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Effect of tiotropium bromide combined with salmeterol fluticasone inhalation on airway function and airway inflammation in patients with moderate−severe stable COPD

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ABSTRACT

Objective: To analyze the effect of tiotropium bromide combined with salmeterol fluticasone inhalation on airway function and airway inflammation in patients with moderate-severe stable COPD. **Methods:** A total of 118 patients with moderate-severe stable COPD were randomly divided into observation group and control group (n=59), control group accepted routine treatment, observation group received tiotropium bromide combined with salmeterol fluticasone inhalation treatment, and then differences in the levels of small airway function and airway wall parameters, the content of inflammatory factors and chemokines in serum and so on were compared between two groups of patients after 2 weeks of treatment. **Results:** After 2 weeks of treatment, small airway function parameters FEF_{25}, FEF_{25-75} and FEF_{75} levels of observation group were significantly higher than those of control group, airway wall parameters WT, WA and T/D levels were significantly lower than those of control group, and AI level was significantly higher than that of control group; MIP-1 α , PCT, NF- κ B, IL-6, CRP, Eotaxin, CCL18, Lymphotactin, sFKN and MCP-1 content in serum of observation group were significantly lower than those of control group while sTNFR content was significantly higher than that of control group. **Conclusions:** Tiotropium bromide combined with salmeterol fluticasone inhalation therapy can optimize the overall condition in patients with moderate-severe stable COPD, which is specifically reflected on the control of the airway function and the degree of inflammation.

1. Introduction

Treatment of patients with moderate-severe stable chronic obstructive pulmonary disease (COPD) has received extensive clinical attention, and acute onset of airway infection in such patients can easily progress to respiratory failure and even systemic inflammatory response syndrome (SIRS)[1]. Oxygen uptake, anti-infection, eliminating phlegm and so on are the common treatment approaches for patients with moderate-severe stable COPD, but they do not intervene in the existing airway functional and anatomical changes, which results in abnormal airway ciliary movement and secreta eduction disorder, and is one of the sources of repeated infection attack in patients. Tiotropium bromide belongs to cholinolytic drug, salmeterol fluticasone belongs to long-acting β 2 receptor agonist, and both can act on the airway smooth muscle cells and exert lasting bronchial dilation effect[2,3]. At present, many studies have confirmed that tiotropium bromide and salmeterol fluticasone have obtained practical and reliable effect on improving the condition in patients with COPD, but there is still less research about the effect of the combination of the two. In the study, tiotropium bromide combined with salmeterol fluticasone inhalation therapy was applied in patients with moderate-severe stable COPD in our hospital, and was specifically elaborated from airway function, degree of inflammation and other aspects.

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2. Materials and methods

2.1. General information

A total of 118 patients with COPD treated in our hospital between October 2013 and October 2015 were selected as the research object, and the inclusion criteria were: (1) diagnosed with moderate-severe stable COPD by imaging, bronchial provocation tests and so on; (2) did not receive bronchodilator, *etc*. in last one month; (3) without acute respiratory infectious diseases in last one month; (4) patients understood the research process and signed the consent form. Exclusion criteria were: (1) with malignant tumor diseases of respiratory system; (2) allergic to tiotropium bromide and salmeterol fluticasone; (3) associated with mental illness and couldn't cooperate with treatment; (4) those who interrupted or volunteered to give up treatment. 118 patients were randomly divided into observation group and control group (n=59), control group included 32 male cases and 27 female cases, they were 49-71 years old and (63.28±6.71) years old in average, and the course of COPD was 7-22 years and (14.38±7.01) years in average; observation group included 31 male cases and 28 female cases, they were 48-72 years old and (62.77±6.82) years old in average, and the course of COPD was 7-21 years and (14.11±7.24) years in average. The two groups of patients showed no statistically significant difference in the distribution of gender, age and course of disease (P>0.05) and they were comparable.

2.2. Treatment methods

Control group received routine therapy for stable COPD, specifically as follows: low-flow oxygen therapy, relieving cough and eliminating sputum as well as relieving asthma. Based on routine therapy, observation group received tiotropium bromide combined with salmeterol fluticasone inhalation therapy, specifically as follows: salmeterol fluticasone 50 μg/time, inhalation, 2 times/d; tiotropium bromide spray, 2 inhalations /time, 2 times/d. 7 d was a course of treatment, and the treatment lasted for at least 2 courses.

2.3. Observation indexes

2.3.1. Small airway function and airway wall parameters

After 2 weeks of treatment, spirometer was used to detect small airway function parameters of two groups of patients, including 25% forced expiratory flow rate (FEF_{25}), maximal mid-expiratory flow rate (FEF_{25-75}) and 75% forced expiratory flow rate (FEF_{75}) levels. 16-slice spiral CT scanner was used to detect the apical-segment bronchial wall of superior lobe of right lung, and the trachea wall thickness (WT), trachea wall area (WA), lumen area (AI) and wall thickness and diameter ratio (T/D) were calculated.

2.3.2. Serum indexes

After 2 weeks of treatment, 3ml of fasting peripheral venous blood was collected from two groups of patients in the morning, let stand at room temperature and centrifuged to get supernatant, and the following indexes were detected: (1) inflammatory factors: ELISA was used to detect macrophage inflammatory protein-1 α (MIP-1 α), procalcitonin (PCT), soluble tumor necrosis factor receptor (sTNFR), monocyte transcription factor (NF)- κ B, interleukin-6 (IL-6) and C-reactive protein (CRP) levels in serum; (2) chemokines: ELISA was used to detect chemotactic factor for eosinophil (Eotaxin), lung activation-regulated chemokine (CCL18), lymphotactin, chemokine FKN (sFKN) and monocyte chemoattractant protein 1 (MCP-1) content in serum.

2.4.Statistical methods

Data in the study was input in software SPSS23.0, measurement data was analyzed by t test and P<0.05 indicated statistical significant differences.

3. Results

3.1. Small airway function parameters

FEF_{25}, FEF_{25-75} and FEF_{75} levels of observation group were significantly higher than those of control group (P<0.05), shown in Table 1.

Table 1
Comparison of small airway function parameter levels between two groups after treatment (L/s).

Groups	Case No.	FEF_{25}	FEF_{25-75}	FEF_{75}
Observation group	59	7.84±0.89	74.38±8.02	83.28±9.11
Control group	59	6.51±0.72	59.74±6.83	54.96±6.15
t		5.783	8.921	11.274
P		<0.05	<0.05	<0.05

3.2. Airway wall parameters

Table 3
Comparison of inflammatory factor content in serum between two groups after treatment.

Groups	Case No.	MIP-1 α (ng/L)	PCT (μg/L)	sTNFR (μg/L)	NF- κ B (ng/L)	IL-6 (ng/L)	CRP (mg/L)
Observation group	59	31.82±4.09	0.07±0.01	4.18±0.34	384.62±40.19	11.37±1.94	28.39±3.01
Control group	59	54.19±6.23	0.13±0.02	3.09±0.54	476.88±51.49	16.84±2.05	40.17±4.53
t		7.823	5.283	6.093	11.274	7.834	8.293
P		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

WT, WA and T/D levels of observation group were significantly lower than those of control group while AI level was significantly higher than that of control group (P<0.05), shown in Table 2.

Table 2
Comparison of airway wall parameter levels between two groups after treatment.

Groups	Case No.	WT (mm)	WA (mm^2)	AI (mm^2)	T/D (mm/mm)
Observation group	59	0.87±0.09	4.73±0.59	16.02±1.98	0.29±0.03
Control group	59	1.41±0.19	6.12±0.84	14.76±1.85	0.43±0.05
t		5.893	6.182	5.983	5.281
P		<0.05	<0.05	<0.05	<0.05

3.3. Inflammatory factors

MIP-1 α , PCT, NF- κ B, IL-6 and CRP content in serum of observation group were significantly lower than those of control group while sTNFR content was significantly higher than that of control group (P<0.05), shown in Table 3.

3.4. Chemokines

Eotaxin, CCL18, Lymphotactin, sFKN and MCP-1 content in serum of observation group were significantly lower than those of control group (P<0.05), shown in Table 4.

4. Discussion

Patients with moderate-severe stable COPD already have more serious airway limitation, and they need to receive long-term low-flow oxygen uptake, eliminating phlegm and relieving asthma as well as other treatment in daily life to discharge the airway secretions and avoid acute onset of infection and COPD aggravation[4]. At present, many experts have put forward that patients with moderate-severe stable COPD still need positive intervention measures in order to furthest reverse the airway remodeling, reduce the probability of occurrence of acute infection and improve patients' quality of life. Both tiotropium bromide and salmeterol fluticasone are clinical popular COPD-targeted drugs, tiotropium bromide is a new long-acting anticholinergic agent, it inhibits the bronchial airway smooth muscle M3 receptor to dilate bronchi, it can also inhibit cholinergic nerve tension and dilate the central and surrounding airway, and research has confirmed that the long-term application of tiotropium bromide can improve patients' lung function[5]. Salmeterol fluticasone is the compound preparation of salmeterol and fluticasone, salmeterol belongs to long-acting β 2 receptor agonist and can directly relax airway smooth muscle, and the fluticasone belongs to inhaled corticosteroids and can play a positive role in increasing β 2 receptor sensitivity, delaying the airway remodeling, inhibiting the inflammatory response and many other links. At present, there is less study about the drug compatibility for patients with moderate-severe stable COPD, and in view of the different mechanisms of action and synergistic interaction of the above two drugs, tiotropium bromide and salmeterol fluticasone were used together in patients with COPD in our hospital so as to furthest improve patients′ airway function and inhibit inflammation.

Early COPD mainly involves patients′ small airway, its resistance accounts for about 20% of the total airway resistance, and many studies have confirmed that the small airway function is one of the most sensitive indexes to reflect the actual changes in COPD condition[6,7]. It was found in the study that the FEF_{25}, FEF_{25-75} and FEF_{75} levels of observation group were higher after 2 weeks of treatment, indicating that the tiotropium bromide combined with salmeterol fluticasone inhalation therapy can effectively optimize the small airway function in patients with COPD and macroscopically improve the overall condition. There is already anatomical airway change in patients with moderate-severe stable COPD, which is mainly characterized by airway wall thickening, tracheal diameter decreasing, ventilation resistance increasing, and so on[8,9]. In the study, 16-slice spiral CT scanner was used to determine the apical-segment bronchial wall of superior lobe of right lung, and it was found that the trachea WT, trachea WA as well as wall T/D of observation group were lower while lumen area (AI) was greater after treatment, confirming that the tiotropium bromide combined with salmeterol fluticasone inhalation therapy can effectively restrain the airway remodeling process in patients with COPD, and it reduces the trachea wall thickness to relatively increase the lumen area and reduce the resistance of ventilation and secreta eduction.

Continuous airway inflammation can not only accelerate the airway remodeling, but can also stimulate massive secretion production, which further weakens the cilia activity ability and redoubles the incidence of acute respiratory infection[10]. In the study, serum levels of a variety of typical inflammatory factors of two groups was detected, and it was found that MIP-1 α , PCT, NF- κ B, IL-6 and CRP content greatly decreased while sTNFR content increased significantly. MIP-1 α has activation and chemotaxis effect on leukocytes, and can induce neutrophil infiltration and enhance endothelial activity in human body. PCT, IL-6 and CRP are typical pro-inflammatory factors that can further prompt the release of a variety of inflammatory mediators and expand systemic inflammatory response[11,12]. STNFR can antagonize the biological activity of TNF- α , it is lowly expressed in a variety of patients with acute infection, and after treatment, sTNFR level will gradually rise

Table 4
Comparison of chemokine content in serum between two groups after treatment.

Groups	Case No.	Eotaxin (ng/L)	CCL18 (ng/mL)	Lymphotactin (μg/L)	sFKN (ng/L)	MCP-1 (ng/L)
Observation group	59	54.38±6.01	0.87±0.09	1.63±0.19	14.72±1.98	23.71±2.98
Control group	59	72.59±7.83	1.34±0.17	2.51±0.34	20.65±2.85	30.16±3.54
t		8.392	5.378	5.982	7.182	8.623
P		<0.05	<0.05	<0.05	<0.05	<0.05

and indicate effective treatment. NF- κ B is released by monocytes and directly involved in the inflammation expansion process[13]. The study results indicate that the tiotropium bromide combined with salmeterol fluticasone inhalation plays a unique role in inhibiting COPD inflammation, which may be directly related to the inhibition of fluticasone, as glucocorticoid, on the activation of inflammatory cells, the production of inflammatory factors and other links.

The study on COPD rat models shows that there are a large number of eosinophils, lymphocytes and monocytes in airway mucosa, and therefore, some scholars put forward that the development of COPD is inevitably accompanied by the increased levels of a variety of chemokines[14]. Chemotactic factor for Eotaxin can induce eosinophil recruitment, eosinophil mediator release and inflammatory airway damage. Lung activation-regulated chemokine (CCL18) content is directly related to the prognosis of COPD, and as CCL18 content increases, the incidence of respiratory failure increases. Lymphotactin has powerful recruitment effect on T cells, further leads to the activation of a variety of inflammatory cells, and cause the start of inflammation "waterfall effect". Chemokine FKN (sFKN) belongs to the CX3C chemokines, has both adhesion and chemotaxis activity, and participates in white blood cell migration to the tissue with inflammatory response. MCP-1 is the macrophage-specific chemokine, and studies have found that anti-MCP-1 antibodies can effectively reduce the inflammatory response in COPD patients[15,16]. In the study, serum levels of above chemokines were detected, and it was found that serum Eotaxin, CCL18, Lymphotactin, sFKN and MCP-1 content of observation group were lower after 2 weeks of treatment, indicating that the combined therapy can effectively suppress the secretion of chemokines in local airway and the whole body, and it is the foundation of the realization of its inflammation inhibition effect.

To sum up, it is concluded as follows: tiotropium bromide combined with salmeterol fluticasone inhalation therapy can optimize the overall condition in patients with moderate-severe stable COPD, it is specifically reflected on the control of the airway function and the degree of inflammation, and it's worth popularization and application in clinical practice in the future.

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