Original Article

A Comparative Evaluation of Glycopyrronium Bromide, A Long-Acting Muscarinic Antagonist *versus* Tiotropium Bromide in Triple Therapy of COPD Patients in an Indian Clinical Setting

Aleemuddin NM[1], Humaira Minhaj[2], Ayemen Fatima[2], Aisha Begum[2] and Syeda Zuleqaunnisa Begum[3]

Department of Respiratory Medicine[1], Deccan College of Medical Sciences and Department of Pharmacy Practice[2], Deccan School of Pharmacy, Hyderabad (Telangana), India

Abstract

Background. Current pharmacological management for patients with chronic obstructive pulmonary disease (COPD) focuses on inhaled long-acting bronchodilators, which are considered as the recommended first-line treatment option for such patients.

Methods. A prospective study was conducted in 70 patients with moderate to severe COPD. Thirty-five patients (Group A) were administered daily glycopyrronium bromide (50µg) and 35 (Group B) received tiotropium bromide (18µg). Patients were assessed for forced expiratory volume in one second (FEV_1) score, COPD assessment scale (CAT), modified Medical Research Council (mMRC) scale, body-mass index, airflow obstruction, dyspnoea and exercise (BODE) index for COPD survival for two consecutive follow-ups after every three months of drug use.

Results. Group A showed a significant improvement with respect to different evaluation methods compared to group B. Significant results were observed for group A parameters were mMRC (0.0001), CAT (0.01), BODE (0.0001) and FEV_1 (0.03).

Conclusions. In patients with moderate to severe COPD, glycopyrronium bromide (50µg) once daily is found to be more beneficial than tiotropium bromide (18µg). **[Indian J Chest Dis Allied Sci 2021;63:29-32]**

Key words: COPD, Glycopyrronium bromide, Tiotropium bromide, Bronchodilator, Long-acting muscarinic antagonist.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease of airways characterised by the inflammation of small airways and parenchymal destruction resulting in lung injury with accelerated decline in the lung functions.[1] Currently COPD is the fourth leading cause of death with a mortality rate of more than three million world wide. By the end of 2020, it has been predicted to be third leading cause of death.[2] Among all aetiologic agents, such as exposure to occupational dusts, silica, asbestos, noxious gases, recurrent respiratory infections and genetic predispositions (*e.g.*, alpha-1-antitrypsin deficiency), smoking stands as a major contributing factor for COPD.[3] COPD patients complains of episodes of shortness of breath, coughing, sputum production, chest tightness, whistling sounds when breathing which are associated with exacerbation and remission.[4] Recently, it has been estimated that one among five patients requires re-hospitalisation within 30 days following hospital discharge for acute exacerbation of COPD (AE-COPD).[5] Therapeutic agents that are recommended for the management includes medications with inhalers: inhaled bronchodilators (beta-2 agonists),[6] anticholinergics (ipratropium/tiotropium)[7] and inhaled corticosteroids (budesonide/fluticasone)[8] along with patient counselling regarding lifestyle modifications, inhaler using techniques and importance of medication adherence. Glycopyrronium bromide is a newer approved drug of class long-acting muscarinic antagonists as bronchodilator once daily for COPD management was found to be effective in improving lung function with better health status outcomes and reduced exacerbation rates in moderate to severe COPD patients.[9]

The aim of our study was to evaluate the impact of once daily administration of glycopyrronium bromide (50µg) *versus* tiotropium (18µg) among moderate to severe COPD patients and assess the health outcomes based on COPD questionnaires, mMRC score and body-mass index, airflow obstruction, dyspnoea and exercise (BODE) index.

[Received: November 10, 2019; accepted: July 29, 2020]

Corresponding author: Dr Aleemuddin NM, Professor, Department of Respiratory Medicine, Deccan College of Medical Sciences, OHRC, Princess Esra Hospital, Owaisi Group of Hospitals, DMRL 'X' Road, Santoshnagar, Kanchan Bagh,Hyderabad-500 058 (Telangana), India; E-mail: aleem95@yahoo.com

Material and Methods

A prospective, observational study on 70 patients of 40-80 years of age with moderate to severe COPD as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2012, stage II and III who were smokers or non-smokers and had a post-bronchodilator forced expiratory volume in one second (FEV_1) >30% and <80% employing parallel design, presenting in the outpatient department of pulmonology and respiratory intensive care unit of Princess Esra Hospital (Owaisi Group of Institutions), Hyderabad, (Telangana), South India from September 2018 to February 2019 was done. Post bronchodilator refers to 15 minutes after inhaled salbutamol (400 µg). Patients who were more than 80 years of age, with respiratory tract infections within four weeks prior to screening, pregnant and lactating females, contraindicated to tiotropium bromide or glycopyrronium bromide, with glaucoma or benign prostatic hyperplasia and those unwilling or unable to give verbal informed consent were excluded from the study. The study was approved by the Institutional Ethics Committee.

The patients were divided into two groups: Group A–patients who were administered glycopyrronium bromide (50µg), (rotacaps [Airz] manufactured by Glenmark Pharmaceuticals Ltd) via the breezhaler device and Group B– who were administered tiotropium bromide (18µg), (rotacaps [Tiova] manufactured by Cipla Ltd), via breezhaler device. Each of the medications were given once daily after the morning meal. They were instructed about the proper use of the device along with the benefits and risks of the study. The patient data was collected from case sheets of in-patients and prescriptions of out-patients. Spirometry was performed through the American Thoracic Society and European Respiratory Society guidelines compliant spirometer and values of post-bronchodilator FEV_1 and other variables were recorded. Other relevant data collected were symptom-based questionnaire, like COPD assessment scale (CAT), modified Medical Research Council Scale (mMRC) for dyspnoea scores from 0-4, BODE index for COPD survival and direct responses to disease specific questionnaire. These measurements were taken for two consecutive follow-ups of the patients after every three months of drug use. The number of exacerbations and hospitalisations prior to the study were compared with those during the six months of the study. COPD exacerbations were defined as worsening of two or more baseline symptoms (dyspnoea,volume of sputum and sputum purulence) for at least two consecutive days or worsening of any major symptom together with any minor symptoms, like cold, fever without other cause, increased cough, wheeze or sore throat for at least two consecutive days.

Statistical Analysis

Statistical analysis was carried out to find the better drug among glycopyrronium bromide and tiotropium bromide. 'T' test was used to find out the significance between the two groups. Mean and degree of freedom were calculated. SAS software was used for statistical calculations.

Results

The mean age of the study patients of group A and B was 62.2 years 57.1 years, respectively. About 51.4% of the patients were diagnosed with severe COPD in group A and 54.3% in group B. The mean score values for different evaluation methods are presented in tables 1 and 2. Values of these evaluation methods show statistically significant difference ($P<0.05$). Further, when we analysed the data by combining mean score of all the visits, group A (glycopyrronium bromide) showed significant reduction with respect to CAT score, mMRC score, FEV_1 values when compared to group B (tiotropium bromide). The exacerbations and hospitalisations prior and during the study have been presented in the figure.

Table 1. Comparison of baseline, visit 1 and visit 2 of three different evaluation systems of both the groups.

Method	(Mean ± SD)	df	F value	P value
Group A				
mMRC (n=35)	3.79±0.63	2	18.04	0.0001
CAT (n=35)	23.07±7.37	2	7.23	0.01
BODE (n=35)	5.47±1.44	2	12.00	0.0001
FEV_1 (n=35)	46.97±10.44	2	6.21	0.03
Group B				
mMRC (n=35)	3.35±0.52	2	1.97	0.11
CAT (n=35)	29.02±3.82	2	0.46	0.63
BODE (n=35)	4.63±1.35	2	1.87	0.15
FEV_1 (n=35)	47.64±8.83	2	0.04	0.96

Definition of abbreviations: mMRC=modified Medical Research Council, CAT=COPD assessment test, BODE=Body-mass index, airflow obstruction, dyspnoea and exercise, FEV_1=Forced expiratory volume in one second.

Table 2. Change in values of parameters from baseline to visit 2

Parametere	Baseline	Visit 2	P value
mMRC			
Group A	3.90±1.55	2.01±0.48	0.05
Group B	3.89±0.63	2.42±0.55	0.07
CAT			
Group A	21.45±9.56	16.54±21.00	0.04
Group B	23.07±7.37	21.00±6.84	0.08
BODE			
Group A	4.93±1.34	3.94±1.29	0.05
Group B	5.47±1.44	4.30±1.26	0.12
FEV_1			
Group A	50.48±19.64	60.45±9.34	0.05
Group B	46.97±10.40	55.07±10.04	0.05

Definition of abbreviations: mMRC=modified Medical Research Council, CAT=COPD assessment test, BODE=Body-mass index, airflow obstruction, dyspnoea and exercise, FEV_1=Forced expiratory volume in one second.

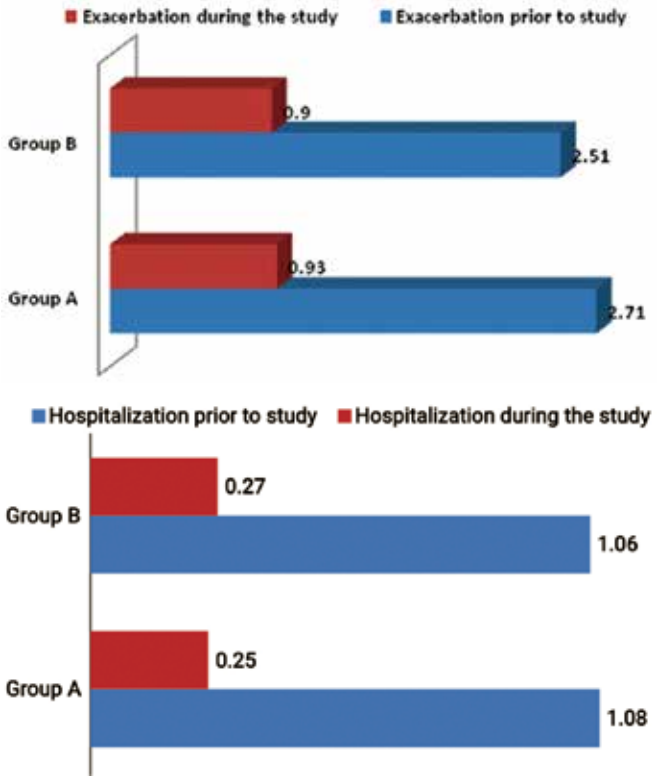

Figure. Showing (A) exerbations and (B) hospitalisation of the patients of both the groups.

Discussion

Chronic obstructive pulmonary disease is the leading cause of death and disability involving chronic inflammation of the lungs which leads to narrowing of peripheral airways and parenchyma. Bronchodilators play an important role in symptomatic management of COPD by selectively blocking the binding of acetylcholine to muscarinic receptors. Long-acting muscarinic antagonists (LAMAs), such as glycopyrronium and tiotropium, and long-acting β_2-agonists (LABAs) are the main group of long-acting bronchodilators. The aim of our study was to find out the best combination of triple regimen in the treatment of moderate to severe COPD by comparing tiotropium and glycopyrronium bromide as long acting muscarinic antagonist. The objectives were to assess the relative efficacy of (tiotropium and glycopyrronium) by means of lung function (FEV_1) at 24 weeks and compare them by evaluating COPD scales and physiological parameters.

In India, LAMA (tiotropium) is the mainstay of the treatment for COPD and is used as a first once-daily inhaled long-acting bronchodilator. Recently, Central Drugs Standard Control Organisation (CDSCO) has approved to study the efficacy of glycopyrronium bromide for further clinical usage as it shows rapid bronchodilation than that of tiotropium. However, a detailed prospective and observational study comparing LAMA efficacy are inadequate for COPD.

In our study, patients treated with glycopyrronium bromide (Group A) have shown improved mMRC, CAT, BODE and FEV_1 values compared to patients treated with tiotropium bromide (Group B). This might be due to the rapid onset of action of glycopyrronium bromide when compared to tiotropium bromide. Patients treated with glycopyrronium (Group A) have shown reduced exacerbations when compared to patients treated with tiotropium.

As glycopyrrolate is a fast-acting muscarinic antagonist, it is now being used in western countries as an effective treatment option for patients with COPD. In our study, we observed that hospitalisation duration was less in glycopyrrolate treated group when compared to patients treated with tiotropium. It can be attributed that glycopyrrolate may improve lung function, thereby reduces the risk of exacerbations, and minimises the adverse symptoms which may lead to less hospitalisation duration and further improves the patients' quality-of-life. Previously, Donald *et al*[10] reported that patients treated with glycopyrrolate had showed improved quality-of-life and less hospitalisation duration when compared to patients treated with tiotropium. The study compared two LAMAs, glycopyrronium bromide and tiotropium bromide, in the combined COPD therapy. The effects of glycopyrronium bromide were found to be more beneficial than tiotropium bromide with a small margin of difference.

The results from the 24 week study demonstrated that in patients with moderate to severe COPD, glycopyrronium (50 μg) (AIRZ), once daily provided improved efficacy in comparison to tiotropium bromide, (18 μg) (TIOVA), once daily.

Significant differences in the mMRC score, CAT score, BODE index and FEV_1 values were observed in patients who were administered with glycopyrronium bromide along with their standard treatment.

Results were not significant in comparison of number of exacerbations and were significant for comparison of number of hospitalisations in both the groups. It improved the lung function, reduced the risk of exacerbations and alleviated the symptoms of breathlessness, which in turn, explains the improvement seen in patient's quality-of-life (analysed through BODE index and CAT score upon administration of glycopyrronium.

No unbearable adverse events were observed in both the groups during the study.

Conclusions

Glycopyrronium is a useful addition to the treatment for COPD. There also appeared to be limited published data examining the head to head comparison of these two LAMAs, hence, there is need for further studies in this area.

Acknowledgements

We express our sincere thanks to Sh M. Phanni, Statistician, Owaisi Hospital and Research Centre, Kanchanbagh, Hyderabad, for his guidance in statistical analysis

References

1. Global Initiative for Chronic Obstructive Lung Disease. *GOLD*, 2019, *Available at URL:* http://www.goldcopd.org/. Accessed on January 25, 2020.
2. Terence H, Cusack RP, Chaudhary N, Satia I, Kurmi OP. Under- and over-diagnosis of COPD: a global perspective." *Breathe (Sheffield, England), Eur Respir Society*, 2019, *Available at URL:* www.ncbi.nlm.nih.gov/pmc/articles/PMC6395975/. Accessed on February 4, 2020.
3. Sutradhar I, Das Gupta R, Hasan M, Wazib A, Sarker M. Prevalence and risk factors of chronic obstructive pulmonary disease in bangladesh: a systematic review. *Cureus* 2019;28:e3970.
4. Dar SA, Bhat BA, Shah NN, Imtiyaz SB. The pattern of psychiatric morbidity in chronic obstructive pulmonary disease: a cross-sectional, case-control study from a tertiary care hospital in Kashmir, North India. *J Neurosci Rural Pract* 2019;10:65–70.
5. Shah T, Press VG, Huisingh-Scheetz M, White SR. COPD readmissions: addressing COPD in the era of value-based health care. *Chest* 2016;150:916–26.
6. Karner C, Cates CJ. Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;4:CD008989.
7. Gartlehner G, Hansen RA, Carson SS, Lohr KN. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. *Ann Fam Med* 2006;4:253–62.
8. Carter NJ. Inhaled glycopyrronium bromide: a review of its use in patients with moderate to severe chronic obstructive pulmonary disease. *Drugs* 2013;73:741–53.
9. Tashkin DP, Gross NJ. Inhaled glycopyrrolate for the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2018;13:1873–88.