CLINICAL OBSERVATION OF TIOTROPIUM BROMIDE POWDER INHALATION COMBINED WITH ROXITHROMYCIN ORAL TREATMENT FOR PATIENTS WITH STABLE BRONCHIECTASIS

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ABSTRACT

Objective: *To observe the clinical efficacy of tiotropium bromide powder combined with roxithromycin in the treatment of patients with stable bronchiectasis.*

Methods: *A total of 120 patients with stable bronchiectasis were selected. Patients in the control group took 0.15 g of roxithromycin capsules orally once a day. In addition to the same roxithromycin capsules, patients in the treatment group also inhaled 18 μg of tiotropium bromide once a day. The course of treatment was three months. Clinical symptoms, dyspnea score, number of acute exacerbations, arterial blood gas and pulmonary function response indices, and cell classification of alveolar lavage fluid were observed.*

Results: *Compared to before treatment, the clinical symptom score and dyspnea score of the treatment group were significantly decreased after treatment ($P < 0.05$), as was the dyspnea score in the control group ($P<0.05$). The clinical symptom score, dyspnea score, and number of exacerbations in the treatment group were significantly lower than those of the control group ($P<0.05$). After treatment, values for the arterial partial pressure of oxygen, forced expiratory volume in one second, and six-minute walk test were significantly increased in both the control and treatment groups, but these increases were significantly greater in the treatment group than in the control group ($P<0.05$). There were no significant changes in partial pressure of carbon dioxide, forced vital capacity, or peak expiratory flow rate ($P>0.05$). Following treatment, the proportion of neutrophils in both groups decreased significantly and the proportion of macrophages increased significantly ($P<0.05$) in comparison to pre-treatment levels, but the proportion of lymphocytes did not change significantly. The inflammation in patients with bronchiectasis may be related to collagenase secreted by neutrophils, which suggests that both treatments may have significant effects on tracheal inflammation – although the proportions of neutrophils and macrophages differed between the two groups, all changes following treatment were statistically significant ($P<0.05$).*

Conclusion: *Tiotropium bromide powder combined with roxithromycin can significantly improve the symptoms of patients with bronchiectasis.*

Keywords: *tiotropium bromide, roxithromycin oral treatment, bronchiectasis*

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Introduction

Bronchiectasis is a chronic inflammation of the pathological expansion of the bronchial tree. The disease recurs and may cause purulent infections, which can cause irreversible damage[(1)]. Due to the continuous inflammation of the bronchi, patients may suffer from airflow obstruction, wheezing, and dyspnea, which seriously affect the quality of daily life. Two important factors for the occurrence of bronchiectasis are bronchial obstruction and bronchial infection. Studies by scholars from various countries in recent years have shown that the increasing incidence has become an important health issue. The treatment of bronchiectasis mainly includes methods of controlling infection, expectoration, and hemostasis. Additionally, research has shown that a short course of antibiotic treatment can effectively control bronchodilator inflammation[(2)]. Tiotropium bromide powder, a selective M3 receptor antagonist,

has been shown in clinical trials to restore patients' lung function, soothe smooth muscles, and relieve the symptoms of dyspnea[3]. This study statistically analyzed the effects of roxithromycin combined with tiotropium bromide powder inhalation on stable bronchiectasis, and provides a new research basis for the treatment of bronchodilation.

Materials and methods

Clinical data

The subjects of this study were 120 patients with stable bronchiectasis. These subjects included 56 males and 64 females, aged 27-67 years (mean age 50.0±10.2 years). Patients in the control group took 0.15 g of roxithromycin capsules orally once a day. Patients in the treatment group were given the same dose of roxithromycin capsules as the control group, while also inhaling 18 μg of tiotropium bromide once a day. The course of treatment was three months.

Diagnostic criteria

Diagnostic criteria included:

• Chronic cough, purulent sputum or repeated hemoptysis, or wet rales in the lungs;

• Chest X-ray results with irregular shadows in lung texture;

• Chest CT showing bronchial wall thickening and expansion or changes.

Inclusion criteria for subjects were:

• Met the diagnostic criteria for stable bronchiectasis;

• Were 18-80 years old;

• Had not taken other anti-bronchodilators within three months;

• Exhibited good compliance and could cooperate with the treatment and follow-up process.

Exclusion criteria were:

• Patients with glaucoma and severe benign prostatic hyperplasia;

• Patients with severe respiratory failure and heart, liver, and kidney insufficiency;

• Tiotropium bromide powder and roxithromycin intolerance.

Observation indicators

The indicators observed in this study included number of acute exacerbations, clinical symptom score, dyspnea score, forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEF), and six-minute walk test distance (6MWT), measured during a six-minute walk test in air-flowing, quiet corridors to measure patients' exercise tolerance.

Item	0 Point	1 Point	2 Points	3 Points	4 Points	5 Points
Cough (times /day)		<5	5–10	11–20	>20	
Fever (°C)	No fever	<38	38–39	>39		
Sputum (mL/day)		<5	5–10	11–20	>20	
Hemoptysis (mL/day)	No hemoptysis	<5	5–10	11–20	>20	
Breathing frequency (times/min)		Chest tightness	<20	21–25	26–30	>30

Table 1: Scoring criteria for symptoms of stable bronchiectasis.

Grade	Description
0	No breathing difficulties unless undergoing strenuous exercise
1	Panting when walking quickly on a flat road or on a ramp
2	Walking slower than peers because of shortness of breath, or needing to stop and rest after walking at their own speed
3	Stopping after 100 m or a few minutes on a flat road
4	Cannot leave the room on foot or feel short of breath when wearing or removing clothes

Table 2: Scoring criteria for symptoms of stable bronchiectasis.

Statistical methods

The data were analyzed using SPSS 18.0, with count data expressed in percent (%). Comparisons were performed by chi-square test, and the t-test was used for measurement data. Multivariate analysis was performed by logistic regression analysis. A P of less than 0.05 was considered statistically significant.

Results

Clinical symptoms, dyspnea, and acute exacerbations before and after treatment

Compared with measurements before treatment, the clinical symptom score and dyspnea score of the treatment group patients were significantly decreased after treatment ($P<0.05$; Table 3), as was the dyspnea score of the control group patients ($P<0.05$). The clinical symptom score, dyspnea score, and number of exacerbations were significantly lower in the treatment group than in the control group ($P<0.05$).

Arterial blood gas and pulmonary function of patients before and after treatment

After treatment, the arterial blood partial pressure of oxygen (PaO_2), FEV1, and 6MWT of both groups significantly increased, with the

increases being significantly greater in the treatment group than in the control group (Ps<0.05; Table 4). In contrast, arterial blood partial pressure of carbon dioxide ($PaCO_2$), FVC, and PEF did not change significantly following treatment (Ps>0.05). Overall, the treatment group appeared to exhibit significantly improved blood gas and lung function.

Observation indicators	Control group		Treatment group	
	Before treatment	After treatment	Before treatment	After treatment
Clinical symptom score	3.2±1.3	3.1±1.1	3.2±1.0	2.2±0.8*#
Dyspnea score	4.9±0.5	4.7±1.6*	4.8±1.2	2.6±0.6*#
Breath exacerbations	--	4.3±1.5	--	2.6±0.8#

Table 3: Comparison of clinical indicators before and after treatment in two groups of patients with bronchiectasis; control group received roxithromycin capsules, treatment group received roxithromycin capsules and tiotropium bromide powder.
**Significantly different from before treatment; #significantly different from control group.*

Test items	Control group		Treatment group	
	Before treatment	After treatment	Before treatment	After treatment
PaO_2 (mm Hg)	66.9±5.4	70.1±4.5*	67.3±6.0	76.5±7.4*#
$PaCO_2$ (mm Hg)	38.4±3.5	39.6±2.4	39.9±1.9	38.8±0.9
FEV1 (L)	1.5±0.1	1.6±0.2*	1.4±0.1	1.8±0.3*#
FVC (L)	2.1±0.7	2.3±1.3	2.1±1.1	2.4±1.0
PEF (L/s)	3.6±2.7	3.9±1.8	3.6±2.1	4.5±2.3*
6MWT (m)	219±54	360±109*	216±63	396±101*#

Table 4: Comparison of arterial blood gas and pulmonary function response indices before and after treatment in two groups of patients with bronchiectasis; control group received roxithromycin capsules, treatment group received roxithromycin capsules and tiotropium bromide powder.
**Significantly different from before treatment; #significantly different from control group.*

Cell classification numbers of alveolar lavage fluid before and after treatment

Before and after the treatment, the two groups of patients underwent a cell classification count examination. In comparison with pre-treatment values, the proportion of neutrophils in both groups after treatment was significantly reduced, and the proportion of macrophages was significantly increased (Ps<0.05; Table 5). The proportion of lymphocytes, however, did not change significantly with treatment or differ between groups (Ps>0.05). The inflammation of bronchiectasis may be related to neutrophils, which suggests that both treatments may have significant effects on tracheal inflammation.

There were significantly greater proportions of neutrophils and macrophages in the treatment group than in the control group (Ps<0.05), indicating that the treatment of tiotropium bromide powder inhalation combined with roxithromycin has a significantly greater effect on bronchodilatory inflammation than does roxithromycin alone.

Observation item	Control group		Treatment group	
	Before treatment	After treatment	Before treatment	After treatment
Macrophages	19.2±9.3	25.6±8.1*	18.8±6.0	34.2±12.8*#
Lymphocytes	6.9±5.5	7.0±3.4	6.9±5.9	7.1±3.6
Neutrophils	73.9±13.3	67.3±15.1*	74.2±16.1	58.5±19.3*#

Table 5: Comparison of cell classification numbers of alveolar lavage fluid before and after treatment in two groups of patients with bronchiectasis; control group received roxithromycin capsules, treatment group received roxithromycin capsules and tiotropium bromide powder.
**Significantly different from before treatment; #significantly different from control group.*

Conclusion

Bronchiectasis is a high-incidence respiratory disease characterized by chronic inflammation and chronic bacterial infections. The main pathogenesis is lung infection, which is related to elastase released by neutrophil aggregation. Long-term airway inflammation destroys the muscle and elastic components of the walls of the tube, and changes the structure of the normal state of the trachea. Long-term past results eventually lead to persistent expansion of the bronchi. Studies have shown that patients with stable bronchiectasis are still more likely to develop airway inflammation[4].

For this reason, reducing the degree of airway inflammation is the primary factor in preventing and treating bronchiectasis. Recently, domestic and foreign studies have found that long-term use of cyclic lactones can reduce the clinical symptoms of patients and improve the symptoms of patients with dyspnea[5]. Tiotropium bromide powder is a highly selective receptor antagonist that can effectively relax flat muscles of the airways, reduce mucus secretion, and improve lung function. In this study, low-dose roxithromycin was used in combination

with inhaled tiotropium bromide powder to treat patients with bronchiectasis.

This study showed that, in comparison to roxithromycin alone, tiotropium bromide powder combined with roxithromycin can effectively reduce cough, sputum, hemoptysis, chest tightness, shortness of breath, and acute exacerbations of breathing, and significantly improve the clinical symptom score and dyspnea score of patients. In another study, Saito and Azuma used tiotropium bromide powder to treat patients with chronic bronchiolitis and bronchiectasis who developed resistance due to long-term use of macrolides[6]. Patients were treated with tiotropium bromide at 18 μg per day and observed after three months. Similar to the results of the current study, the patients' cough, sputum, and asthma symptoms improved, although there was no significant improvement in lung imaging.

The lung function of patients with bronchiectasis declines over time, with the volume of forced expiratory air (FEV1) in patients with bronchiectasis decreasing by approximately 50 mL per year. The long-term bacterial colonization of Pseudomonas aeruginosa in patients with bronchiectasis is related to this change of lung function. The effects of tiotropium bromide powder may occur through, for example, sterilization or reduction of bacterial colonization and airway inflammation, achieving the effect of improving lung function[7, 8]. After three months of treatment in this study, the lung function indicators FEV1 and PEF improved by a statistically significant amount. Moreover, the PaO_2 and FEV1 of the treatment group differed significantly from those of the control group, indicating that tiotropium bromide powder inhalation can delay the decline of lung function in patients with stable bronchiectasis.

After treatment, the proportions of macrophages and neutrophils in the control group differed significantly from those before the treatment. The neutrophils were significantly reduced after treatment, indicating that the airway inflammation was controlled, which is consistent with research by Kawassaki and colleagues[9]. The inflammation in patients with bronchiectasis may be related to collagenase secreted by neutrophils, so the results of this study likely indicate that both treatments have significant effects on tracheal inflammation, although the proportions of neutrophils and macrophages in the treatment group differed significantly from those in the control group ($P<0.05$).

Overall, this study showed that tiotropium bromide powder inhalation combined with roxithromycin was effective in the treatment of dyspnea, and pulmonary function and inflammation, and was more effective than roxithromycin alone in the treatment of bronchiectasis.

References

1) Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 2013; 309(12): 1251-1259.
2) Liu J, Zhong X, He Z, Wei L, Zheng X, et al. Effect of low-dose, long-term roxithromycin on airway inflammation and remodeling of stable noncystic fibrosis bronchiectasis. Mediators Inflamm 2014; 2014: 708608.
3) Li XL, Cai SX, Zhao HJ, Dong LM, Shen XB, et al. [Therapeutic effect of tiotropium bromide powder inhalation in patients with stable bronchiectasis]. Nan Fang Yi Ke Da Xue Xue Bao 2010; 30(5): 1072-1074.
4) Raissy HH, Kelly HW. Tiotropium Bromide in Children and Adolescents with Asthma. Paediatr Drugs 2017; 19(6): 533-538.
5) Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015; (9): CD009552.
6) Saito Y, Azuma A, Morimoto T, Fujita K, Abe S, et al. Tiotropium ameliorates symptoms in patients with chronic airway mucus hypersecretion which is resistant to macrolide therapy. Intern Med 2008; 47(7): 585-591.
7) Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2016; 12(12): CD005305.
8) Aherne A, Kilpatrick J. Combination LABA Inhalers Compared with High-Dose Inhaled Steroids for Adults with Asthma. Am Fam Physician 2018; 97(5): Online.
9) Zinner NR. Trospium chloride: an anticholinergic quaternary ammonium compound for the treatment of overactive bladder. Expert Opin Pharmacother 2005; 6(8): 1409-1420.

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