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Research Article
Doxofylline Combined with Budesonide Exert Obvious Therapeutic Effects on Patients with Bronchial Asthma

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Abstract

Background and Objective: Bronchial asthma has become one of the global public health problems currently. This study aimed to assess the effects of doxofylline combined with budesonide on the pulmonary function of patients with bronchial asthma based on changes in the levels of T helper type 1 (Th1), Th2 and Th17 cells in peripheral blood. **Materials and Methods:** A total of 120 patients with bronchial asthma treated were randomly divided into experimental and control groups (n = 60). The control group received budesonide suspension inhalation therapy, while the experimental group was treated with doxofylline tablets in addition to the treatment for the control group. The disappearance time of main symptoms was recorded. Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1), Peak Expiratory Flow (PEF) and the levels of Th1, Th2 and Th17 cells in peripheral blood and interferon-gamma (IFN-γ), interleukin-4 (IL-4) and IL-17 in serum were measured before and after 3 months of treatment. **Results:** After treatment, the disappearance time of wheezing, cough, short breath and pulmonary wheezing sound in the experimental group was significantly shorter than that in the control group ($p<0.05$). FVC, FEV1 and PEF in both groups rose and the experimental group had a more significant increase ($p<0.05$). The level of Th1 cells and Th1/Th2 rose, while those of Th2 and Th17 cells declined in both groups, especially in the experimental group ($p<0.05$). The serum level of IFN-γ increased, while those of IL-4 and IL-17 decreased in both groups, particularly in the experimental group ($p<0.05$). During treatment, the incidence rate of adverse reactions was 3.33% in both groups ($p>0.05$). **Conclusion:** Doxofylline combined with budesonide can effectively relieve the imbalances of inflammatory response and immune mechanism in patients with bronchial asthma, thus ameliorating clinical symptoms and pulmonary function.

Key words: Doxofylline, budesonide, pulmonary function, bronchial asthma, T cell

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Bronchial asthma (or asthma) as a common type of chronic respiratory disease with high incidence and recurrence rates have become one of the global public health problems currently. It can be found in all ages and has a long disease course, with major clinical manifestations such as long-term repeated cough, wheezing and chest tightness. If not controlled effectively, it can easily trigger chronic obstructive pulmonary emphysema, seriously affecting the physical and mental health and quality of life of patients and bringing severe challenges to the stability of social public health[1]. The pathogenesis of bronchial asthma is not completely clear yet. However, factors such as genetic genes, living environment and autoimmune regulation disorders in patients all affect the onset of bronchial asthma[2]. Currently, inhaled bronchodilators and glucocorticoids are mainly selected for clinical intervention. However, long-term use of these drugs will lead to adverse reactions such as decreased immune function and osteoporosis[3]. Therefore, in-depth investigation of the pathogenesis of bronchial asthma and the formulation of focused treatment plans have important guiding significance for improving the total effectiveness of clinical treatment and minimizing the incidence rate of adverse reactions in patients. Bronchial asthma is a chronic and persistent inflammatory disease of the airway under stress, which involves a variety of structural cells (such as airway epithelial cells and fibroblasts), effector cells (including eosinophils, neutrophils, mast cells, T lymphocytes and other immune cells) and cytokines[4]. The immune imbalance between T helper type 1 (Th1) and Th2 cells plays an important role in immune tolerance and regulatory disorders of asthma[5]. Zarneshan *et al.*[6]. demonstrated that effectively improving the Th1/Th2 ratio could markedly facilitate the pulmonary function of bronchial asthma patients. According to the study of Ramakrishnan *et al.*[7], Th17 cells played a very vital role in regulating the immune disorder during the occurrence and development of bronchial asthma through the pro-inflammatory effect induced by excessive secretion of IL-17. In this study, the changes in the levels of Th1, Th2 and Th17 cells in peripheral blood of 120 bronchial asthma patients were observed to evaluate the effect of doxofylline (a commonly used bronchodilator) combined with budesonide (a commonly used clinical glucocorticoid) on the pulmonary function of patients with bronchial asthma.

MATERIALS AND METHODS

Baseline clinical data: A total of 120 patients with bronchial asthma who were treated in the hospital from July, 2018 to February, 2019 were selected as subjects.

Inclusion criteria[8]:

- Patients with an age $\geq$18 years old
- Those whose results of pulmonary auscultation, pulmonary function examination and laboratory examinations met the relevant standards of Chinese Expert Consensus on Bronchial Asthma Control (2013) by the Asthma Workgroup of Chinese Thoracic Society, Chinese Medical Association
- Those with bronchial asthma at the chronic persistent stage and clinical remission stage, uncontrolled or partially controlled and having $\geq$2 asthma attacks in the last year
- Those with allergen confirmed by allergen-specific IgE antibody screening
- Those that could be effectively treated by diagnostic treatment with antiasthmatic drugs
- Those who were informed of the treatment plan had complete clinical data and were cooperative

Exclusion criteria:

- Patients with chronic cough driven by other causes such as severe upper respiratory tract infection, pneumonia and tuberculosis, or bronchial symptoms triggered by foreign bodies in the trachea or postnasal drip syndrome
- Those with other respiratory diseases such as respiratory failure
- Those with signs of severe infection or ineffective treatment with antibiotics for a relatively long time
- Those that had glucocorticoid treatment within 4 weeks before treatment
- Those who suffered from respiratory tract infection within 2 weeks before treatment
- Those complicated with chronic wasting diseases, endocrine, systemic immune system diseases, genetic metabolic diseases or chronic or severe malnutrition
- Those allergic to relevant pharmaceutical ingredients in this study
- Those who were pregnant or breastfeeding

All the patients or their family members signed the informed consent and this study was reviewed and approved by the Ethics Committee of the hospital.

Grouping: According to the admission number, the patients were divided into an experimental group (n = 60) and a control group (n = 60) using a random number table. In the experimental group, the male-female ratio was 3:2, the age was 18-65 years old, with an average of (49.73±14.22) years old and the course of the disease was 7 months-15 years, with a mean of (8.25±1.37) years. In the control group, the male-female ratio was 7:3, the age was 19-65 years old, with an average of (48.62±15.03) years old and the course of the disease was 1-16 years, with a mean of (9.13±0.92) years. No significant differences were observed in the above baseline data between the two groups ($p>0.05$), which were comparable.

Administration methods: After admission, all patients were given routine interventions, such as facilitating expectoration, relieving cough, anti-inflammation and forbidding smoking and those with bacterial infections were treated with appropriate antibiotics. Meanwhile, patients in the control group were also administered with budesonide inhalation suspension (registration number: H20090902, AstraZeneca Pty Ltd., Australia) at 200 μg/time, once daily. In addition to the treatment in the control group, patients in the experimental group were dosed with doxofylline tablets (certification number: H20030633, Shanghai Qinyi Nantong Pharmaceutical Co., Ltd.) at 0.2 g/time twice a day. All patients were treated continuously for 3 months.

Evaluation of therapeutic effects:

- **Cured:** The symptoms disappeared and the pulmonary wheezing sound was mild
- **Markedly effective:** The symptoms were markedly improved and the pulmonary wheezing sound was prominently alleviated
- **Effective:** The symptoms were improved and the pulmonary wheezing sound was alleviated
- **Ineffective:** The symptoms and wheezing sound exhibited no obvious changes or even aggravated. The total effective rate was calculated Eq.:

$$\text{Total effective rate (\%)} = \frac{\text{Cured cases+markedly effective cases+effective cases}}{\text{Total cases}} \times 100$$

Recording of remission time of clinical symptoms: The disappearance time of main symptoms such as wheezing, cough, short breath and the pulmonary wheezing sound was recorded.

Pulmonary function detection: The pulmonary function indices including Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1) and Peak Expiratory Flow (PEF) were measured using an RSFJ1000 pulmonary function instrument before treatment and after 3 months of treatment.

Detection of immune cells: Besides, 6 mL of fasting elbow venous blood was taken before treatment and after 3 months of treatment and divided into 2 portions (3 mL/portion). One of the portions was used for the determination of the expression of Th1, Th2 and Th17 cells through flow cytometry and the Th1/Th2 ratio was calculated. The normal reference ranges for Th1, Th2, Th1/Th2 and Th17 are 0.39-0.84, 0.28-0.45, 1.2-1.8 and 17-26%, respectively. The other portion was centrifuged and then the upper-layer serum was collected for the measurement of Th1 cytokine interferon-gamma (IFN-γ), Th2 cytokine interleukin-4 (IL-4) and Th17 cytokine IL-17 using ELISA kits strictly following the instructions. The normal reference intervals were as follows: IFN-γ: 0-11.6 pg mL^{-1}, IL-4: 1.3-5.8 ng mL^{-1} and IL-17: 0-15 ng mL^{-1}.

Observation of adverse reactions: The adverse reactions such as tachycardia, vasodilation, nausea, vomiting, abdominal pain, fatigue, vertigo and skin rashes were observed in the patients and recorded in time.

Statistical analysis: SPSS 16.0 software was used for data analysis. The numerical data were expressed as a percentage and intergroup comparisons were conducted by chi-square test or Fisher's exact test. The quantitative data were expressed as Mean±standard deviation ($\bar{\chi}\pm s$), paired t-test was conducted for intragroup comparison before and after treatment and independent t-test was conducted for intergroup comparison. The $p<0.05$ suggested that the differences were statistically significant.

RESULTS AND DISCUSSION

Clinical therapeutic effects: Budesonide targets glucocorticoid receptors, as a common drug for the clinical treatment of asthma. It can regulate the transcription of target

genes in airway cells and inhibit the exudation of inflammatory cells and the release of cytokines. Additionally, aerosol inhalation allows the drug to directly affect the respiratory tract and to rapidly work. It also has the advantages of small dosage, fast onset and safety[9]. Doxofylline is a bronchodilator that can directly relax the bronchial smooth muscle, with obvious anti-inflammatory and anti-asthmatic effects[10].

Herein study compared the therapeutic effects of Doxofylline combined with budesonide on bronchial asthma. After treatment, the total effective rate in the experimental group was significantly higher than that in the control group (96.67 vs. 81.67%), with a significant difference ($p<0.05$) in Table 1.

Disappearance time of main clinical symptoms: The typical symptoms of bronchial asthma are wheezing, coughing, shortness of breath and rale in the lungs. After treatment, the disappearance time of wheezing, cough, short breath and pulmonary wheezing sound in the experimental group [(4.79±0.82), (4.22±1.10), (3.86±0.85), (5.41±1.50) days] was significantly shorter than those in the control group [(5.66±1.34), (6.11±1.08), (5.96±1.50), (6.12±1.63) days] ($p<0.05$) shown in Table 2.

Pulmonary functions: FVC, FEV1 and PEF are commonly used lung function indices. Before treatment, there were no significant differences in pulmonary function indices between the two groups ($p>0.05$). After treatment, FVC, FEV1 and PEF rose significantly in both groups and the experimental group exhibited more significant increases in FVC, FEV1 and PEF [(2.87±0.54 L), (2.65±0.54 L), (93.90±5.77 L s^{-1})] than those of the control group [(2.54±0.45 L) L, (2.22±0.40 L), (89.21±5.86 L s^{-1})] ($p<0.05$) in Table 3.

Levels of Th1, Th2 and Th17 cells in peripheral blood: Th2 cell-dominant Th1/Th2 cell imbalance causes bronchial asthma, as the immunological basis for the progression of airway eosinophilic inflammation. The transcription factors of Th1 helper cells maintain the balance by participating in the regulation of cellular immune response and resist the immune response of intracellular bacteria and protozoa[11]. Th1 cells are CD^{4+} cells that can secrete IFN-γ, IL-2, TNF, etc. Especially, IFN-γ can activate macrophages and enhance phagocyte-mediated anti-infective immunity. It can also promote the production of IgG, exerting an inhibitory effect on asthma attacks. The transcription factors of Th2 helper cells (STAT6 and GATA, etc) maintain the balance by participating in the regulation of cellular immune response and fight against the immune response of extracellular multicellular parasites[12]. Excessive activation of Th2 leads to allergic diseases of mast cells and eosinophils, such as allergic rhinitis and bronchial asthma. As a new T cell subgroup, Th17 also plays a crucial role in the immune disorder of bronchial asthma. Unlike Th1 and Th2 cells, Th17 has an independent differentiation pathway and can promote the release of inflammatory factors by a variety of cells. It can secrete IL-17 which in turn facilitates the activation of T cells and stimulates immune cells to produce more cytokines, finally inducing airway obstruction and structural changes in the airway and lung tissues[13]. Before treatment, there were no significant differences in the levels of Th1, Th2 and Th17 cells in peripheral blood between the two groups ($p>0.05$). After treatment, the level of Th1 cells and Th1/Th2 rose significantly, while the levels of Th2 and Th17 cells declined significantly and experimental group exhibited more significant increases in the level of Th1 and Th1/Th2 [(0.71±0.15%), (1.15±0.20%)] and more significant decreases in the levels of Th2 and Th17 cells [(0.61±0.16%), (0.49±0.10%%)] than those of control group [(0.63±0.14%), (0.92±0.19%), (0.71±0.17%), (0.67±0.15%)] ($p<0.05$) in Table 4.

Before treatment, there were no significant differences in the levels of IFN-γ, IL-4 and IL-17 between the two groups ($p>0.05$). After treatment, the level of IFN-γ rose significantly, while the levels of IL-4 and IL-17 dropped significantly in the two groups and the experimental group had a more significant increase in the level of IFN-γ [(18.34±3.45 pg mL^{-1})] and a more significant decrease in the levels of IL-4 and IL-17 [(34.95±5.27), (27.32±5.44) ng mL^{-1}] than those of control group [(18.43±3.15 pg mL^{-1}); (34.97±6.22 ng mL^{-1}), (23.23±4.78 ng mL^{-1})] ($p<0.05$) in Table 5.

Incidence rates of adverse reactions: Adverse reactions, such as tachycardia, nausea and vomiting, dizziness and skin rashes, often occur during drug treatment. During treatment, the incidence rate of adverse reactions was 3.33% in both groups, without statistically significant difference ($p>0.05$) in Table 6.

With the deterioration of the environment and changes in dietary structure and lifestyle, the global incidence rate of bronchial asthma (or asthma) is increasing annually. As is all known to all, exposure to pollen, dust, cold air, dirt, oil fume or other stimuli in the environment can easily lead to asthmatic attacks in asthma patients. The symptoms mainly include wheezing, coughing and short breath, which generally occurs or aggravate at night or in the early morning. Besides, the disease is recurrent and refractory, seriously affecting the

Table 1: Clinical therapeutic effects (%)

Groups	n	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Experimental	60	13 (21.67)	19 (31.67)	17 (28.33)	11 (18.33)	49 (81.67)
Control	60	17 (28.33)	22 (36.67)	19 (31.67)	2 (2.33)	58 (96.67)
χ^2						5.316
p						0.021

Table 2: Disappearance time of main clinical symptoms ($\bar{\chi}\pm$s, day)

Groups	n	Wheezing	Cough	Short breath	Pulmonary wheezing sound
Experimental	60	4.79±0.82	4.22±1.10	3.86±0.85	5.41±1.50
Control	60	5.66±1.34	6.11±1.08	5.96±1.50	6.12±1.63
t		4.29	3.361	9.435	2.483
p		0.001	0.001	0.001	0.001

Table 3: Pulmonary functions (n = 60,$\bar{\chi}\pm$s)

	FVC (L)		FEV1 (L)		PEF (L s^{-1})	
Groups	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental	1.86±0.41	2.87±0.54*#	1.51±0.26	2.65±0.54*#	68.12±5.74	93.90±5.77*#
Control	2.01±0.49	2.54±0.45#	1.49±0.24	2.22±0.40#	68.05±5.79	89.21±5.86#

#p<0.05 vs. before treatment, *p<0.05 vs. control group, FVC: Forced vital capacity, FEV1: Forced expiratory volume in the first second and PEF: Peak expiratory flow

Table 4: Levels of Th1, Th2 and Th17 cells in peripheral blood (n = 60, $\bar{\chi}\pm$s)

	Th1 (%)		Th2 (%)		Th1/Th2		Th17 (%)	
Groups	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental	0.50±0.13	0.71±0.15*#	0.89±0.23	0.61±0.16*#	0.60±0.15	1.15±0.20*#	1.85±0.20	0.49±0.10*#
Control	0.53±0.12	0.63±0.14#	0.86±0.17	0.71±0.17#	0.61±0.17	0.92±0.19#	1.88±0.21	0.67±0.15#

#p<0.05 vs. before treatment, *p<0.05 vs. control group

Table 5: Serum levels of IFN-γ, IL-4 and IL-17 (n=60,$\bar{\chi}\pm$ s)

	IFN-γ (pg mL^{-1})		IL-4 (ng mL^{-1})		IL-17 (ng mL^{-1})	
Groups	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental	27.32±5.44*#	18.34±3.45	10.43±1.97*#	34.95±5.27	23.79±4.45*#	27.32±5.44*#
Control	23.23±4.78#	18.43±3.15	13.14±2.27#	34.97±6.22	27.25±5.39#	23.23±4.78#

#p<0.05 *vs.* before treatment, *p<0.05 vs. control group

Table 6: Incidence rates of adverse reactions (%)

Groups	n	Tachycardia	Nausea and vomiting	Vertigo	Skin rashes	Incidence rate
Experimental	60	1 (1.67)	1(1.67)	0 (0.00)	0 (0.00)	2 (3.33)
Control	60	0 (0.00)	1(1.67)	1(31.67)	0 (0.00)	2 (3.33)
χ^2						0
p						1.000

quality of life and the physical and mental health of patients and impeding the healthy and sustainable development of social public health[14]. Currently, there is no radical treatment for bronchial asthma. Treatment plans for bronchial asthma can only be formulated through the measurement of corresponding biomarkers of asthma, such as the determination of biochemical molecules in sputum, bronchoalveolar lavage fluid, exhaled breath condensate, bronchial biopsy and peripheral blood, supplemented by the real-time symptoms in patients, their medical history and airway responses and related drugs are used to alleviate the conditions or control the symptoms[15]. Therefore, in-depth investigation of the molecular mechanism of asthma based on the pathogenesis of the disease and active exploration of the specific novel biomarker molecules of asthma are helpful for the selection of more effective treatment plans for the patients and conducive for clinicians to understand the patients' responses to the first-line treatment drugs, optimize and improve intervention measures in time, ultimately benefiting the patients.

Immune dysfunction is the immunological basis of inflammatory progression in bronchial asthma[16]. Zhu *et al.*[17]. confirmed that the imbalance between Th1 and Th2 cells directly promoted the cascade amplification of airway

inflammatory stress in bronchial asthma. Generally, the Th1/Th2 ratio is maintained at a normal level in human bodies. Once influenced by external or internal adverse factors, the balance of Th1/Th2 may be broken, thus triggering relevant diseases. Branchett *et al.*[18] found that in mice with type 2 asthma, the T lymphocyte Th1 secreted IFN-γ, activated macrophages and enhanced phagocyte-mediated anti-infective immunity (against intracellular pathogen infection) and could facilitate the production of antibodies *in vivo*. Brightling *et al.*[19] reported that down-regulating the level of Th2 cells in the case of severe asthma could markedly suppress the release of IL-4, reducing the activity of mast cells and ameliorating airway remodelling in patients. According to the study of Schultheiß *et al.*[20], in the case of asthma caused by COVID-19, Th17 cells promoted the release of inflammatory factors by multiple cells and IL-17 secreted by Th17 cells could amplify the inflammatory cascade and facilitate the formation of respiratory tract obstruction, resulting in substantial pathological changes in lung tissue and respiratory tract structure. Budesonide, targeting glucocorticoid receptors, is a common drug in the clinical treatment of asthma. It can regulate the transcription of target genes in airway cells and repress the exudation of inflammatory cells and the release of cytokines by initiating a series of gene transcriptional regulations. Moreover, atomizing inhalation enables the drug to act directly on the respiratory tract and produce drug effects quickly utilizing high-speed oxygen flow atomization solution, which possesses the advantages of small dosage, quick efficacy and high safety[21]. Meanwhile, doxofylline (a new type of theophylline), as a bronchodilator, can directly act on the bronchi and relax bronchial smooth muscle. Besides the ideal anti-inflammatory and relaxing effects, doxofylline also exhibits a powerful antiasthmatic effect[22]. The combination of the two is more helpful to strengthen the anti-inflammatory and antiasthmatic effects, thereby relieving the immune disorder and improving the clinical symptoms and pulmonary function of patients[23].

Based on the above analysis, the peripheral blood samples, easier to be obtained than induced sputum and bronchial biopsy, were used in this study for observation of changes in the levels of Th1, Th2 and Th17 cells in the peripheral blood of patients. The results manifested that after treatment, the experimental group exhibited a more significant increase in the level of Th1 cells and Th1/Th2, a more obvious decrease in the levels of Th2 and Th17 cells in the peripheral blood, more evident elevation in the serum level of IFN-γ and more prominent declines in the levels of IL-4 and IL-17 than the control group. These results confirmed that doxofylline combined with budesonide can effectively improve the inflammatory response and immune mechanism imbalance in patients with bronchial asthma. Hence, in this study, the disappearance time of wheezing, cough, short breath and pulmonary wheezing sound in patients was markedly shortened in the experimental group and the FVC, FEV1 and PEF were notably higher in the experimental group than those in the control group, inconsistency with the study of Rajanandh *et al.*[24]. Therefore, doxofylline combined with budesonide is recommendable for the treatment of bronchial asthma.

CONCLUSION

In summary, doxofylline combined with budesonide in the treatment of bronchial asthma facilitates the balance of Th1/h2 in the peripheral blood of patients, down-regulates the level of Th17 cells and improve the pulmonary function of patients, with few adverse reactions. Thus, it is worthy of popularizing in clinical practice.

SIGNIFICANCE STATEMENT

This study discovered the combination of doxofylline with budesonide that can be beneficial for the pulmonary function of patients with bronchial asthma. This study will help the researchers to uncover the critical areas of effective asthma treatment based on changes of peripheral blood T cells that many researchers were not able to explore. Thus, a new theory on drug therapy for bronchial asthma may be arrived at.

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