Tropical Journal of Pharmaceutical Research December 2022; 21 (12): 2701-2706
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i12.27

Original Research Article

Co-administration of indacaterol and tiotropium bromide for the treatment of chronic obstructive pulmonary disease and bronchiectasis, and effect on IL-8 and CRP levels

Xuerong Wang, Xiaodong Wu, Huating Han*
Department of Respiratory Medicine, Yuyao People's Hospital, Yuyao 315400, China

For correspondence:* ***Email:* *hanhuating6563@outlook.com*

Sent for review: 19 February 2022 *Revised accepted: 17 November 2022*

Abstract

Purpose: *To investigate the efficacy of indacaterol plus tiotropium bromide in chronic obstructive pulmonary disease (COPD) complicated by bronchiectasis and the impact on IL-8 and C reactive protein (CRP) levels.*
Methods: *Sixty enrolled patients with COPD and bronchiectasis who received treatment in Yantai Qishan Hospital, Yuyan, China from June 2017 to December 2019 were randomly allocated to group A (n = 30) and group B (n = 30). Group A received inhalation of indacaterol plus tiotropium bromide. Group B received only tiotropium bromide inhalation therapy. Therapeutic effects and appropriate serum indicators were compared.*
Results: *Maximal mid-expiratory flow (MMF), maximal voluntary ventilation (MVV), and forced expiratory volume in one second (FEV1.0) levels of the patients were significantly elevated, and group A showed a significantly higher values than group B ($p < 0.05$). The serum levels of IL-8, CRP, and serum calcitonin (PCT) in both groups were lower than before treatment, but the decrease in group A was significantly greater than that in group B ($p < 0.05$). The SaO_2, PaO_2, and PaO_2/FiO_2 levels in both groups increased, but the increase in group A was higher than that in group B ($p < 0.05$). Group A showed a significantly lower total incidence of complications than group B ($p < 0.05$).*
Conclusion: *Indacaterol plus tiotropium bromide produced significant effects in the treatment of COPD with bronchiectasis, which ameliorate lung function and inflammation status in the body and therefore have the potential of being utilized in clinical practice.*

Keywords: *Indacaterol, Tiotropium bromide, COPD patients with bronchiectasis, Inflammation*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is primarily characterized by continuous airflow limitation [1]. It is more prevalent in middle-aged and elderly men, especially those with a history of smoking. The clinical symptoms of COPD are dyspnea, chest tightness, shortness of breath, cough, sputum, and even death in severe cases [2,3]. The clinical treatments for COPD patients with bronchiectasis include oxygen therapy, lung function training, drug inhalation therapy, and phlegm and cough reduction, which can ameliorate the respiratory and immune functions

of the patients [4]. Tiotropium bromide, an anticholinergic bronchodilator, is often utilized clinically for the maintenance treatment of patients with diverse lung diseases, which can significantly improve dyspnea and high-level inflammation. However, some severe patients are not well-treated, and their inflammatory status is not significantly improved [5,6]. Several clinical studies have explored the use of tiotropium bromide and indacaterol in patients with COPD and bronchiectasis and have reached controversial conclusions, and few studies have observed the effect of the combination of the two. Therefore, the investigation into the clinical efficacy of indacaterol plus tiotropium in COPD patients with bronchiectasis became this study's target.

METHODS

Clinical profile of patients

Sixty patients with COPD and bronchiectasis who received treatment in Yantai Qishan Hospital from June 2017 to December 2019 were enrolled (36 men and 24 women, with the age of 48 - 69 years old (mean age 61.37 ± 5.28 years)). The participants were randomly allocated into either group A (n = 30) or group B (n = 30). This study was approved by the ethics committee of Yuyao People's Hospital (approval no. 201401156B), and it met the criteria in the Declaration of Helsinki [7]. All patients submitted signed consent forms.

Inclusion criteria

Patients that have been clinically diagnosed with COPD and bronchiectasis [8], patients aged ≥ 18 years, patients with complete clinical data, and patients with no allergies to the drugs used for this treatment were all included in the study.

Exclusion criteria

Any case meeting the following criteria was excluded: (1) congenital immunodeficiency or severe infectious diseases, (2) mental diseases or poor mental condition, and unable to independently cooperate with the study, (3) expected survival time ≤ 3 months.

Treatments

Both groups of patients were given conventional treatment measures such as breathing training, oxygen therapy, and phlegm removal. Patients in group B were treated with tiotropium bromide (Boehringer Ingelheim Pharma GmbH & Co.KG, Germany, H20140933) inhalation treatment, 1 capsule, once a day for 2 months. In addition to the therapy of tiotropium bromide, group A also received indacaterol (Novartis Europharm Ltd, H20160302) inhalation therapy, for 2 months.

Evaluation of parameters/indices

All indices were measured, 1 day before treatment, and 2 months after treatment.

Pulmonary function

Maximal mid-expiratory flow (MMF), maximal voluntary ventilation (MVV), and forced expiratory volume in one second (FEV1.0) levels were recorded using the CHEST-pulmonary function instrument (Nanjing Aobang Medical Technology Co., Ltd.).

Inflammation-related indicators

Fasting venous blood (6 mL) was collected from each patient and left for 30 min at 4 °C. After the whole blood had spontaneously coagulated, the supernatant was centrifuged at 1000 - 2000*g* for 10 min at 4 °C to obtain the supernatant. The serum calcitonin (PCT) level was determined by an immunoluminescence assay (Shenzhen Tisenc Medical Devices Co., Ltd.). C reactive protein (CRP) level in serum was measured by the dry chemical method (Beijing Spectrum Analysis Technology Co., Ltd.). Serum interleukin-8 (IL-8) levels were determined using the ELISA kit (Shanghai HengYuan Biological Technology Co., Ltd.).

Oxygenation function

A 4 mL volume of arterial blood was collected from each patient. The GEM3500 blood gas analyzer (Nanjing Hanyu Medical Technology Co., Ltd.) was used for determining arterial oxygen saturation (SaO_2), arterial partial pressure of oxygen (PaO_2), and oxygenation index (PaO_2/FiO_2) levels in strict accordance with the instrument instructions.

Complications within 2 months after treatment

Complications principally included spontaneous pneumothorax, respiratory failure, chronic pulmonary heart disease, lung infection, gastric ulcer, and sleep breathing disorders.

Statistical analysis

Statistical Package for the Social Sciences (SPSS 25.0) software was used for statistical analysis. The measurement data were expressed

as mean ± standard deviation (SD). Two independent samples non-parametric test was used for inter-group analysis. Count data were expressed as percentages. Comparisons between the two groups were performed using the chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

General patient information

Patients were followed up to determine their survival. One and three cases were lost in groups A and B, respectively. No statistically significant differences were observed in gender, age, BMI, lung function classification, and underlying diseases between both groups (all $p > 0.05$, Table 1).

Lung function

Before treatment, the differences in MMF, MVV, and FEV1.0 levels between the two groups of patients were not significant ($p > 0.05$). Combined treatment of indacaterol and tiotropium bromide or single treatment of tiotropium bromide elevated MMF, MVV, and FEV1.0 levels, but the former had a greater effect ($p < 0.05$, Figure 1).

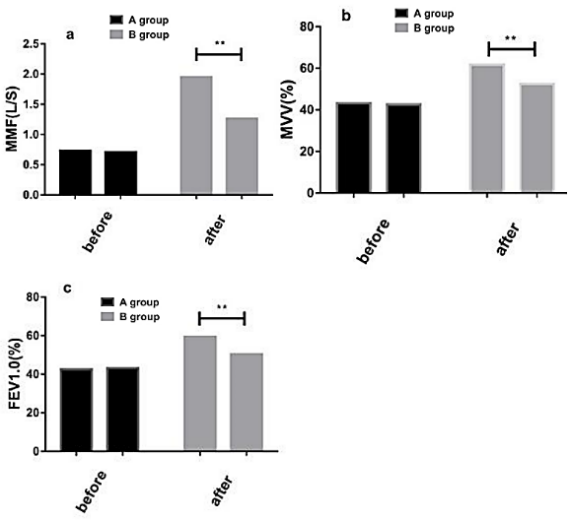

Figure 1: Comparison of lung function between the two groups (a) maximum mid-expiratory volume (MMF), (b) maximal voluntary ventilation (MVV), (c) forced expiratory volume in one second (FEV1.0) before treatment. $^{**}P < 0.001$

Inflammation-related indicators

Before treatment, no significant difference was shown in serum levels of IL-8, CRP, and PCT levels between the two groups of patients ($P > 0.05$). However, tiotropium bromide treatment could suppress serum IL-8 and CRP, and additional treatment with indacaterol contributed to a better efficacy ($P < 0.05$, Table 2).

Table 1: Comparison of general information of the two groups of patients (n = 30)

Parameter		Group		X^2/T	*P*-value
		A	B		
Gender	M	17	19	0.631	0.427
	F	13	11		
Age (years)		61.83±5.42	60.75±5.14	0.583	0.517
BMI (kg/m^2)		22.51±1.07	22.84±1.13	0.542	0.516
Lung function classification	I∼II	9	9	0.642	0.438
	III∼IV	13	15		
	V	8	6		
Basic diseases	yes	17	19	0.591	0.536
	no	13	11		

Table 2: Comparison of inflammation index levels between the two groups (n = 30)

Parameter		Group		T	*P*-value
		A	B		
CRP	Before	1237.53±213.14	1235.74±216.46	0.637	0.425
	After	506.73±141.48[a]	814.36±172.16[a]	6.473	0.001
IL-8	Before	334.65±42.49	332.41±43.07	0.583	0.524
	After	156.42±20.54[a]	251.26±30.36[a]	7.283	0.001
PCT	Before	683.45±117.39	685.14±119.26	0.549	0.521
	After	247.73±35.18[a]	414.39±72.54[a]	6.845	0.001

[a]$P < 0.05$ compared with before treatment

Related indicators of blood gas analysis

The differences in SaO_2, PaO_2, and PaO_2/FiO_2 levels between the two groups of patients before treatment were not statistically significant ($P > 0.05$). Combined treatment of indacaterol and tiotropium bromide caused an increase in the three indicators, showing more excellent outcomes than a single treatment of tiotropium bromide ($P < 0.05$, Figure 2).

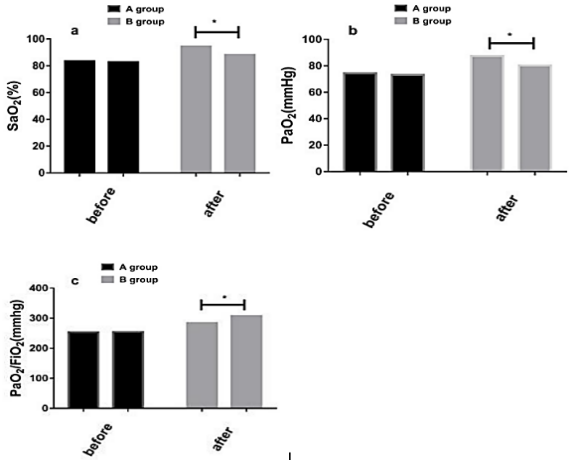

Figure 2: Comparison of related indicators of blood gas analysis between the two groups (a) Arterial oxygen saturation (SaO_2), (b) arterial oxygen partial pressure (PaO_2), (c) oxygenation index (PaO_2/FiO_2), *$P < 0.01$

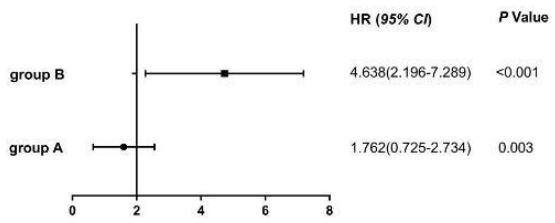

Figure 3: Comparison of the incidence of complications after nursing between the two groups. Group A: HR (95 % CI) = 4.638 (2.196 - 7.289), $p < 0.001$. Group B: HR (95 % CI) = 1.762 (0.725- 2.734), $p = 0.00$

Incidence of complications

A lower overall incidence of post-treatment complications was observed in patients receiving combined treatment of indacaterol and tiotropium bromide than those receiving a single treatment of tiotropium bromide ($P < 0.05$) (Table 3, Figure 3).

DISCUSSION

According to relevant statistics, the incidence of COPD in people over 40 years worldwide in 2019 is as high as 10 %, and COPD has become a usual disease among middle-aged and elderly people [9]. The clinical symptoms of patients with COPD are principally manifested as poor lung function, hyperactive inflammatory responses in the body, etc., and may be combined with lung infection [10]. Bronchiectasis, the prevalent comorbidity in COPD patients in the middle and late stages, exacerbates lung function and bronchial function damage in patients to a certain extent and enlarges the difficulty of treatment. Indacaterol and tiotropium bromide are widely utilized clinical drugs for COPD patients with bronchiectasis. This study evaluated the efficacy of indacaterol and tiotropium bromide and provide a reference for clinically diagnosing and treating COPD patients with bronchiectasis.

Tiotropium bromide, a long-acting anticholinergic drug, accommodates good affinity for 5 muscarinic receptors of M1 - M5 type and is capable of repressing contraction of the trachea caused by the release of acetylcholine from the parasympathetic nerve terminal through binding to muscarinic receptors on bronchial smooth muscles [11,12]. In the trachea, tiotropium bromide binds to the muscarinic M1 and M3 receptors for a longer time and can inhibit bronchial smooth muscle contraction and continue to relax the bronchus. Ultimately, it can significantly improve lung function and dyspnea, and finally, promote the prognosis of COPD patients with bronchiectasis [13,14].

Table 3: Comparison of the incidence of complications after treatment between the two groups (n = 30)

Parameter	Group		X^2	*P*-value
	A	B		
Spontaneous pneumothorax	1	2	-	-
respiratory failure	0	1	-	-
Chronic pulmonary heart disease	0	1	-	-
Pulmonary infection	1	1	-	-
gastric ulcer	1	2	-	-
Sleep breathing disorders	1	3	-	-
Total number	4	10	-	-
Total incidence （%）	13.33	33.33	7.352	0.001

Studies have shown that inflammation is one of the main triggers for COPD and bronchiectasis development. C reactive protein is an acute protein whose expression increases rapidly after infection or tissue damage [15]. It is one of the dominating non-specific inflammatory markers in the human body. Pathological enhancement of CRP expression has been observed in many diseases such as tissue injury, inflammation, and bacterial infection, and it can be used as a biological indicator to evaluate its recovery effect. As the predominant inflammatory cytokine in the body, IL-8 is tightly connected to the emergence and progression of multiple inflammatory or infectious diseases, such as pneumonia, lung infection, and COPD [16].

The PCT is a staple indicator for the diagnosis and evaluation of bacterial inflammation and fungal infections, which is abnormally elevated in severe fungal, and parasitic infections, and multi-organ failure diseases. A previous study demonstrated that COPD patients with bronchiectasis usually present more severe lung inflammation and may be accompanied by varying degrees of lung infection [17]. Combined treatment was more effective to reduce serum IL-8, CRP, and PCT levels than a single treatment, indicating that patients' lung inflammation and infection status were alleviated. Tiotropium bromide in combination with indacaterol improved the respiratory function of COPD patients with bronchiectasis and promoted recovery from the inflammatory activity and infection status.

The COPD patients with bronchiectasis usually exhibit severe dyspnea symptoms, and it can trigger severe hypoxia [18]. Normal human arterial blood SaO2 concentration is 98 %. If it is lower than 94 %, it means that the body is insufficiently supplied with oxygen. The level of PaO2 principally depends on the oxygen partial pressure of the inhaled gas and the functional state of respiration *in vitro*. The oxygenation index PaO2/FiO2 is the prime goal of clinical respiratory therapy. Its normal value is usually 400 - 500 mmHg. If it is lower than 300 mmHg, it indicates that the lung function of the body is impaired [19]. The SaO2, PaO2, and PaO2/FiO2 were affected more by combined treatment than a single treatment, suggesting that patients' lung function and hypoxia *in vivo* were significantly improved. Group A possessed a lower incidence of complications after treatment than group B. Indacaterol plus tiotropium bromide can improve pulmonary function and inflammatory status in COPD patients with bronchiectasis, and effectively reduce the incidence of complications after treatment.

CONCLUSION

Indacaterol plus tiotropium bromide have good clinical efficacy in treating COPD with bronchiectasis, which can significantly improve lung function and inflammation *in vivo* and have the potential for possible application in clinical practice.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This study was approved by the ethics committee of Yuyao People's Hospital (approval no. 201401156B).

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 on claims relating to the content of this article will be borne by the authors. Xuerong Wang and Huating Han conceived and designed the study and drafted the manuscript. Xuerong Wang, Xiaodong Wu, and Huating Han collected, analyzed, and interpreted the experimental data. Xuerong Wang and Xiaodong Wu revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. *Zhang S, Liu Q, Chu Z, Wang L, Jiang F. Effect of a combination of low-dose aminophylline and budesonide on lung function, serum inflammatory factors and quality of life of patients with chronic obstructive pulmonary disease. Trop J Pharm Res 2021; 20(6): 1273-1278.*
2. *Lindenauer PK, Dharmarajan K, Qin L, Lin Z, Gershon AS, Krumholz HM. Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease. Am J Resp Crit Care 2018; 197(8): 1009-1017.*
3. *Kirby M, Tanabe N, Tan WC, Zhou G, Obeidat M, Hague CJ, Leipsic J, Bourbeau J, Sin DD, Hogg JC, et al. Total airway count on computed tomography and the risk of chronic obstructive pulmonary disease progression. Findings from a population-based study. Am J Respir Crit Care Med 2018; 197(1): 56-65.*
4. *Heraganahally SS, Wasgewatta SL, Mcnamara K, Mingi JJ, Mehra S, Eisemberg CC, Maguire G. 2004 chronic obstructive pulmonary disease with and without bronchiectasis in Aboriginal Australians: a comparative study. Intern Med J 2020; 47(5): 1505-1513.*
5. *Cardona-Villa R, Tejada-Giraldo M. Recent evidence on the use of tiotropium bromide in pediatric asthma: Summary results of eight clinical trials. Curr Treat Option All 2018; 42(7): 23-27.*
6. *Gregory JA, Kemi C, Ji J, Karén J, Delin I, Gerde P, Pieper MP, Adner M, Larsson K. Effects of tiotropium bromide on airway hyperresponsiveness and inflammation in mice exposed to organic dust. Pulm Pharmacol Ther 2018; 48(7): 203-210.*
7. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
8. *Labaki WW, Han MK. Impact of bronchiectasis on the frequency and severity of respiratory exacerbations in COPD. Intjour Chrobs Puldis 2018; 13(4): 2335-2338.*
9. *Amundsen T, Torheim G, Waage A, Bjermer L, Steen PA, Haraldseth O. Perfusion magnetic resonance imaging of the lung: Characterization of pneumonia and chronic obstructive pulmonary disease. A feasibility study. Magn Reson Imaging 2015; 12(2): 224-231.*
10. *Hackx M, Bankier AA, Gevenois PA. Chronic obstructive pulmonary disease: ct quantification of airway dimensions, numbers of airways to measure, and effect of bronchodilation. Radiol 2015; 265(1): 34-48.*
11. *Toumpanakis D, Loverdos K, Tzouda V, Vassilakopoulou V, Litsiou E, Magkou C, Karavana V, Pieper M, Vassilakopoulos T. Tiotropium bromide exerts anti-inflammatory effects during resistive breathing, an experimental model of severe airway obstruction. Int J Chronic Obstr 2017; 12(3): 2207-2220.*
12. *Mosley JF, Smith LL, Dutton BN. tiotropium bromide/olodaterol (Stiolto respimat): once-daily combination therapy for the maintenance of COPD. Pat 2016; 41(2): 97-102.*
13. *Radovanovic D, Santus P, Blasi F, Mantero M. The evidence on tiotropium bromide in asthma: from the rationale to the bedside. Mult Resp Med 2017; 12(1): 37.*
14. *Ohbayashi H. Comparison of the rapid effects of single inhalations of formoterol and tiotropium bromide on respiratory function and COPD symptoms in a randomized crossover study. Respir Invest 2017; 55(6): 348-356.*
15. *Fermont JM, Masconi KL, Jensen MT, et al. Biomarkers and clinical outcomes in COPD: A systematic review and meta-analysis. Thorax 2019; 47(5): 439-446.*
16. *Li D, Wang J, Sun D, Gong X, Jiang H, Shu J, Wang Z, Long Z, Chen Y, Zhang Z, et al. Tanshinone IIA sulfonate protects against cigarette smoke-induced COPD and down-regulation of CFTR in mice. Sci Rep 2018; 8(1): 376.*
17. *Kume H, Hojo M, Hashimoto N. Eosinophil inflammation and hyperresponsiveness in the airways as phenotypes of COPD, and usefulness of inhaled glucocorticosteroids. Front Pharmacol 2019; 10(3): 765.*
18. *Wen X H, Li Y, Han D, Sun L, Ren P, Ren D. The relationship between cognitive function and arterial partial pressure O2 in patients with COPD: A meta-analysis. Med 2018; 97(4): e9599.*
19. *Ribeiro F, Oueslati F, Saey D, Lépine PA, Chambah S, Coats V, Maltais F. Cardiorespiratory and muscle oxygenation responses to isokinetic test in COPD. Med Sci Sport Exer 2019; 52(4): 841-849.*