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Review Article

Clarithromycin plus tiotropium bromide improves pulmonary and immune function in patients with chronic obstructive pulmonary disease

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Abstract: Objective: To explore the effect of clarithromycin (CAM) plus tiotropium bromide (TB) in patients with chronic obstructive pulmonary disease (COPD). Methods: A total of 120 patients with COPD admitted to the respiratory department of our hospital from March 2018 to October 2019 were allocated into group A (n=57, TB) and group B (n=63, CAM plus TB). The pulmonary and immune function, effective rate, adverse reactions and quality of life (QOL) in the two groups were evaluated. Results: Group B presented with enhanced pulmonary and immune function compared to group A after treatment ($P < 0.05$). The adverse reactions in group B were fewer than those in group A ($P < 0.05$). The effective rate and QOL in group B were higher than those in group A ($P < 0.05$). Conclusion: The combination therapy of CAM plus TB is effective in the treatment of COPD.

Keywords: Clarithromycin, tiotropium bromide, chronic obstructive pulmonary disease, pulmonary function, immune function

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with multiple phenotypes and symptoms characterized by frequent recurrent attacks and hospitalization [1], it is also a progressive disease that interferes with normal breathing [2]. COPD is the third leading cause of death in the world and is induced by long-term exposure of the lungs to toxic particles and gases [3] and it resulst in decreased pulmonary function. The symptoms and pathological manifestations vary in patients with COPD; for example, different severities, different degrees of emphysema, and different disease progression rates [4]. COPD symptoms occur with decreased motor ability and respiratory failure as the disease progresses [5], resulting in 3 million deaths worldwide every year [6]. Although several drug and non-drug interventions have been shown to be effective in relieving those symptoms, little progress has been made on the impact of immune function.

Tiotropium bromide (TB), a drug for COPD [7], has various auxiliary effects on inflammation, airway remodeling, mucus production and cough reflex, and shows high safety and effectiveness in different disease phenotypes [8]. M3 receptors in airway smooth muscle play a vital pathophysiological role in the respiratory system by contracting the bronchus and secreting mucus, and TB is able to bind to all M3 receptor subtypes and selectively inhibit M1 and M3 subtypes [9]. As a macrolide, clarithromycin (CAM) has immunomodulatory properties [10] and is the preferred drug for treating COPD. It regulates inflammatory factors, reduces airway mucus hypersecretion, and prevents the formation of bacterial biofilms and the production of virulence factors [11]. A study reveals that CAM reduces the one-year post-hospitalization rates and cardiovascular mortality in patients with COPD and pneumonia [12]. This study aimed to explore the effect of the combination of CAM and TB on COPD patients, and to provide clinic reference for the treatment of COPD.

Data and methods

General data

A total of 120 patients with COPD admitted to the respiratory department of our hospital from March 2018 to October 2019 were allocated into group A (n=57, TB) and group B (n=63, CAM plus TB).

Exclusion and inclusion criteria

Inclusion criteria: patients confirmed with COPD by laboratory tests, with a forced vital capacity (FVC) of less than 70% (pulmonary function) [13]; patients aged 43-71 years old; patients with aggravated wheezing, shortness of breath, cough and expectoration, or those with fever and purulent sputum. All participants signed the informed consent form and this study was approved by the medical ethics committee of Ningbo Ninth Hospital.

Exclusion criteria: patients with communication difficulties or mental disorders, hepatic or renal insufficiency, drug allergy, or other lung disease; patients with abnormal hematopoietic system or severe cardiology diseases; patients taking anti-inflammatory drugs or vasodilators before enrollment; patients with a history of bronchial asthma or lobectomy.

Methods

All patients were pre-treated with conventional anti-asthmatic treatment, oxygen inhalation, expectorant and anti-inflammatory therapies.

Patients in group A inhaled TB (18 μg/ pill, CTTQ Pharma, SFDA Approval No. H20060454), 18 μg/ time, once/day.

Patients in group B were additionally treated with CAM (0.25g, Shanghai Abbott Pharmaceutical Co., Ltd, SFDA Approval No. H20033044), 250 mg/ time, once/day.

The treatment lasted for 28 days, during which other drugs were suspended and the patients' physical signs were monitored.

Outcome measures

Pulmonary function indexes: forced expiratory volume in the first second (FEV1), FVC, FEV1/FVC, and 6-minute walking distance (6MWD).

Venous blood (5 mL) sampled from patients after surgery was let rest for 20 min. Afterwards, serum was obtained with a centrifuge (at 10×g/4°C for 15 min, Beijing BMH Instruments Co., Ltd.) and frozen in liquid nitrogen and stored at -80 C. Enzyme-linked immunosorbent assay (ELISA) (Suzhou Els Biotechnology Co., Ltd.) was employed to quantify immunoglobulin G (IgG), IgM, CD3, CD4 and C-reactive protein (CRP).

Borg scale [14] evaluated the improvement of dyspnea, with a full score of 10. A lower score indicated better improvement.

Curative effect was assessed according to the symptoms and characteristics of COPD complicated with respiratory failure [15]: Markedly effective: symptoms were completely relieved; Effective: symptoms partially relieved; Ineffective: symptoms were rarely relieved.

The 36-item short form (SF-36) [16] scored the quality of life (QOL), with a full score of 100. A higher score indicated higher QOL.

Statistical methods

Statistical analysis was carried out with SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). The measurement data were expressed by mean ± standard deviation (sd), and inter- and intra-group comparisons were performed by *t*-test and paired *t*-test, respectively. The counting data were expressed by [n (%)], and the inter-group comparison was performed by Chi-square test. When $P < 0.05$, the difference was statistically significant.

Results

General data

There was no difference in general data between the two groups ($P > 0.05$). See **Table 1** for details.

Comparison of pulmonary function indexes

There was no difference in pulmonary function indexes (FEV1, FVC, FEV1/FVC, 6MWD) between the two groups before treatment ($P > 0.05$). Although those indexes improved in both groups after treatment, the improvement in the group B was more significant than that in group A ($P < 0.05$), as shown in **Figure 1**. Therefore,

Table 1. General data ($\bar{x} \pm sd$) [n (%)]

Classification	Group A (n=57)	Group B (n=63)	t/χ^2	*P*
Sex			0.132	0.715
Male	38 (66.67)	40 (63.49)		
Female	19 (33.33)	23 (36.51)		
Age (years)	65.34±5.79	66.29±5.24	0.943	0.347
Weight (kg)	68.52±6.28	67.24±6.35	1.108	0.269
Height (cm)	174.69±6.34	173.57±6.23	0.975	0.331
Course of disease (years)	1.43±0.35	1.45±0.31	0.332	0.740
Nationality			0.762	0.091
Han nationality	43 (75.44)	46 (73.02)		
Minority nationalities	14 (24.56)	17 (26.98)		
Residence			0.969	0.001
Urban	36 (63.16)	40 (63.49)		
Rural	21 (36.84)	23 (36.51)		
Education level			0.950	0.621
< secondary school	16 (28.07)	19 (30.16)		
High school/vocational school	29 (50.88)	35 (55.56)		
≥ college	12 (21.05)	9 (14.29)		
Fasting glucose			0.072	0.787
≥ 7.0 mmol/L	24 (42.11)	25 (39.68)		
< 7.0 mmol/L	33 (57.89)	38 (60.32)		
Blood pressure			0.246	0.619
Systolic pressure ≥ 140 mmHg	21 (36.84)	26 (41.27)		
Systolic pressure < 140 mmHg	36 (63.16)	37 (58.73)		
Smoking			2.210	0.137
≥ Six consecutive or cumulative months	48 (84.21)	46 (73.02)		
< Six consecutive or cumulative months	9 (15.79)	17 (26.78)		
Drinking			0.010	0.918
Yes	34 (59.65)	37 (58.73)		
No	23 (40.35)	26 (41.27)		
Exercise			0.066	0.796
Yes	33 (57.89)	35 (55.56)		
No	24 (42.11)	28 (44.44)		
Phasing			0.246	0.619
Acute exacerbation	21 (36.84)	26 (41.27)		
Stable phase	36 (63.16)	37 (58.73)		

CAM plus TB contributes to the enhanced improvement of pulmonary function of patients.

Comparison of immunologic function

There was no difference in immunologic factor (CD3, CD4, IgG, IgM) levels between the two groups before treatment ($P > 0.05$), and those levels in group B were higher than those in group A after treatment ($P < 0.05$). See **Figure 2** for details. Therefore, CAM plus TB is effective in improving the immunologic function of patients.

Comparison of CRP

There was no difference in inflammatory factor (CRP) level between the two groups before treatment ($P > 0.05$). After treatment, there was a significant decrease and the CRP level in group B was lower than that in group A ($P < 0.05$), as shown in **Figure 3**. Therefore, CAM

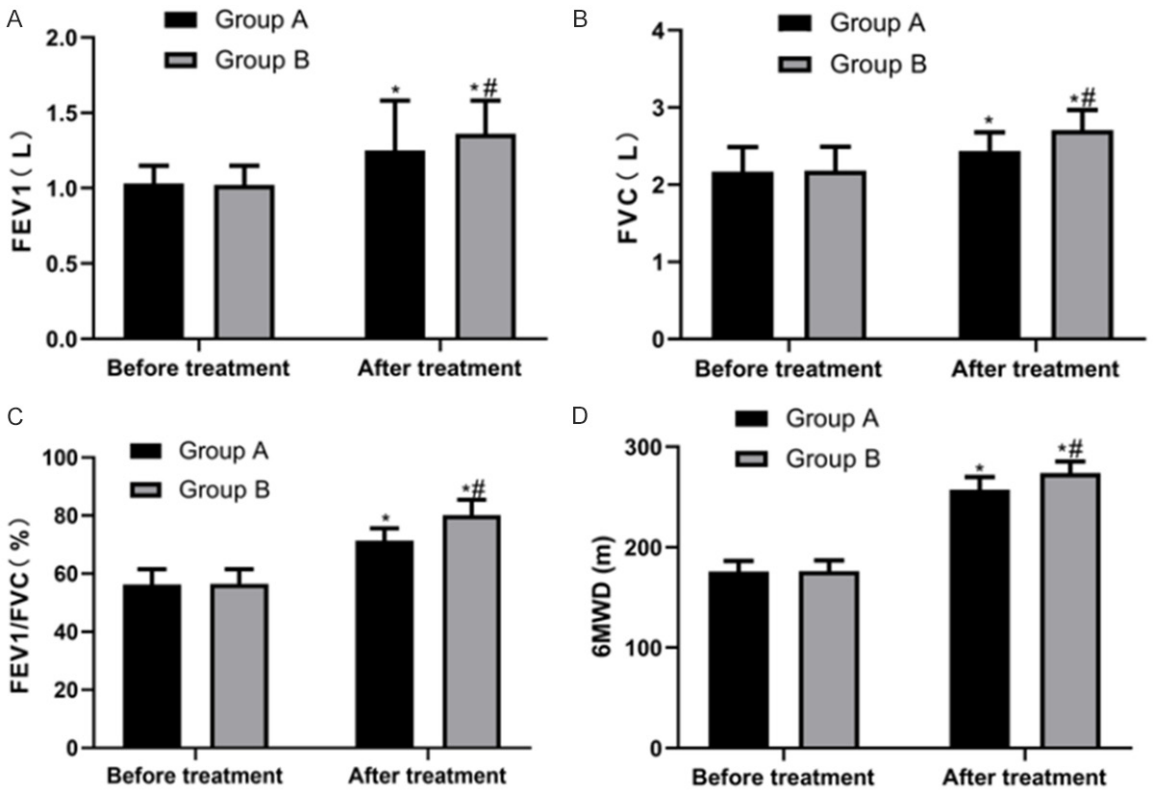

Figure 1. Comparison of pulmonary function indexes. A. Comparison of FEV1: There is no difference in FEV1 between the two groups before treatment ($P > 0.05$); The FEV1 in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A. B. Comparison of FVC: There is no difference in FVC between the two groups before treatment ($P > 0.05$); The FVC in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A. C. Comparison of FEV1/FVC: There is no difference in FEV1/FVC between the two groups before treatment ($P > 0.05$); The FEV1/FVC in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A. D. Comparison of 6MWD: There is no difference in 6MWD between the two groups before treatment ($P > 0.05$); The 6MWD in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A.

plus TB can decrease the level of inflammatory factors.

Comparison of Borg score

The improvement of dyspnea was evaluated by Borg scale. It turns out that there was no ignificant difference before and after treatment between the two groups ($P > 0.05$), but the score in group B was significantly lower than those in group A after treatment ($P < 0.05$), as shown in **Figure 4**. These indicate that CAM plus TB alleviates dyspnea of patients.

Adverse reactions after treatment

The incidence of adverse reactions in group B was lower than that in group A ($P < 0.05$) (**Table 2**), suggesting that CAM plus TB causes fewer adverse reactions.

Comparison of effective rate

Group B showed higher effective rate than group A ($P < 0.05$) (**Table 3**), suggesting the high efficacy of the combination of CAM and TB.

Comparison of QOL

Scores of physical functioning, daily life functioning, psychological functioning, and QOL in group B were higher than those in group A ($P < 0.05$) (**Table 4**), indicating that CAM plus TB is able to improve the QOL of patients.

Discussion

Human IgG, the most abundant glycoprotein in serum, is essential for protective immunity [17]. IgG accounts for 10-20% of all plasma proteins and 70-75% of total Ig, and has a variety of

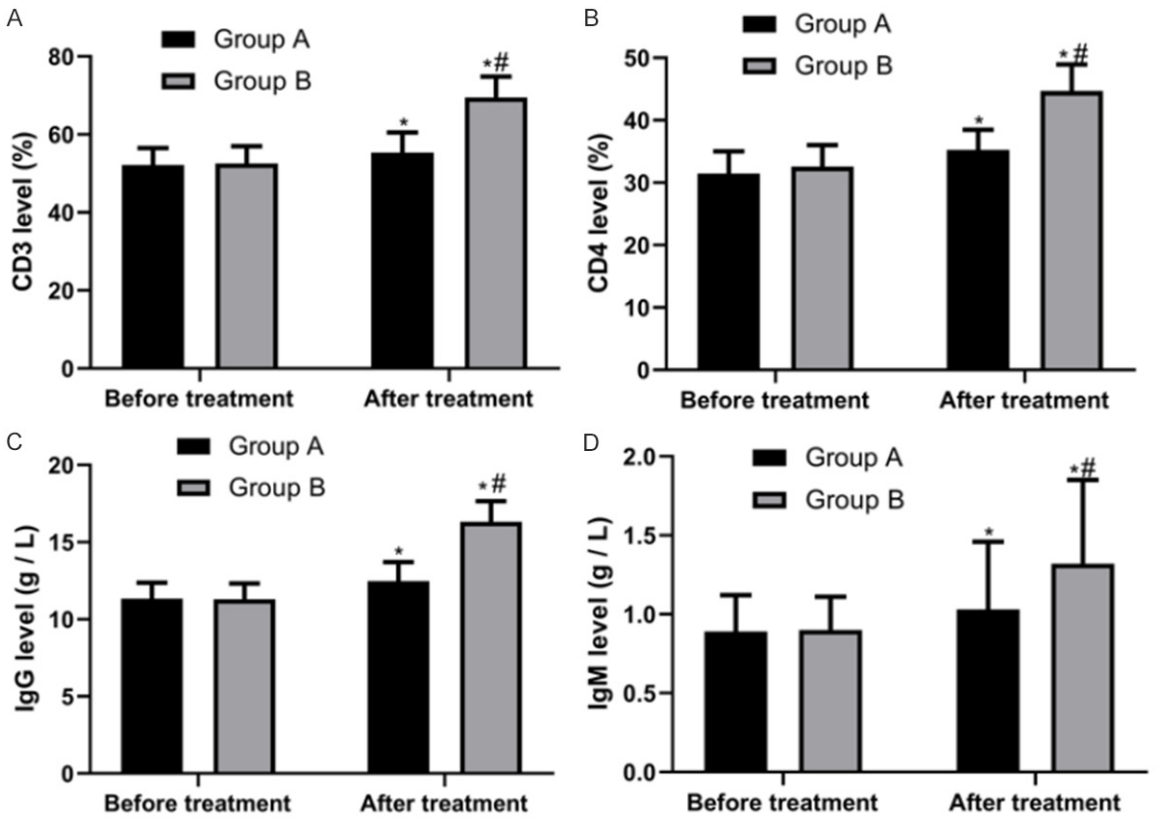

Figure 2. Comparison of immunologic function. A. Comparison of CD3: There is no difference in CD3 between the two groups before treatment ($P > 0.05$); The CD3 in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A. B. Comparison of CD4: There is no difference in CD4 between the two groups before treatment ($P > 0.05$); The CD4 in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A. C. Comparison of IgG: There is no difference in IgG between the two groups before treatment ($P > 0.05$); The IgG in group B is remarkably higher than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A. D. Comparison of IgM: There is no difference in IgM between the two groups before treatment ($P > 0.05$); After treatment the IgM in group B is remarkably higher than that in group A IgM ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment; $^{\#}P < 0.05$ *vs* group A.

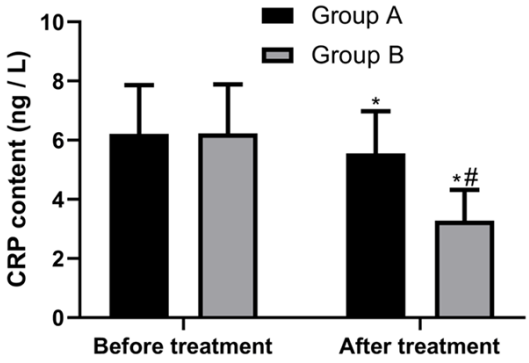

Figure 3. Comparison of CRP level. There is no difference in CRP level between the two groups before treatment ($P > 0.05$); The CRP level in group B is lower than that in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment in the same group; $^{\#}P < 0.05$ *vs* group A.

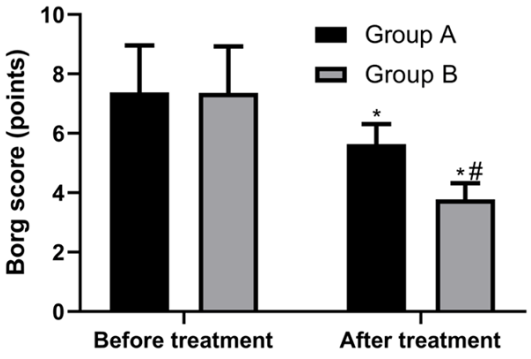

Figure 4. Comparison of Borg score. There is no significant difference in Borg score between the two groups before treatment ($P > 0.05$), and the score in group B was lower than those in group A after treatment ($P < 0.05$). Note: $^{*}P < 0.05$ *vs* before treatment in the same group; $^{\#}P < 0.05$ *vs* group A.

Table 2. Comparison of adverse reactions [n (%)]

Adverse reaction	Group A (n=57)	Group B (n=63)	χ^2	*P*
Headache	2 (3.51)	1 (1.59)	-	-
Fever	3 (5.26)	2 (3.17)	-	-
Abdominal distension	1 (1.75)	0 (0.00)	-	-
Diarrhea	2 (3.51)	0 (0.00)	-	-
Nausea	3 (5.26)	1 (1.59)	-	-
Dizziness	3 (5.26)	1 (1.59)	-	-
Vomiting	2 (3.51)	0 (0.00)	-	-
Total incidence rate	16 (28.07)	5 (79.37)	8.402	0.003

Table 3. Comparison of curative effect [n (%)]

Curative effect	Group A (n=57)	Group B (n=63)	χ^2	*P*
Markedly effective	21 (36.84)	34 (53.97)	-	-
Effective	22 (38.60)	23 (36.51)	-	-
Ineffective	14 (24.56)	6 (9.52)	-	-
Effective rate	43 (75.44)	57 (90.48)	4.872	0.027

Table 4. Comparison of QOL (x±sd)

Group	n	Physical functioning	Daily life functioning	Psychological functioning	Quality of life
Group A	57	76.23±3.43	81.24±3.53	75.24±4.37	84.28±4.41
Group B	63	85.12±4.53	88.98±2.23	87.43±3.85	96.14±3.52
T		12.020	14.500	16.240	16.350
P		< 0.001	< 0.001	< 0.001	< 0.001

effector functions. Although harmful IgGs may induce immune responses and several inflammatory and autoimmune diseases, IgG antibodies are vital effectors that contribute to antimicrobial immunity [18]. IgM, the first antibody isotype appearing in the process of evolution, ontogeny and immune responses, is not only the first line of defense against infection, but also plays an important role in immune regulation [19]. Patients with immunodeficiency are more likely to suffer from respiratory diseases and recurrent infections [20]. Enhanced immune markers were discovered in patients undergoing combination therapy, indicating that the combination of TB and CAM improves the immunologic function of patients. This improvement may be attributed to the role of macrolide in regulating the immune response, destroying biofilms and enhancing the protective performance of respiratory mucosa [21]. Macrolide antibiotics exert immunoregulatory activity by reducing the production of cytokines from airway epithelial cells [22]. The Borg scale is a self-managed one-dimensional evaluation tool that analyzes dyspnea upon exertion [23]. It was adopted to evaluate the improvement of dyspnea of patients in this study, and it turned out that patients treated with TB plus CAM had significantly improved dyspnea and pulmonary function, which was consistent with the results of pulmonary function index tests. It can be concluded that the additional use of CAM is better for the improvement of pulmonary function in COPD. The combination of TB and macrolides inhibits airway mucus secretion [24]. CRP is generated in smooth muscle cells and increases in infected or inflamed sites. It has traditionally been considered as a marker of infection and cardiovascular events, and now there are increasing reports on its role in inflammatory process and host response to infection [25].

COPD often occurs suddenly due to infection-induced acute exacerbation, leading to greatly increased morbidity and mortality [26]. In this study, we speculated the decreased CRP in patients treated with combination therapy was

related to the alleviation of symptoms and the improvement of pulmonary function. Inflammation is a biological reaction of the immune system triggered by pathogens, damaged cells, toxic compounds and other factors that may cause acute or chronic inflammatory reactions in organs and may lead to tissue damage or diseases [27]. The acute exacerbation of COPD results in most COPD-related costs, and frequent attacks lead to a significant reduction in QOL. Owing to the better curative effect, patients treated with combination therapy presented higher QOL, shorter hospital stay and lower recurrence rate. Although there are no relevant studies indicating the role of the combination therapy in COPD; TB, an anticholinergic bronchodilator, has been reported to effectively inhibit goblet-cell metaplasia caused by neutrophil elastase and mucin production and reduce mucus secretion. CAM, a macrocyclic lactone compound, has both antibacterial activity and immunomodulatory activity and inhibits inflammation and excessive mucus secretion in airways [28], thereby evidently enhancing pulmonary function.

There are still several limitations in this study. The comparison of high- and low-dose CAM plus TB, evaluation on prognosis, or detection of other inflammatory factors have not been carried out. We will address these limitations and update our results in future studies.

To sum up, combination therapy of CAM plus TB is effective in the treatment of COPD.

Disclosure of conflict of interest

None.

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