ORIGINAL RESEARCH

Study on the Efficacy and Clinical Value of Aminophylline and Doxofylline in the Clinical Treatment of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective • To study and compare the efficacy and clinical value of aminophylline and doxofylline in the clinical treatment of chronic obstructive pulmonary disease (COPD).

Method • The study analyzed the clinical data of 92 patients with chronic obstructive pulmonary disease who received either aminophylline or doxofylline treatment in the hospital from January 2020 to June 2022. The patients were divided into a control group composed of 46 COPD patients who received aminophylline treatment and a study group composed of 46 COPD patients who received doxofylline treatment. The two groups' total effective rate and incidence of adverse reactions were compared. The serum inflammatory factor indicators, symptom scores, pulmonary ventilation function, arterial blood gas, chest and lung responsiveness, sleep status indicators, and quality of life scores of the two groups before and after treatment were compared.

Results • At the end of treatment, the total effective rate was higher in the study group compared to the control group ($P < .05$). Regarding adverse reactions, the study group's total incidence was lower than the control group's ($P < .05$). After treatment, the levels of serum inflammatory factor indicators of CRP, PCT, and TNF- α in both groups were decreased compared with those before treatment; while comparing the above indicators between the groups, it was found that the values in the study group were lower (all $P < .05$). After treatment, the scores of symptoms such as cough, expectoration, and shortness of breath in both groups of patients were significantly lower than before treatment, while compared to the control group, the scores of all symptoms were lower in the study group ($P < .05$). After treatment, compared with FEV1, FEV1/FVC, PaO_2, and $PaCO_2$ before treatment, the above indicators in both groups were significantly improved. However, compared with various indicators in the control group, the values of FEV1, FEV1/FVC, and PaO_2 in the study group were higher, while the values of $PaCO_2$ in the study group were lower (all $P < .05$). After treatment, the measured values of indicators such as thoracic compliance, lung compliance, and total compliance in the two groups were significantly higher compared with those before the treatment, while compared to the control group, the values of all indicators in the study group were higher ($P < .05$). After treatment, compared with the control group's monitoring of various indicators of nighttime sleep, the study group obtained better data on monitoring of sleep latency and actual sleep duration. The group obtained lower scores in sleep quality evaluation, while the two groups significantly improved their sleep-related data in night-time monitoring and evaluation compared to those before treatment, with all $P < .05$. After treatment, the scores in various aspects of the quality of life of patients in both groups were significantly increased compared to those before treatment, and after comparing the scores of various quality of life between the two groups, it was found that the study group was higher than the control group (all $P < .05$).

Conclusion • After the onset of COPD, doxofylline treatment can achieve better effects than aminophylline treatment. (*Altern Ther Health Med.* [E-pub ahead of print.])

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Chronic obstructive pulmonary disease (COPD), is one of the common chronic underlying diseases in clinical practice, mainly occurring in the elderly population.[1-3] After the onset of chronic obstructive pulmonary disease, patients may experience symptoms such as coughing, expectoration, and shortness of breath. Their respiratory function is limited, which seriously affects their daily life. In addition, this disease is characterized by a long course, often with recurrent episodes, which will cause chronic pain to patients.[4-6] Medication is typically used to treat COPD, with, Theophylline being a widely recognized and effective bronchodilator.[7,8] Aminophylline and doxofylline are commonly used theophylline drugs in the treatment of respiratory diseases in clinical practice, both of which have the effect of dilating the bronchus.[9,10] This study selected two groups of patients with chronic obstructive pulmonary disease who received treatment with aminophylline and doxofylline in hospitals from January 2020 to June 2022, with 46 cases in each group. A retrospective study was conducted between the two groups of patients.

DATA AND METHODS

General data

The study analyzed clinical data from 46 patients with chronic obstructive pulmonary disease who received

aminophylline treatment and 46 patients who received doxofylline treatment, selected from those who received medication treatment in the hospital from January 2020 to June 2022.

Inclusion criteria: (1) The patients who were diagnosed with chronic obstructive pulmonary disease (COPD) through symptom observation and lung function testing, and in the acute phase of attack; (2) The patients aged between 60 and 80 years old.; (3) The patients who were conscious when seeking medical treatment, voluntarily accepted medication treatment, and could cooperate with the treatment, and complete the treatment; (4) The patients with complete clinical data.

Exclusion criteria: (1) The patients who were complicated with severe liver and kidney dysfunction; (2) The patients with mental and cognitive impairments; (3) The patients with malignant tumors; (4) The patients with a history of allergies to theophylline drugs in the past; (5) Patients were lost to follow-up and dropped out of the study.

Methods

After admission, all patients underwent routine examinations such as complete blood count and CT scans. Based on the examination results, patients were treated with anti-infection, oxygen therapy, sputum elimination, and glucocorticoid therapy, while also preventing and treating water and electrolyte disorders. The control group received Aminophylline Injection (Hubei Tiansheng Pharmaceutical Co., Ltd., National Medical Products Administration Approval Number: H42021837, Specification: 2ml:0.25g). The dosage was 0.25g per dose, twice a day, and the aminophylline Injection was diluted with a 5% glucose injection solution and administered intravenously for 7 successful days. The study group received Doxofylline Injection (Sichuan Hongming Bosi Pharmaceutical Co., Ltd., National Medical Products Administration Approval Number: H20183230, Specification: 10ml:0.1g). The dosage was 0.3g per dose, once a day, and the Doxofylline Injection was diluted with 5% glucose injection solution and administered intravenously for 7 successive days.

Observation indicators

The total effective rate and the incidence of adverse reactions between the two groups were compared, and the serum inflammatory factor indicators, symptom scores, pulmonary ventilation function, arterial blood gas, chest and lung compliance, sleep status indicators, and quality of life scores before and after treatment were compared between the two groups.

Curative effect: Clinical efficacy judgments refer to the "Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease". Cure: cough, sputum, dyspnea, and lung auscultation recover to the level before acute attacks, blood gas and routine blood indicators are normal, and chest X-ray or CT scan shows significant improvement. Improve: cough, sputum, dyspnea, and lung auscultation are significantly reduced but have not fully recovered to the level before acute attacks, blood gas, and routine blood indicators show significant improvement, and chest X-ray or CT scan shows improvement. Invalid: no change or worsening in the above clinical manifestations, and no improvement or worsening in the auxiliary examination indicators. The total effective rate is the percentage of the sum of cured and improved cases among all cases.

Serum inflammatory factors: Before and after the commencement of the treatment, fasting morning venous blood samples (4ml) were collected from the patients. The samples were centrifuged at 3000 r/min for 20 minutes at 4°C using a centrifuge. The upper layer of serum was collected and stored at 4°C for the detection of serum inflammatory factors, including C-reactive protein (CRP), procalcitonin (PCT), and tumor necrosis factor-alpha (TNF-α). The corresponding detection methods were immunoturbidimetry, immunochromatography, and enzyme-linked immunosorbent assay.

Symptoms: The severity of various symptoms of chronic obstructive pulmonary disease (COPD) in patients evaluated, such as cough, expectoration, and shortness of breath. When evaluating, the Likert 4-level scoring method was used to score, with 0 indicating no symptoms and 1, 2, and 3 indicating mild, moderate, and severe symptoms. The higher the score obtained, the more severe the symptoms.

Pulmonary ventilation function was detected by a pulmonary function detector, which was used to measure two pulmonary ventilation function indicators, namely, forced breathing volume in one second (FEV1) and the ratio of FEV1 to vital capacity (FEV1/FVC).

Arterial blood gas was detected by a full-automatic blood gas analyzer. The analyzer was used to measure three indicators during arterial blood gas analysis, namely, arterial partial pressure of oxygen (PaO_2) and arterial blood partial pressure of carbon dioxide ($PaCO_2$).

Sleep: Monitoring of the sleep latency and actual sleep duration at night was carried out among patients. Multi-channel sleep map instruments were used to monitor patients' sleep data at night. At the same time, the sleep quality of patients was scored at night using the Pittsburgh Sleep Quality Index (PSQI) scale. The highest score is set at 21 points. The higher the score, the more serious the problems encountered during nighttime sleep.

Quality of Life Rating: The quality of life assessment tool was the WHO Quality of Life Assessment Brief (WHOQOL-BREF). The scale sets the highest evaluation score for physiological, psychological, environmental, and social relationships at 100 points. The higher the evaluation score, the higher the quality of life level.

Statistical methods

The data were analyzed by SPSS 22.0 software. Quantitative data that follows a normal distribution is represented by the mean ± standard deviation ($\bar{x} \pm s$) and is compared using a t test. Qualitative data is represented by frequency and percentage (%) and is compared using the χ^2 test. $P < .05$ indicated that the difference was statistically significant.

Table 1. Comparison of total effective rates between two groups [n (%)]

group	Number of cases	cure	improve	invalid	Total effective rate
Control group	46	23 (50.00%)	16 (34.78%)	7 (15.22%)	39 (84.78%)
Research Group	46	28 (60.87%)	17 (36.96%)	1 (2.17%)	45 (97.83%)[a]

[a]indicates comparison with the control group, $P < .05$.

Table 2. Comparison of the incidence of adverse reactions between two groups [n (%)]

group	Number of cases	dizzy	nausea	diarrhea	Total incidence
control group	46	3 (6.52%)	4 (8.70%)	1 (2.17%)	8 (17.39%)
Research Group	46	1 (2.17%)	1 (2.17%)	0 (0%)	2 (4.35%)[a]

[a]indicates comparison with the control group, $P < 0.05$.

Figure 1. Histogram of clinical efficacy in two groups

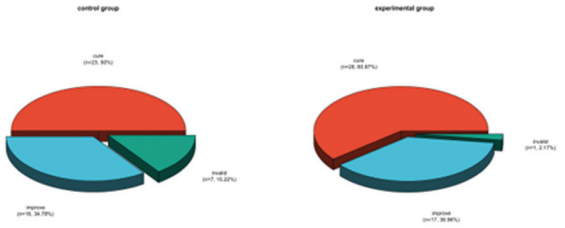
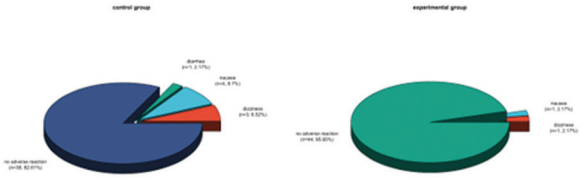


Figure 2. Histogram of the incidence of adverse reactions in two groups



RESULTS

Comparison of total effective rates between two groups

At the end of treatment, the overall effective rate of the research group was significantly higher than that of the control group ($P < .05$). See Table 1 and Figure 1.

Comparison of the incidence of adverse reactions between two groups

Regarding adverse reactions, the total incidence of the study group was significantly lower compared to the control group ($P < .05$). See Table 2 and Figure 2.

Comparison of serum inflammatory factor indicators between two groups

After treatment, the levels of inflammatory markers such as CRP, PCT, and TNF-α in the serum of patients in both groups significantly decreased compared to before treatment ($P < .05$). In addition, after treatment, the levels of CRP, PCT, TNF-α, and other inflammatory markers in the serum of patients in the research group were significantly lower compared to the control group ($P < .05$). See Table 3 and Figure 3.

Comparison of symptom scores between two groups

After treatment, the scores of symptoms such as cough, expectoration, and shortness of breath in both groups of patients were significantly lower than before treatment, while compared to the control group, the scores of all symptoms were significantly lower in the research group ($P < .05$). See Table 4 and Figure 4.

Comparison of pulmonary ventilation function and arterial blood gas indicators between the two groups

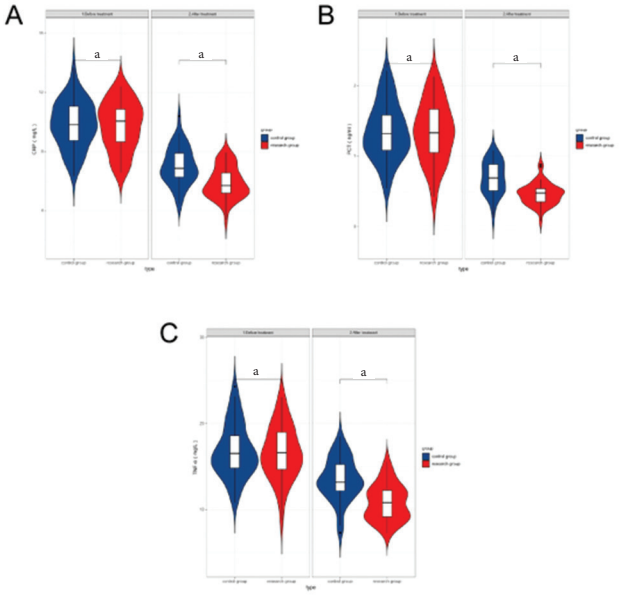
After treatment, compared with FEV1, FEV1/FVC, PaO_2, and $PaCO_2$ before treatment, the above indicators in both groups were significantly improved ($P < .05$). However, compared with various indicators in the control group, the values of FEV1, FEV1/FVC, and PaO_2 in the research group were significantly higher, while the values of $PaCO_2$ in the research group were significantly lower (all $P < .05$). See Table 5 and Figure 5.

Table 3. Comparison of serum inflammatory factor indicators between two groups ($\bar{x} \pm s$)

group	time	CRP (mg/L)	PCT (ng/ml)	TNF- α (mg/L)
Control group (n=46)	Before treatment	9.83±1.61	1.35±0.40	16.81±3.10
	After treatment	7.02±1.27[a]	0.69±0.23[a]	13.49±2.46[a]
Research group (n=46)	Before treatment	9.72±1.64	1.34±0.43	16.62±3.12
	After treatment	5.89±1.06[a,b]	0.46±0.15[a,b]	10.83±2.07[a,b]

[a]indicates comparison with before treatment, $P < .05$
[b]indicates comparison with control group, $P < .05$.

Figure 3. Histograms of serum inflammatory factor indicators in two groups



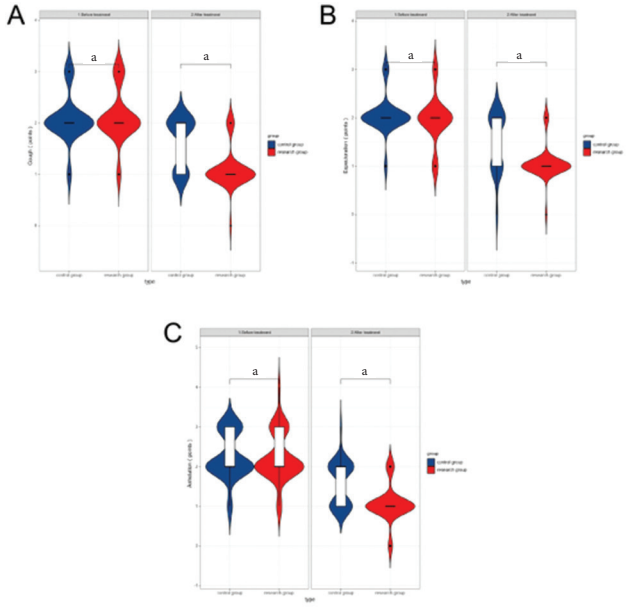
[a]indicates $P < .0001$

Table 4. Comparison of symptom scores between two groups ($\bar{x} \pm s$, points)

group	time	Cough	Expectoration	Shortness of breath
Control group (n=46)	Before treatment	2.09±0.46	2.07±0.39	2.26±0.57
	After treatment	1.63±0.49[a]	1.50±0.59[a]	1.57±0.54[a]
Research group (n=46)	Before treatment	2.13±0.50	1.98±0.49	2.24±0.60
	After treatment	1.11±0.38[a,b]	1.07±0.33[a,b]	1.07±0.44[a,b]

[a]indicates comparison with before treatment, $P < .05$
[b]indicates comparison with control group, $P < .05$.

Figure 4. Histograms of symptom scores for two groups



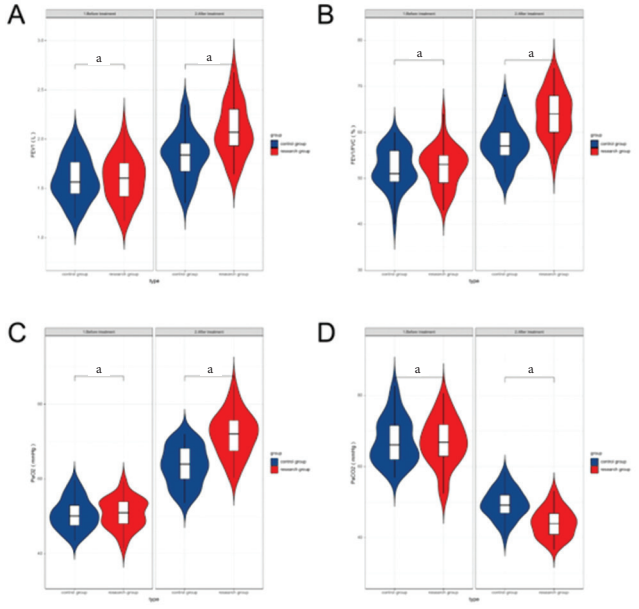
[a]indicates $P < .0001$

Table 5. Comparison of pulmonary ventilation function and arterial blood gas indicators between the two groups ($\bar{x} \pm s$)

group	time	FEV1 (L)	FEV1/FVC (%)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)
Control group (n=46)	Before treatment	1.59±0.22	52.13±4.38	50.61±4.12	67.32±6.49
	After treatment	1.83±0.24[a]	57.63±4.50[a]	63.54±5.26[a]	49.47±4.23[a]
Research group (n=46)	Before treatment	1.60±0.23	52.39±4.35	50.76±4.03	67.09±6.72
	After treatment	2.09±0.27[a,b]	64.02±5.06[a,b]	71.92±5.84[a,b]	44.18±4.06[a,b]

[a]indicates comparison with before treatment, $P < .05$
[b]indicates comparison with control group, $P < .05$.

Figure 5. Histogram of pulmonary ventilation function and arterial blood gas indicators of the two groups



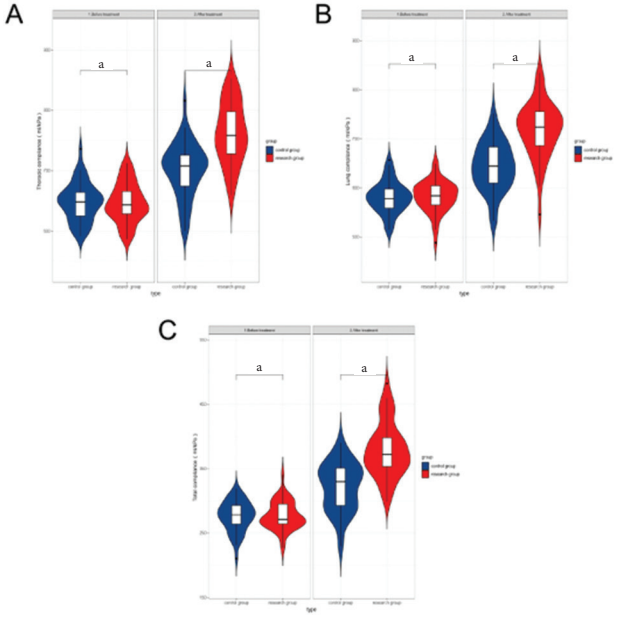
[a]indicates $P < .0001$

Table 6. Comparison of chest lung compliance indicators between two groups ($\bar{x} \pm s$, ml/kPa)

group	time	Thoracic compliance	Lung compliance	Total compliance
Control group (n=46)	Before treatment	648.31±31.42	581.09±32.18	276.48±23.57
	After treatment	701.47±45.19[a]	643.52±49.34[a]	321.58±37.60[a]
Research group (n=46)	Before treatment	647.02±32.37	582.40±32.05	277.25±21.62
	After treatment	762.95±50.23[a,b]	719.13±56.48[a,b]	378.93±42.34[a,b]

[a]indicates comparison with before treatment, $P < .05$
[b]indicates comparison with control group, $P < .05$.

Figure 6. Histograms of two groups of chest-lung compliance indicators



[a]indicates $P < .0001$

Comparison of chest lung compliance indicators between two groups

After treatment, the measured values of indicators such as thoracic compliance, lung compliance, and total compliance in the two groups were significantly higher compared with those before the treatment($P < .05$), while compared to the control group, the values of all indicators in the research group were significantly higher ($P < .05$). See Table 6 and Figure 6.

Comparison of sleep status indicators between two groups

After treatment, compared with the control group's monitoring of various indicators of nighttime sleep, the research group obtained better data on monitoring of sleep latency and actual sleep duration. The group obtained lower scores in sleep quality evaluation, while the two groups significantly improved their sleep-related data in nighttime monitoring and evaluation compared to those before treatment (all $P < .05$). See Table 7 and Figure 7.

Comparison of quality of life scores between two groups

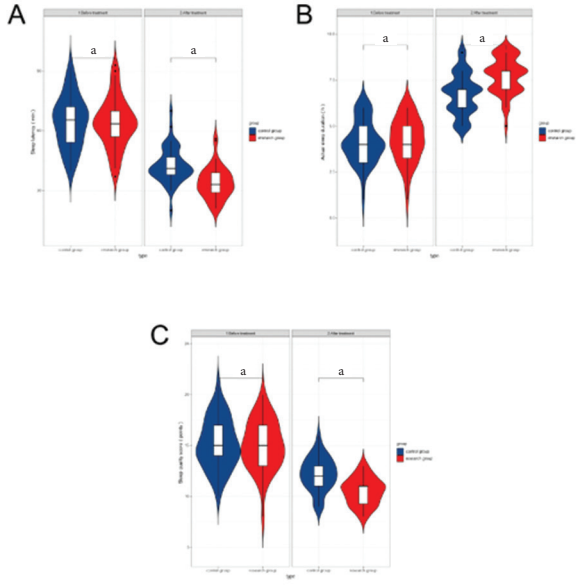
After treatment, the scores in various aspects of the quality of life of patients in both groups were significantly increased

Table 7. Comparison of sleep status indicators between two groups ($\bar{x} \pm s$)

group	time	Sleep latency (min)	Actual sleep duration (h)	Sleep quality score (points)
Control group (n=46)	Before treatment	64.50±12.70	4.13±1.17	15.17±2.45
	After treatment	42.63±8.78[a]	6.74±1.12[a]	12.20±1.65[a]
Research group (n=46)	Before treatment	64.02±12.62	4.24±1.20	15.02±2.44
	After treatment	33.76±7.87[a,b]	7.74±0.98[a,b]	10.48±1.33[a,b]

[a]indicates comparison with before treatment, $P < .05$
[b]indicates comparison with control group, $P < .05$.

Figure 7. Histograms of two groups of sleep status indicators



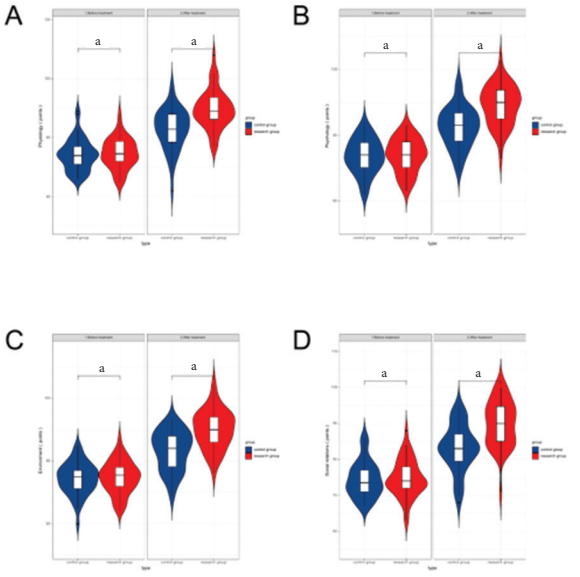
[a]indicates $P < .0001$

Table 8. Comparison of quality of life scores between two groups ($\bar{x} \pm s$, points)

group	time	physiology	psychology	environment	social relations
Control group (n=46)	Before treatment	74.26±5.32	73.65±5.29	74.48±5.12	74.41±4.98
	After treatment	82.93±6.89[a]	82.41±6.12[a]	83.26±6.29[a]	83.17±6.50[a]
Research group (n=46)	Before treatment	74.67±5.11	73.93±5.17	74.80±5.20	74.76±5.13
	After treatment	89.74±6.50[a,b]	89.11±6.10[a,b]	90.13±6.16[a,b]	89.91±6.31[a,b]

[a]indicates comparison with before treatment, $P < .05$
[b]indicates comparison with control group, $P < .05$.

Figure 8. Histograms of quality of life scores between two groups



[a]indicates $P < .0001$

compared to those before treatment, and after comparing the scores of various quality of life between the two groups, it was found that the research group was significantly higher than the control group (all $P < .05$). See Table 8 and Figure 8.

DISCUSSION

The high-risk population for chronic obstructive pulmonary disease is the elderly, and it is one of the most common chronic underlying diseases among the elderly population, with a long course of disease.[11-12] After an acute attack of COPD, patients may experience symptoms such as coughing, expectoration, and shortness of breath, and their respiratory airflow is restricted. This airflow restriction has the characteristic of incomplete reversibility.[13-14] As the condition of the COPD e worsens, the patient's respiratory disorders gradually worsen, which may lead to respiratory failure and pose a serious threat to their life safety. Moreover, due to the persistent nature of this disease, it can recur and cause more distress to patients in daily life, resulting in a significant decrease in their quality of life.[15-17]

For chronic obstructive pulmonary disease (COPD), during the acute phase, spasmolytic, expectorant, and anti-infective drugs and other drugs are often used in clinical practice to treat this disease, which can control the patient's condition to a certain extent. In addition, bronchodilators are also commonly used drugs in clinical treatment of chronic obstructive pulmonary disease. Theophylline is a common bronchodilator chosen for the treatment of COPD. It belongs to the purine receptor blocker and is a product derived from xanthine, which can promote the gradual relaxation of airway smooth muscle. It can also enhance the contraction force of the diaphragm, reduce diaphragmatic fatigue in patients, and enhance diaphragmatic endurance, which can improve respiratory function.[18-20]

Currently, the preferred treatment option for COPD in clinical practice is drug therapy. Aminophylline, Doxofylline, and other medications are commonly used in clinical settings. These drugs can effectively alleviate patients' clinical symptoms and help control the progression of the disease. The mechanism of action of these two drugs in COPD patients is similar. It is generally believed that theophylline drugs exert their effects through multiple mechanisms: Antagonizing adenosine receptors, promoting the release of endogenous catecholamines, affecting Ca^{2+} transport, and indirectly causing bronchodilation; Inhibiting phosphodiesterases to slow down the breakdown of cAMP in airway smooth muscle cells, increasing cAMP levels, and inducing a special phosphorylation process that results in airway expansion; Directly enhancing respiratory muscle contractility, relieving respiratory fatigue, increasing cardiac output, stimulating the respiratory center, enhancing respiratory depth, promoting ciliary movement in the airway, and strengthening mucociliary clearance speed. The frequencies of

clinical application of aminophylline and doxorubicin in the treatment of chronic obstructive pulmonary disease are relatively high, but the efficacy of these two theophylline drugs in treating chronic obstructive pulmonary disease remains to be explored. This study explored this issue and selected two groups of chronic obstructive pulmonary disease patients who were treated with aminophylline and doxofylline respectively for retrospective comparison. In this study, compared to the control group, the symptoms, lung function, sleep quality, and arterial blood gas of the research group patients showed significant improvements. The overall treatment effectiveness rate was significantly higher. These findings indicate that doxofylline treatment during acute exacerbations of COPD can enhance efficacy, and improve lung function parameters and sleep quality. It can be considered as a primary measure in the treatment of the disease, helping patients improve their quality of life. The above research results can confirm that doxofylline has better therapeutic effects on chronic obstructive pulmonary disease than aminophylline. The reason for this is that doxofylline is a novel methylxanthine derivative. It has an additional 3-dioxybutyl ring structure at the N7 position of the Aminophylline molecule. Consequently, its effects on the respiratory system are similar to Aminophylline but stronger. Doxofylline can inhibit both central and peripheral phosphodiesterases, which can reduce airway hyperresponsiveness and relieve respiratory spasms through multiple pathways, resulting in clinical efficacy.

The imbalance between oxidative and anti-oxidant functions in the patient's body is a relevant factor in the occurrence and development of acute exacerbations of COPD. When oxidative stress reactions cause a large influx of lymphocytes and macrophages in the airways, the body's inflammatory response intensifies. The accumulated inflammatory cells can release reactive oxygen species, leading to the production of complex sugars in the airways, subsequently damaging alveolar epithelial cells and weakening mucosal function. At the same time, inflammatory cells promote the secretion of prostaglandins and leukotrienes in the airways, further exacerbating airway injury. In this study, the levels of inflammatory markers such as CRP, PCT, and TNF-α in the serum of the research group patients were significantly lower than those in the control group. This indicates that doxofylline has better anti-inflammatory properties compared to aminophylline. The reason behind this is that doxofylline can inhibit the degranulation of neutrophils in the lungs, thereby reducing the release of oxygen free radicals, alleviating the body's inflammatory response, and reducing lung damage, leading to therapeutic effects.

When measuring the therapeutic effects of aminophylline and doxofylline on chronic obstructive pulmonary disease, it is also necessary to consider medication safety, which is an important indicator for determining whether the drug can be promoted and applied. Adverse reactions are the main indicator of medication safety. In this study, the total incidence of adverse reactions in the study group was lower than that in the control group ($P < .05$), indicating that doxofylline has better medication safety for patients with chronic obstructive pulmonary disease than aminophylline. The reasons for this are that doxofylline acts on the cyclic structure of xanthine, which can weaken its inhibitory effect on adenosine receptors, and can reduce irritation to the patient's cardiovascular and gastrointestinal systems, thereby avoiding the occurrence of adverse reactions in the gastrointestinal and cardiovascular systems after medication.

To sum up, after the onset of COPD patients, doxofylline treatment can achieve better effects than aminophylline treatment. Moreover, doxofylline can reduce the occurrence risk of adverse reactions in patients after application, with good safety. In the future, further exploration will be conducted to investigate the potential mechanisms of action, potential synergistic effects, and differences in modulating airway inflammation and bronchodilation between aminophylline and doxofylline in the treatment of COPD.

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