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Original Research Article

Effects of combination treatment with theophylline sustained-release tablets and thymalfasin on pulmonary function, immunity, and inflammation in elderly patients with chronic obstructive pulmonary disease and respiratory failure

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Abstract

Purpose: *To investigate the effect of combined administration of theophylline sustained-release tablets and thymalfasin on pulmonary function, immunity, and inflammation in elderly patients with chronic obstructive pulmonary disease (COPD) and respiratory failure.*
Methods: *A total of 122 elderly patients in Fujian Geriatric Hospital, Fuzhou, China who suffered from acute attack of COPD with respiratory failure from January 2019 - January 2020 were selected for this study. The patients were divided randomly and evenly into study and control groups. Theophylline sustained-release tablets were administered to subjects in the control group, while theophylline sustained-release tablets and thymalfasin were administered to subjects in the study group. Pulmonary function indicators, viz, forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC), blood gas indicators (PaCO2, PaO2, and SaO2), inflammatory factors (sICAM-1, PGE2, and hs-CRP), immune cells (Th17, Treg, and Th17/Treg), as well as exercise ability (the 6 min walking distance test) were evaluated for each group. Adverse reactions were also assessed.*
Results: *There were no significant differences in pulmonary function, blood gas, inflammation, immunity, and exercise ability between the two groups before treatment ($p < 0.01$). However, all parameters improved significantly for both groups after treatment, with better outcomes for all parameters in the study group. A proportion of (14.75 %) patients in the study group showed adverse events, while 13.11 % of the patients in the control group exhibited adverse effects, meaning that the study group had a slightly but not significantly higher rate of adverse events.*
Conclusion: *The combined administration of theophylline sustained-release tablets and thymalfasin reduces inflammation and improves physical immunity, leading to enhancement of blood gas and pulmonary function in elderly patients with COPD and respiratory failure. However, further clinical trials are required prior to application of this combination therapy in clinical practice.*

Keywords: *Theophylline sustained-release tablets, Thymalfasin, Chronic obstructive pulmonary disease, Respiratory failure, Pulmonary function, Immunity, Inflammation*

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INTRODUCTION

Clinical data have shown that chronic obstructive pulmonary disease (COPD) is a common disease of the respiratory system, and that patients with COPD are prone to respiratory failure, which leads to further deterioration of the patient's condition and puts the patient's life and health in danger [1]. At present, combined application of mechanical ventilation and tiotropium bromide is the main clinical treatment for COPD with respiratory failure. Although this treatment effectively alleviates and improves the blood gas indicators and the bronchus state, its comprehensive efficacy needs to be improved further [2].

Recent clinical research has found that there is a relationship between abnormal immunity and COPD complicated with respiratory failure[3]. Thus, targeting the regulation of human immunity could have practical significance for the clinical treatment of COPD with respiratory failure. In our hospital, clinical efficacy has been achieved in the treatment of COPD with respiratory failure using theophylline sustained-release tablets in combination with thymalfasin [4]. To further study the effects of theophylline sustained-release tablets in combination with thymalfasin on pulmonary function, immunity, and inflammation in elderly COPD patients with respiratory failure, a total of 122 elderly patients in Fujian Geriatric Hospital who suffered an acute attack of COPD with respiratory failure from January 2019 to January 2020 were selected as study subjects. Their relevant clinical indicators and treatments were evaluated.

METHODS

Clinical profile

A total of 122 elderly patients in Fujian Geriatric Hospital who suffered an acute attack of COPD with respiratory failure from January 2019 to January 2020 were selected as the study subjects; 52 of the subjects were male and 70 of the subjects were female. The patients were 67 – 74 years old with a mean age of 70.25 ± 1.53 years and BMI of 20.38 ± 0.56 kg/m^2. The duration of COPD in these patients was 5 – 11 years (mean, 7.24 ± 1.05 years). With regard to respiratory failure classification, 33 patients had type I respiratory failure, while 89 subjects had type II respiratory failure. Furthermore, 61 patients had complications of hypertension, 37 diabetic mellitus, and 24 had other diseases. With regard to poor habits, 75 patients consumed alcohol regularly while 58 smoked regularly.

The patients were divided randomly into a study group and a control group, with 61 subjects in each group. Among the 61 patients in the study group, 25 were male and 36 were female. In the study group, the ages ranged from 67 – 74 years, with an average age of 70.28 ± 1.56 years and average BMI of 20.56 ± 0.51 kg/m^2. The duration of COPD in the study group was 5–11 years, with an average of 7.26 ± 1.09 years. As for to the respiratory failure classification in the study group, 16 subjects had type I respiratory failure, and 45 had type II respiratory failure. As for patient's complications in the study group, 30 subjects had hypertension, 19 subjects had diabetic mellitus, and 12 subjects had other diseases. As for patient's bad habits in the study group, 37 subjects consumed alcohol regularly and 30 subjects smoked regularly.

Among the 61 patients in the control group, 27 were males and 34 were females. In the control group, the ages ranged from 67–74 years, with an average age of 70.21 ± 1.51 years and an average BMI of 20.21 ± 0.56 kg/m^2. The duration of COPD in the control group was 6–11 years, with an average of 7.21 ± 1.02 years. With regards to the respiratory failure classification in the control group, 17 subjects had type I respiratory failure and 44 subjects had type II respiratory failure. As for patient's complications in the control group, 31 subjects had hypertension, 18 subjects had diabetic mellitus, and 12 subjects had other diseases. As for patient's bad habits in the control group, 38 subjects consumed alcohol regularly and 28 subjects smoked regularly. There were no statistically significant differences in clinical data between the two groups, and the data were comparable. This study was approved by the Ethics Committee of Fujian Geriatric Hospital (approval no. 20190101) and conducted in line with the guidelines of World Medical Association Declaration of Helsinki [5]. Written informed consent for anonymized patient information to be published in this article was obtained from legally authorized representatives of the patients.

Treatments

After admission, patients in the two groups were treated with expectorants, antispasmodics, glucocorticoids, and anti-infective therapy. All patients received non-invasive positive pressure ventilation (NIPPV; Beijing Hangyusida Technology Development Co. Ltd). By setting the ventilator to S/T mode and an oxygen flow of 3 – 7 L/min, percutaneous blood oxygen saturation was > 90 %. All patients were also given 18 μg of tiotropium bromide (Nanchang Hongyi

Pharmaceutical Co. Ltd.; SFDA approval no. H20130110) by inhalation once a day.

Control group patients were given 0.2 g of theophylline extended-release tablets (Jilin Lisheng Pharmaceutical Co. Ltd; SFDA approval no. H22023973) via oral administration twice a day. In addition to the same treatments given to the control group, patients in the study group received 1.6 mg of thymalfasin (SciClone Pharmaceuticals Italy; S.R.L. approval and import drug registration certificate no. H20120531) by i.v. injection twice a week. Therapeutic efficacies were calculated after 4 weeks of treatment between the two groups.

Evaluation of parameters/indices

Pulmonary function indicators included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC. Blood gas indicators included arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), and blood oxygen saturation (SaO_2). Inflammatory factors included soluble cell adhesion molecule-1 (sICAM-1), prostaglandin E2 (PGE2), and hypersensitive C-reactive protein (hs-CRP). Immune cells included T helper cell 17 (Th17), regulatory T cell (Treg), and Th17/Treg. Exercise ability was assessed by the 6 min walking distance (6MWD). Adverse reactions were also monitored and compared before and after treatment in the two groups.

Statistical analysis

Data were analyzed with SPSS 22.0 software. Quantitative data are presented as mean ± standard deviation (SD) and analyzed using the t test. Enumeration data are presented as percentages (%) and analyzed using the Chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Pulmonary function

Before treatment, the levels of various pulmonary function indicators were similar between the two groups, and they improved upon treatment ($p < 0.05$). These indicators were significantly improved in the study group compared with the control group ($p < 0.05$; Table 1).

Blood gas indicators

Before treatment, various blood gas indicators did not differ significantly between the two groups, and they improved upon treatment ($p < 0.05$). Increased improvement of these indicators was observed in the study group when compared with the control group ($p < 0.05$; Table 2).

Immune cell levels

Prior to treatment, various immune cell levels did not differ significantly between the two groups, and they were ameliorated upon treatment ($p < 0.05$). Increased improvement of these indicators was observed in the study group compared with the control group ($p < 0.05$; Table 4).

Exercise ability

Before treatment, the 6MWD did not differ significantly between the two groups, and the 6MWD increased upon treatment ($p < 0.05$). A higher 6MWD was observed in the study group compared with the control group ($p < 0.05$; Table 5).

Incidence of adverse reactions

In the study group, 9 patients had adverse reactions, i.e., incidence of adverse events of 14.75 %, which is slightly but not significantly higher than in control group, which was 13.11 % (Table 6).

DISCUSSION

Clinical studies have suggested that chronic inflammatory and immune responses in the lung and blood vessels of the trachea play important roles in the onset and progression of COPD with respiratory failure [6,7]. The dual effect of continuous airway inflammation and decreased blood flow is continuous decreases in lung function leading to abnormal blood gas and decreased oxygenation, which aggravates the condition of the patient [8,9]. As a result of the continuous increase in immunology-related clinical research, it has been shown that immunomodulatory dysfunction contributes to the occurrence and progression of COPD with respiratory failure, and that regulation of immune function improves the condition of the patient [10]. The traditional clinical treatment of COPD with respiratory failure is based on conventional methods such as anti-inflammatory, anti-infective, and expectorant treatments to ameliorate the clinical symptoms by alleviating the inflammatory response. Traditional treatment achieves some clinical efficacy, but the overall anti-inflammatory effect remains unsatisfactory due to a lack of immune regulation [11].

Table 1: Comparison of pulmonary function between the two groups

Group	FEV1 (L)				FVC (L)				FEV1/FVC (%)			
	Before treatment	***After treatment***	***t***	***P-value***	***Before treatment***	***After treatment***	***t***	***P-value***	***Before treatment***	***After treatment***	***t***	***P-value***
Study	1.21 ± 0.11	1.89 ± 0.05	43.9539	0.0000	2.12 ± 0.10	2.84 ± 0.13	34.2864	0.0000	56.83 ± 6.02	66.86 ± 3.70	11.0862	0.0000
Control	1.22 ± 0.09	1.51 ± 0.03	23.8749	0.0000	2.11 ± 0.12	2.42 ± 0.09	16.1412	0.0000	57.70 ± 5.75	62.62 ± 2.71	6.0451	0.0000
t	0.5495	50.899	——	——	0.5	20.7465	——	——	0.8162	7.2205	——	——
P-value	0.5837	0.0000	——	——	0.6180	0.0000	——	——	0.4160	0.0000	——	——

Table 2: Comparison of blood gas indicators between the two groups (mean ± SD, n = 61)

Group	$PaCO_2$ (mmHg)				PaO_2 (mmHg)				SaO_2 (%)			
	Before treatment	***After treatment***	***t***	***P-value***	***Before treatment***	***After treatment***	***t***	***P-value***	***Before treatment***	***After treatment***	***t***	***P-value***
Study	65.16 ± 5.16	40.25 ± 2.16	34.7798	0.0000	50.35 ± 4.22	94.35 ± 6.37	44.9744	0.0000	79.35 ± 5.16	94.06 ± 6.39	13.9882	0.0000
Control	65.21 ± 5.19	50.24 ± 3.21	19.1593	0.0000	50. 29 ± 4.17	86.09 ± 5.11	42.3934	0.0000	79.29 ± 5.09	86.15 ± 6.05	6.7766	0.0000
t	0.0534	20.1662	——	——	0.079	7.8998	——	——	0.0647	7.0206	——	——
P-value	0.9575	0.0000	——	——	0.9372	0.0000	——	——	0.9486	0.0000	——	——

Table 3: Comparison of inflammatory factor levels between the two groups (mean ± SD, n = 61)

Group	sICAM-1 (ng/mL)				PGE2 (pg/mL)				Hs-CRP (ng/L)			
	Before treatment	***After treatment***	***t value***	***P-value***	***Before treatment***	***After treatment***	***t value***	***P-value***	***Before treatment***	***After treatment***	***t value***	***P-value***
Study group	212.25 ± 11.25	96.35 ± 3.16	77.465	0.0000	20.65 ± 1.26	9.59 ± 0.45	64.5627	0.0000	36.19 ± 2.15	10.25 ± 1.06	84.5178	0.0000
Control group	213.01 ± 10.98	129.35 ± 5.16	53.8579	0.0000	20.71 ± 1.19	12.16 ± 0.79	46.7514	0.0000	35.97 ± 2.09	17.56 ± 1.12	60.6393	0.0000
t value	0.3776	42.5963	——	——	0.2704	22.0775	——	——	0.5731	37.0234	——	——
P-value	0.7064	0.0000	——	——	0.7873	0.0000	——	——	0.5677	0.0000	——	——

Table 4: Comparison of immune cells between the two groups (mean ± SD, n = 61)

Group	Th17 (%)				Treg (%)				Th17/Treg			
	Before treatment	***After treatment***	***t-value***	***P-value***	***Before treatment***	***After treatment***	***t-value***	***P-value***	***Before treatment***	***After treatment***	***t-value***	***P-value***
Study group	4.56 ± 0.21	1.34 ± 0.06	115.1494	0.0000	5.35 ± 0.45	2.08 ± 0.08	55.8783	0.0000	85.89 ± 8.63	64.13 ± 3.83	18.0000	0.0000
Control group	4.59 ± 0.16	2.16 ± 0.11	97.7463	0.0000	5.37 ± 0.51	3.16 ± 0.11	33.0836	0.0000	86.30 ± 9.09	68.20 ± 4.53	13.9191	0.0000
t value	0.8875	51.1127	——	——	0.2297	62.0159	——	——	0.2555	5.3586	——	——
p value	0.3766	0.0000	——	——	0.8187	0.0000	——	——	0.7988	0.0000	——	——

Table 5: Comparison of exercise ability between the two groups (mean ± SD, n = 61)

Group	6MWD (m)			
	Before treatment	***After treatment***	***t***	***P-value***
Study	301.25 ± 15.24	379.34 ± 16.35	27.2871	0.0000
Control	298.15 ± 14.98	320.64 ± 14.26	8.493	0.0000
t	1.133	21.1322	——	——
P-value	0.2595	0.0000	——	——

Table 6: Comparison of the adverse reactions between the two groups

Group	Nausea	Dizziness	Erythra	Diarrhea	Incidence of adverse events
Study	4 (6.56)	3 (4.92)	1 (1.64)	1 (1.64)	9 (14.75)
Control	3 (4.92)	3 (4.92)	1 (1.64)	1 (1.64)	8 (13.11)
χ^2			——		0.0683
P-value			——		0.7938

Clinical studies have shown that theophylline is a common methylxanthine derivative that effectively improves pulmonary artery resistance [12], which plays a critical role in promoting bronchiectasis in COPD with respiratory failure. Theophylline enhances the contractility of septum muscles by resisting the contraction caused by adenosine in the respiratory tract, leading to favorable clinical efficacy for COPD with respiratory failure. Thymalfasin is a drug commonly used as an immunomodulator that regulates the structure and composition of immune cells in the human body, improves lymphocyte differentiation, promotes antibody production, and improves the defense function of the human immune system [13]. Therefore, combination treatment with theophylline sustained-release tablets and thymalfasin reduce acute attacks of COPD with respiratory failure.

In this study, pulmonary function and blood gas indicators, levels of inflammatory factors and immune cells, and exercise ability of patients in the two groups did not differ before treatment, and they all improved after treatment in both groups ($p < 0.05$) with better effects observed in the study group than in the control group ($p < 0.05$). The study group showed an incidence of adverse events of 14.75 %, which was slightly but not significantly higher than the 13.11 % rate of adverse events in the control group. Consistent with similar local and international studies, our results showed that combination treatment with theophylline sustained-release tablets and thymalfasin was effective in the treatment of COPD with respiratory failure [14,15]. It has been reported that sICAM-1, PGE2, and hs-CRP are clinically serum inflammatory factors [16,17]. ICAM-1 is an important cell surface adhesion molecule that is usually expressed at low levels in the human body. Under the influence of inflammatory factors, it sheds from the cell surface and dissolves into the blood to become sICAM-1. hs-CRP is an important marker and reactive protein that is expressed in response to acute inflammation. The Th17 cells regulate the immune response by eliminating pathogens. Responses to Th17-related immune regulation differ among individuals with various degrees of pathological damage induced in some patients. Treg cells exert immunosuppressive effects by inhibiting IL-17-related responses, thereby protecting normal tissues from inflammatory damage. An imbalance in the ratio of Th17 and Treg cells indicates an immune system disorder.

Thymalfasin improves and optimizes patient immunity and ameliorates the inflammatory response by regulating immune function. Thus, theophylline sustained-release tablets and thymalfasin combination treatment is advantageous for the treatment of COPD with respiratory failure in the elderly [18]. This combination treatment also simultaneously addresses both the symptoms and the root causes of COPD with respiratory failure.

CONCLUSION

The combination treatment of theophylline sustained-release tablets and thymalfasin reduces inflammation and improves immunity, thus enhancing blood gas and pulmonary function in elderly patients with COPD involving respiratory failure. Therefore, this treatment strategy may be safe and reliable in clinical practice.

DECLARATIONS

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None provided.

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. All authors contributed to the study's conception and design. Material preparation and experiments were performed by Yu Liu and Chunhui Zhang. Data collection and analysis were performed by all authors. The first draft of the manuscript was written by Yu Liu, and all authors commented on drafts of the manuscript. All authors read and approved the final manuscript.

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