### Keywords

Jianpi Yifei Decoction, Nikethamide, Chronic obstructive pulmonary disease, Respiratory failure

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### Abstract

**Background** To explore the clinical effects of Jianpi Yifei Decoction combined with nikethamide in the treatment of patients with chronic obstructive pulmonary disease (COPD) and respiratory failure. **Methods** From January 2020 to January 2022, 126 patients with COPD with respiratory failure were randomly divided into a control group and an observation group, with 63 cases in each group. Patients in control group were treated with nikethamide for 14 days, on the basis of which patients in observation group were additionally treated with Jianpi Yifei Decoction for 14 days. Clinical symptoms, lung function, blood gas indexes, and serum factor levels were determined by APACHE II and mMRC scores, pulmonary function instrument, blood gas analyzer and ELISA kits. **Results** After treatment, the scores of APACHE II and mMRC scores, as well as levels of partial pressure of carbon dioxide (PaCO<sub>2</sub>) in arterial blood, C-reactive protein (CRP), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-8 (IL-8), and procalcitonin (PCT) were significantly lowered, and those in the observation group were remarkably lower than those in the control group. Levels of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEF), arterial partial pressure (PaO<sub>2</sub>) and blood oxygen saturation (SaO<sub>2</sub>) were soared after treatment, with the levels in the observation group higher than those in the control group. **Conclusion** Jianpi Yifei Decoction combined with nikethamide alleviates clinical symptoms, improves lung function and blood gas analysis indexes, and attenuates the body's inflammatory response of patients with COPD and respiratory failure.



### 1 Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by progressive airflow limitation, with high morbidity, high mortality and poor prognosis (1). Respiratory failure is one of the most common complications of COPD. Patients with long-term unhealed COPD experience alveolar collapse, respiratory muscles weakness, alveolar ventilation reduction, lung function impairment, and respiratory distress, and eventually suffer from respiratory failure (2). Western medicine (WM) recommends medication and mechanical ventilation as the main treatments for COPD combined with respiratory failure which can provide immediate relief of clinical symptoms such as cyanosis and dyspnea (3, 4). Nikethamide, a respiratory stimulant, is commonly used in clinical treatment for respiratory depression rescue (5). Combined with oxygen administration, nikethamide can effectively restore respiratory function in patients with COPD combined with respiratory failure (6). However, due to the short-acting and high recurrence rate of these therapies, the long-term life quality of patients is not guaranteed (7). Besides, long-term use of Western medicine could cause various adverse reactions, thus posing greater safety risks to patients (7).

Traditional Chinese medicine (TCM) advocates the syndrome differentiation and treating both the symptoms and the root cause in critical illnesses with fewer side effects and less drug dependence (8). For

this reason, TCM has attracted great attention in recent years (8). As for COPD, it has been proved that the use of Chinese herbal medicine in addition to Western pharmacotherapies could alleviate clinical symptoms, improve quality of life and clinical efficiency and reduce the exacerbation frequency of COPD patients (9). In addition, a systematic review by Peifen Huang et al. indicated that TCM combined with WM can effectively treat the symptoms related to COPD (10). Therefore, the present study aims to investigate the clinical effects of Jianpi Yifei Decoction (a Chinese herbal decoction prepared from multiple herbs) combined with nikethamide in the treatment of COPD combined with respiratory failure and its effects on lung function, blood gas status and serum factors, so as to provide a reference for clinical treatment. The findings are as follows.

### 2 Data and methods

#### 2.1 General data

126 patients with COPD combined with respiratory failure admitted to our hospital from January 2020 to January 2022 were included in the study, and randomly divided into the observation group (n=63) and the control group (n=63). The differences in gender, age, body mass index (BMI), course of disease (COD), underlying diseases, smoking and alcohol history between the two groups were not statistically significant (Table1,  $P>0.05$ ). The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

Table1 Comparisons of general data

Group		Observation group (n=63)	Control group (n=63)	$\chi^2/t$	<i>P</i>
Gender (case)	Male	34	32	0.127	0.721
	Female	29	31		
Age (years old)		64.44±5.57	64.03±5.86	0.403	0.688
COD (year)		7.79±1.23	7.82±1.30	-0.133	0.894
BMI (kg/m <sup>2</sup> )		21.88±1.95	22.12±2.05	-0.673	0.502
Smoking history (case)		13	15	0.184	0.668
Alcohol history (case)		14	12	0.194	0.660
Underlying diseases (case)	hypertension	30	31	0.237	0.888
	hyperlipidemia	11	9		
	diabetes	24	25		

### 2.1.1 Diagnosis criteria

WM diagnosis referred to the diagnostic criteria for COPD and respiratory failure in *Internal Medicine* (11); TCM syndrome differentiation referred to syndromes of COPD respiratory failure with deficiency of lung, spleen and kidney as well as phlegm-heat obstructing lung in *the International Clinical Practice Guideline of Chinese Medicine Chronic Obstructive Pulmonary Disease* (12), including: coughing, dyspnea, yellow/white sticky dry sputum, red tongue proper, yellow greasy tongue coating, and rapid or sliding pulse.

### 2.1.2 Inclusion criteria

(1) Patients meet the diagnosis criteria for COPD combined with respiratory failure in TCM and WM; (2) Patients with complete clinical data and no history of drug allergy.

### 2.1.3 Exclusion criteria

(1) Patients combined with serious diseases in heart, liver, kidney and other vital organs, mental illness, blood immune diseases; (2) Patients combined with malignant tumours; (3) Patients combined with bronchial asthma, pulmonary tuberculosis and other pulmonary diseases; (4) Patients combined with convulsions, hyperspasmia and other contraindications to nikethamide.

### 2.2 Treatment

Patients in both groups were given routine treatments for COPD respiratory failure such as asthma relieving, correction of water-electrolyte disorder, anti-infection and bi-level positive pressure ventilation (BiPAP) based on their conditions. Patients in the control group received an intravenous injection of 0.375 g (repeat within 1-2 hours in terms of patients' condition) nikethamide once a day (Shanghai Harvest Pharmaceutical Co., Ltd., Shanghai, China, Approval number of National Medical Products Administration: H31021527, specification: 0.375 g × 10 pieces). Patients in the observation group, on the basis of the control group, were further treated with 400 mL Jianpi Yifei Decoction, one dose a day (main ingredients: 30

g each of milkvetch root and tangshen, 15 g each of largehead atractylodes rhizome, rhizoma dioscoreae, poria cocos and Chinese magnoliavine fruit, 10 g each of prepared rehmannia root and epimedium herb, 12 g each of ephedra and bitter apricot seed, 6 g each of dried tangerine peel and liquorice root, with dosage adjusted according to the severity of syndromes). Each dose was decocted 2 times and warm Decoction was taken once in the morning and once in the evening. The therapeutic course in both groups was consecutive 14 days (d).

### 2.3 Detection indexes

(1) Acute physiology and chronic health status rating system II (APACHE II) and mixed respiratory distress index (mMRC) scores: Before treatment and after 7 d of treatment respectively, patients' conditions were assessed using the APACHE II (13) which covers 3 dimensions of acute physiology score, age score and chronic health score, with a total of 71 points, and the severity of the condition increases with the total score. Patients' dyspnea was assessed by the modified British medical research society mMRC score (14), and higher scores represent increasing dyspnea intensity of patients. (2) Pulmonary function: Before treatment and after 14 d of treatment, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow rate (PEF) of patients in the two groups were analyzed using a pulmonary function instrument (Geratherm Medical AG, Geschwenda, Germany, Spirostik Complete, GXZJ registration certificate number: 20152070890). (3) Blood gas indexes: arterial blood carbon dioxide partial pressure (PaCO<sub>2</sub>), oxygen partial pressure (PaO<sub>2</sub>) and oxygen saturation (SaO<sub>2</sub>) were measured by a blood gas analyzer (Radiometer, Boulder, CO, USA, GXZJ registration certificate number: 20172401025) before and after 14 d of treatment. (4) Serum factors: Fasting hemospasia was performed in the morning in all patients to collect 5 mL venous blood for laboratory tests before and 14 d after treatment. Serum C-reactive protein (CRP), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-8 (IL-8) and calcitoninogen (PCT) levels were detected by

enzyme-linked immunosorbent assay (ELISA) with an ELISA kit (Bohui Biotechnology Co., Guangzhou, China).

### 2.4 Statistical analysis

Statistical analysis was performed using SPSS 20.0. Counting data were compared using the  $\chi^2$  test, and measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). Differences between two groups were assessed with unpaired *t*-tests, while differences in the same group at different time points were evaluated using the paired sample *t*-test. Statistical

significance was established at  $P < 0.05$ .

## 3 Results

### 3.1 Comparisons of APACHE II and mMRC scores between two groups before and after treatment

Before treatment, there was no statistically significant difference between the APACHE II and mMRC scores of the two groups (Table 2,  $P > 0.05$ ); after treatment, the APACHE II and mMRC scores were significantly lower than those before treatment ( $P < 0.05$ ), and the scores in the observation group were notably lower than those in the control group ( $P < 0.05$ ).

Table 2 Comparisons of APACHE II and mMRC scores between two groups before and after treatment ( $\bar{x} \pm s$ , score)

Group	Case	APACHE II Score		mMRC Score	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	63	23.46 $\pm$ 4.05	13.18 $\pm$ 3.08*	3.55 $\pm$ 0.34	2.40 $\pm$ 0.22*
Control group	63	23.56 $\pm$ 3.82	15.80 $\pm$ 3.02*	3.57 $\pm$ 0.37	2.92 $\pm$ 0.30*
<i>t</i>		-0.143	-4.821	-0.316	-11.094
<i>P</i>		0.887	0.000	0.753	0.000

\*vs. Pre-treatment; \* $P < 0.05$

### 3.2 Comparison of pulmonary function between two groups before and post treatment

Before treatment, no significant difference was found in the levels of FEV1, FVC and PEF between the two groups (Table 3,  $P > 0.05$ ); after treatment, the levels of FEV1, FVC and PEF between both groups were significantly upregulated than those before treatment ( $P < 0.05$ ), and the levels in the observation group were much higher than those in the control group ( $P < 0.05$ ).

### 3.3 Comparison of blood gas indexes between both groups before and after treatment

Before treatment, the levels of PaO<sub>2</sub>, PaCO<sub>2</sub> and SaO<sub>2</sub> showed no significant difference between the two groups (Table 4,  $P > 0.05$ ); While after treatment, the PaO<sub>2</sub> and SaO<sub>2</sub> levels in the two groups were remarkably higher than those before treatment and the PaCO<sub>2</sub> level was explicitly lower than that before treatment ( $P < 0.05$ ). Moreover, PaO<sub>2</sub> and SaO<sub>2</sub> levels

in the observation group were prominently higher than those in the control group, whereas the PaCO<sub>2</sub> level in the observation group was signally lower than that in the control group (Table 4,  $P < 0.05$ ).

### 3.4 Comparison of serum factor levels between both groups before and after treatment

Before treatment, there was no statistically significant difference between the levels of CRP, TNF- $\alpha$ , IL-8 and PCT in the two groups (Table 5,  $P > 0.05$ ). However, the treatment of Jianpi Yifei Decoction and nikethamide reduced the levels of CRP, TNF- $\alpha$ , IL-8 and PCT in patients in both groups ( $P < 0.05$ ). Compared with nikethamide treatment alone, the combination of Jianpi Yifei Decoction and nikethamide exhibited greater effects on the reduction of CRP, TNF- $\alpha$ , IL-8 and PCT levels in patients ( $P < 0.05$ ).

Table 3 Comparison of pulmonary function between two groups before and post-treatment ( $\bar{x}\pm s$ )

Group	Case	FEV1 (L)		FVC (L)		PEF (L/s)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
		nt	nt	nt	nt	nt	nt
Observation group	63	0.90±0.19	1.88±0.27*	1.54±0.38	2.72±0.46*	2.36±0.48	3.85±0.47*
Control group	63	0.93±0.15	1.24±0.27*	1.55±0.41	2.25±0.58*	2.38±0.44	3.06±0.47*
<i>t</i>		-0.984	13.304	-0.142	5.039	-0.244	9.434
<i>P</i>		0.327	0.000	0.887	0.000	0.808	0.000

\* vs. Pre-treatment; \**P*<0.05

Table 4 Comparison of blood gas indexes between both groups before and after treatment ( $\bar{x}\pm s$ )

Group	Case	PaO <sub>2</sub> (mmHg)		PaCO <sub>2</sub> (mmHg)		SaO <sub>2</sub> (%)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
		nt	nt	nt	nt	nt	nt
Observation group	63	48.67±8.11	67.65±7.24*	67.79±8.05	43.17±7.01*	82.27±6.05	96.06±6.94*
Control group	63	48.00±7.79	60.31±8.59*	67.94±7.79	53.01±7.51*	82.44±6.46	92.06±7.36*
<i>t</i>		0.473	5.186	-0.106	-10.400	-0.152	3.138
<i>P</i>		0.637	0.000	0.916	0.000	0.879	0.002

\* vs. Pre-treatment; \**P*<0.05

Table 5 Comparison of serum factor levels between both groups before and after treatment ( $\bar{x}\pm s$ )

Observation indexes	Observation group (n=63)		Control group (n=63)	<i>t</i>	<i>P</i>
	Pre-treatment	Post-treatment			
CRP (mg/L)	Pre-treatment	36.64±8.38	36.77±7.42	-0.092	0.927
	Post-treatment	12.00±2.50*	21.27±4.37*	-14.615	0.000
TNF-α (pg/L)	Pre-treatment	79.96±4.21	80.24±4.28	-0.370	0.712

	Post-treatment	13.64±2.68*	23.74±3.12*	-19.491	0.000
IL-8 (ng/L)	Pre-treatment	46.03±3.83	46.66±4.00	-0.903	0.368
	Post-treatment	11.99±1.34*	23.06±1.79*	-39.296	0.000
PCT (µg/L)	Pre-treatment	6.16±1.05	6.08±1.10	0.418	0.677
	Post-treatment	0.49±0.07*	1.25±0.28*	-20.901	0.000

\* vs. Pre-treatment; \* $P < 0.05$

#### 4 Discussion

In TCM, COPD was defined as the syndrome of "dyspnea" and "pulmonary distension", which is caused by the deficiency of pulmonary to the spleen and then to the kidney (15). Just as Shen Jinao stated, coughing is caused by impaired lung, spleen impairment leads to chronic cough and kidney impairment results in fire pattern. According to *Danxi's Coughing Methods (Danxi Xinfu)*, pulmonary distension-induced coughing leads to asomnia and phlegm complicated with static blood causes the stoppage of lung-Qi, which further contributes to the development of diseases (15). Therefore, on the one hand, strengthening body resistance should focus on promoting blood flow and dissipating phlegm to treat coughing. On the other hand, it should target at invigorating the lung and nourishing the kidney, auxiliary by tonifying the kidney (16). The present study explored the clinical effects of Jianpi Yifei Decoction combined with nikethamide treatment in COPD patients combined with respiratory failure and its effects on pulmonary function, blood gas indexes and serum factor levels. The results indicated a better therapeutic efficacy in the combination of Jianpi Yifei Decoction and nikethamide, which was similar to the literature of Peifen Huang et al. (10).

Patients with COPD experience alveolar collapse with low ventilation and the inability of diffusing circulating oxygen to the alveoli, which leads to oxygenation dysfunction, causing abnormal blood gas status (17). It has been documented that lower PaO<sub>2</sub> and SaO<sub>2</sub> levels as well as a higher PaCO<sub>2</sub> level are observed in COPD patients with respiratory failure, as compared with those in the healthy population, and

this normally leads to serious complications such as hypercapnia and affects the prognosis of patients (18). In addition, patients with COPD who suffer from long-term low ventilation will experience sustained lung dysfunction injury (18). Since pulmonary function indicators can directly reflect pulmonary ventilation, they can be used as physiological criteria to assess the severity of COPD combined with respiratory failure (19). FEV<sub>1</sub>, FVC and PEF are common indicators for pulmonary function, and higher levels of FEV<sub>1</sub>, FVC and PEF are associated with greater pulmonary function (20). The results of this study revealed that after treatment, APACHE II and mMRC scores as well as PaCO<sub>2</sub> level in both groups were largely downregulated as compared with those before treatment, and those in the observation group were significantly lower than those in the control group. Besides, the levels of FEV<sub>1</sub>, FVC, PEF, PaO<sub>2</sub> and SaO<sub>2</sub> in both groups were augmented in response to the treatment of Jianpi Yifei Decoction and nikethamide, with the levels in the observation group notably higher than those in the control group. Nikethamide is a first-line drug for respiratory depression rescue, which can excite the medullary respiratory centre, stimulate the chemoreceptors of the carotid sinus and aortic body to reflexively excite the respiratory centre, improve the sensitivity of the respiratory centre to carbon dioxide and elevate the respiratory tidal volume (21). The milkvetch root and tangshen in Jianpi Yifei Decoction served as the principal drug in invigorating primordial Qi, spleen and lung, while largehead atractylodes rhizome, poria cocos and rhizoma dioscoreae reinforce the spleen to replenish Qi (22). Epimedium herb invigorates the

kidney and supports yang, whereas Chinese magnoliavine fruit and prepared rehmannia root consolidate essence and primordial Qi (23). Ephedra and bitter apricot seed help to relieve cough and asthma and dried tangerine peel dries dampness to eliminate phlegm (24). Liquorice root invigorates the spleen and replenishes Qi, moistens the lung for arresting cough and also functions as a mediator for other drugs (25). The prescription enriches yin, invigorates the kidney and spleen, consolidates essence as well as relieves cough and asthma. It involved a combined treatment of both manifestation and the root cause of disease and included both the treatment and prevention of the disease (26, 27). Modern pharmacology has shown that milkvetch root could regulate immune function, protect pulmonary vascular endothelial cells and reduce lung tissue damage; largehead atractylodes rhizome, poria cocos combined with Chinese magnoliavine fruit and prepared rehmannia root contributed to the relieved respiratory muscle fatigue, enhanced respiratory muscle tone, increased respiratory tidal volume and attenuated respiratory depression and other symptoms; Ephedra and bitter apricot seed could relax bronchial smooth muscle, relieve cough and asthma and improve pulmonary function (24). In this study, our findings were consistent with the above studies that Jianpi Yifei Decoction combined with nikethamide can alleviate clinical symptoms of COPD patients with respiratory failure, and improve pulmonary function as well as blood gas status.

Inflammatory response and immune defence are the basis for the progression of COPD combined with respiratory failure (28). Overexpression of inflammatory factors CRP, TNF- $\alpha$  and IL-8 will activate immune cascades, damaging lung tissue, affecting pulmonary gas exchange and eventually inducing respiratory failure (29). Furthermore, PCT is a precursor protein of calcitonin, whose level in serum will be largely upregulated when immune cascades were triggered by hypoxia and oxidative stress caused lung tissue damage in COPD patients (29). The results of this study showed that after treatment, the levels of CRP, TNF- $\alpha$ , IL-8 and PCT were significantly lower

in both groups than those before treatment, and the levels in the observation group were obviously lower than those in the control group. Nikethamide can suppress the body's inflammatory response by increasing the ventilation frequency, improving the tidal volume and relieving hypoxia (6). According to modern pharmacological studies, milkvetch root and tangshen contain active components such as quercetin, kaempferol and mignonette that can inhibit the immune-inflammatory response and oxidative stress *in vivo*; Saponins, flavonoids and polysaccharides in poria cocos, rhizoma dioscoreae and dried tangerine peel possess anti-inflammatory and anti-oxidant free radical activity abilities; Chinese magnoliavine fruit contains lignans and organic acids with antibacterial, anti-inflammatory and immunity-boosting effects and accordingly modulate CRP, TNF- $\alpha$ , IL-8 and PCT expression levels in serum (24). Similarly, we found that Jianpi Yifei Decoction combined with nikethamide can effectively reduce the inflammatory response in patients with COPD combined with respiratory failure.

## 5 Conclusion

In conclusion, the combination of Jianpi Yifei Decoction with nikethamide exhibits profound effects in COPD patients with respiratory failure and helps to attenuate clinical symptoms, improve pulmonary function and blood gas status as well as reduce the inflammatory response.

## Acknowledgements

Not applicable.

## Conflict of Interest

The authors declare no conflicts of interest.

## Author contributions

Conceptualization, Wu.J.Z and Wen.J.Z; Data curation, Y.H.Z; Formal analysis, Y.H.Z; Methodology, Y.H.Z; Writing-Original draft, Wu.J.Z and Wen.J.Z; Writing-review and editing, Wu.J.Z and Wen.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 patients were informed and consented.

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### Availability of Data and Materials

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

### Supplementary Material

Not applicable

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