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A randomized controlled trial to compare the efficacy and safety of glycopyrronium bromide + salmeterol/fluticasone and tiotropium bromide + salmeterol/fluticasone in chronic obstructive pulmonary disease

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ABSTRACT

Objective: To compare the efficacy and safety of glycopyrronium bromide + salmeterol/fluticasone and tiotropium bromide + salmeterol/fluticasone in chronic obstructive pulmonary disease (COPD) in a randomized controlled trial.

Methods: This study was an open labeled randomized controlled trial. Patients diagnosed with COPD were included in the study. The patients were divided into 2 groups each consisted 75 patients. Group I- COPD patients on Tiotropium bromide + Salmeterol/Fluticasone; Group II – COPD patient on Glycopyrronium bromide + Salmeterol/Fluticasone. A detailed history and clinical examination was done for each case. Pulmonary Function Test (PFT) was performed at 0, 6 and 12 weeks.

Results: There was no significant ($p>0.05$) difference in the basic characteristics of patients between the groups showing comparability of the groups in terms of basic characteristics. FEV1 was observed to be significantly higher in Group II than Group I at 12 weeks ($p=0.03$). There was no significant ($p>0.05$) difference in PEFR between the groups at all the time periods. FEF was observed to be significantly higher in Group II than Group I at 12 weeks ($p=0.04$). There was no significant ($p>0.05$) difference in FEV1/FVC between the groups at all the time periods. MVV was found to be significantly higher in Group II compared to Group I at 6 weeks ($p=0.03$) and 12 weeks ($p=0.04$).

Conclusion: Once-daily GLY demonstrated similar effects to TIO when combined with SAL/FP in patients with moderate and severe COPD.

Key words: Chronic obstructive pulmonary disease–Glycopyrronium bromide–Tiotropium bromide–Efficacy–Safety

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease of the respiratory system characterized by airflow limitation which is not completely reversible. This is associated with systemic effects especially of the cardiovascular system[1]. COPD is commonly complicated by acute exacerbations which contribute to physical impairment and increased health care use. The COPD GOLD (Global Initiative for Obstructive Lung Disease) stage positively correlates with both severity and frequency of acute exacerbations [2].

COPD is a main public health burden. The current prevalence of COPD is assessed to be approximately 8-10% in adults aged 40 years or more in developed countries. However, in developing countries, the prevalence of COPD varies widely. It is difficult to estimate due to different definitions used to identify cases of COPD [3]. Regardless of the burden that COPD places on health care systems, COPD remains a condition which is all too often sub-optimally managed. Since, COPD is a chronic lung disease with significant sys-

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temic manifestations, it is important to have chronic disease management programs. Specifically, targeting individuals with COPD designed to improve their overall quality of life.

Spirometry is a regularly performed pulmonary function test. It is a measurement of the amount of air which breathes. This involves the measurements of both the volume and rate of air that can be inhaled and exhaled as a function of time. Both ATS and ERS publish guidelines for performing and interpreting pulmonary function tests in respiratory diseases like COPD and Asthma. Based on spirometry testing results, patient can be divided further into an obstructive or restrictive pattern of pulmonary disease[4,5].

Tiotropium had been shown to prolong the time to first exacerbation compared to placebo, in addition in decreasing the frequency of exacerbations and associated hospitalization. It is known that acetylcholine increases neutrophil chemotactic activity in COPD. This effect is attenuated *in vitro* by tiotropium, suggesting a possible anti-inflammatory mechanism, though it remains controversial[6].

Salmeterol has been combined with fluticasone propionate in an MDI (Advair HFA, GlaxoSmithKline) and a DPI (Advair Diskus, GlaxoSmithKline) formulation. Advair HFA (fluticasone/salmeterol) is available in 3 strengths: 45μg/21 μg, 115 μg /21 μg, and 230 μg /21 μg. Each inhaler provides 120 metered inhalations. The usual dose is 1-2 inhalations twice daily. Advair Diskus (fluticasone/ salmeterol) is also available in 3 strengths: 100 μg /50 μg, 250 μg /50 μg, and 500 μg /50 μg. The usual dose is one inhalation twice daily. Although onset of action typically starts after 10 -15 min post-dose, the median time to onset of clinically important bronchodilation ranges from 30 min to 45 min, peaks at 120 min, and lasts 12 hours in most patients [7].

Glycopyrronium acts as a highly potent, competitive muscarinic receptor antagonist that binds to muscarinic receptors in bronchial smooth muscle and inhibits acetylcholine-mediated bronchoconstriction. Glycopyrronium binds with high affinity to M_{1-3} receptors. It exhibits higher selectivity (4–5-fold) for M_1 and M_3 subtypes over M_2, and shows faster dissociation from M_2 than from M_1 and M_3 Tiotropium shares similar characteristics. There are some subtle differences when compared with tiotropium, shown in vitro comparisons during the drug development process. Glycopyrronium exhibits greater binding selectivity for M_3 over M_2 receptors than tiotropium, and has higher kinetic selectivity and faster dissociation from M_2 receptors than from M_3 receptors when compared with tiotropium [8].

This study aimed to compare the efficacy and safety of glycopyrronium bromide + salmeterol/fluticasone and tiotropium bromide + salmeterol/fluticasone in chronic obstructive pulmonary disease in a randomized controlled trial.

2 MATERIAL AND METHODS

This study was an open labeled randomized controlled trial conducted in the Department of Pharmacology and Pulmonary Medicine at Prasad Institute of Medical Sciences, Unnao. Patients diagnosed with COPD were included in the study. Patients suffering from other associated chronic diseases such as diabetes mellitus, hypertension, liver disease, allergic to anti cholinergics, recent eye surgery within 2 months, and patients undergoing major surgery within 3 months were excluded from the study. The study was approved by the Ethical Committee of the Institute and consent was taken from each participant before enrolling in the study.

Methods

The patients were divided into 2 groups each consisted 75 patients. Group I- COPD patients on Tiotropium bromide + Salmeterol/Fluticasone; Group II – COPD patient on Glycopyrronium bromide + Salmeterol/Fluticasone.

The drugs were given to the patients on the basis of physician's discretion depending upon the PFT report.

Tiotropium bromide: 18 mcg OD

Glycopyrronium bromide: 50 mcg OD

Along with Salmeterol 50 mcg/Fluticasone 100mcg

A detailed history and clinical examination was done for each case. Pulmonary Function Test (PFT) was performed at 0, 6 and 12 weeks.

For seeing bronchodilator response, spirometry was performed 15-30 minutes after administering a short acting beta-agonist like salbutamol or terbutaline.

Statistical analysis

The results are presented in frequencies, percentages and mean±SD. The Chi-square test was used to compare categorical variables between the groups. Students Unpaired and Paired *t*-test was used to continuous variables between the groups. The $p<0.05$ was considered significant. All the analysis was carried out on SSPS 16.0 version for Windows (Chicago, Inc., USA).

3 RESULTS

The mean age of patients in Group I and Group II was 55.56±7.31 and 57.15±8.03 years respectively. Majority of patients of both Group I (73.3%) and Group II (77.3%) were males. More than half of patients in both Group I (53.3%) and Group II (61.3%) were smoker. Moderate severity of disease was among majority of patients in both Group I (94.7%) and Group II (92%). There was no significant ($p>0.05$) difference in the basic characteristics of patients between the groups showing comparability of the groups in terms of basic characteristics (Table-1).

No significant ($p>0.05$) difference was observed in all the PFT parameters between the groups at 0 week. FEV1 was observed to be significantly higher in Group II than Group I at 12 weeks ($p=0.03$). There was no significant ($p>0.05$) difference in PEFR between the groups at all the time periods. FEF was observed to be significantly higher in Group

II than Group I at 12 weeks (p=0.04). There was no significant (p>0.05) difference in FEV1/FVC between the groups at all the time periods. MVV was found to be significantly higher in Group II compared to Group I at 6 weeks (p=0.03) and 12 weeks (p=0.04) (Table-2).

There was clinical improvement among majority of patients in both the groups (Table-3).

Table 1. Distribution of basic characteristics of patients between the groups

Groups	Group I (n=75)	Group II (n=75)	p-value1
Age in years, mean±sd	55.56±7.31	57.15±8.03	0.20
Gender, no. (%)			
Male	55 (73.3)	58 (77.3)	0.57
Female	(20 (26.7)	17 (22.7)	
Smoking habit, no. (%)			
Present	40 (53.3)	46 (61.3)	0.32
Absent	35 (46.7)	29 (38.7)	
Severity of disease, no. (%)			
Moderate	71 (94.7)	69 (92.0)	
Severe	4 (5.3)	6 (8.0)	

[1]Unpairedt-test/Chi-square test

Table 2. Comparison of PFT between the groups across the time periods

Time periods	Group I (n=75)	Group II (n=75)	p-value1
FEV1			
0 week	1.37±0.41	1.35±0.44	0.84
6 weeks	1.46±0.40	1.59±0.44	0.06
12 weeks	1.54±0.42	1.68±0.34	0.03*
PEFR			
0 week	3.31±1.39	3.32±1.22	0.98
6 weeks	3.54±1.33	3.87±1.16	0.10
12 weeks	3.67±1.39	4.02±1.08	0.08
FEF			
0 week	0.96±0.60	0.99±0.50	0.74
6 weeks	0.98±0.63	1.14±0.49	0.07
12 weeks	1.08±0.77	1.29±0.50	0.04*
FEV1/FVC			
0 week	65.38±5.34	62.62±5.47	0.06
6 weeks	66.51±5.24	65.73±5.40	0.37
12 weeks	67.20±5.12	67.40±5.31	0.82
MVV			
0 week	50.67±19.42	51.84±16.17	0.68
6 weeks	54.72±20.70	61.13±15.82	0.03*
12 weeks	56.64±20.95	62.92±15.95	0.04*

[1]Unpairedt-test, *Significant

4 DISCUSSION

Patients with moderate-severe stable, COPD already had more serious airway limitation. 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 [9].

Table 3. Comparison of clinical improvement between the groups

Clinical improvement	Group I (n=75)		Group II (n=75)		p-value1
	No.	%	No.	%	
Improved	73	97.3	73	97.3	1.00
Not improved	2	2.7	2	2.7	

[1]Chi-squaretest

Combining inhaler therapies from different classes of drugs for COPD is frequently recommended and usually pursued[10-12]. However, it is important to know if there is merit in doing so; in particular if there is comparable efficacy for medications from the same therapeutic class and whether therapy with GLY+LABA/ICS has advantages over therapy with LABA/ICS in patients with moderate to severe disease. The GLISTEN study demonstrates that TIO and GLY are comparable when added to a LABA/ICS combination in moderate to severe COPD patients, but more importantly shows the superiority of using GLY+LABA/ICS over using a LABA/ICS alone. This is the first time this has been effectively demonstrated.

In this study, there was no significant (p>0.05) difference in the basic characteristics of patients between the groups showing comparability of the groups in terms of basic characteristics. The mean age of patients in Group I and Group II was 55.56±7.31 and 57.15±8.03 years respectively. Majority of patients of both Group I (73.3%) and Group II (77.3%) were males. These findings of this study are in consistent with the study by Peter et al[13] in which the mean age of patients was 68.2±8.38 and 68.0 ±7.74 years in Glycopyrronium +SAL/FP and Tiotropium +SAL/FP groups respectively. They reported that 63.4% and 62% were males in Glycopyrronium +SAL/FP and Tiotropium +SAL/FP groups respectively. They found that 35.4% and 35.7% were smokers in Glycopyrronium +SAL/FP and Tiotropium +SAL/FP groups respectively.

The findings of this study in terms of FEV1 are inconsistent with results for GLY versus TIO non-inferiority studies in a monotherapy setting, as demonstrated in both open-label and blinded randomised controlled trials. Although not measured in the current study, GLY has been shown in other studies to be superior to TIO in terms of time to onset and on peak FEV1 results[14,15].

There have been many studies comparing LABA/ICS therapy with individual monotherapies (ICS, LABA, LAMA). A systematic review by Kew et al[16] of 71 randomised controlled trials (n=73 062; >6 months' duration) comparing LABA, LAMA, ICS or combined LABA/ICS and PLA, showed health status and lung function were improved most if taking LABA/ICS. The review also concluded that LAMAs and LABAs had similar efficacy although triple therapies were not included in their analysis.

This study found that there was no significant (p>0.05) difference in PEFR between the groups at all the time periods. FEF was observed to be significantly higher in Group

II than Group I at 12 weeks (p=0.04). There was no significant (p>0.05) difference in FEV1/FVC between the groups at all the time periods. MVV was found to be significantly higher in Group II compared to Group I at 6 weeks (p=0.03) and 12 weeks (p=0.04). Xiang[17] analyzed the effect of tiotropium bromide combined with salmeterol fluticasone inhalation on airway function and airway inflammation in patients with moderate-severe stable COPD and found that after 2 weeks of treatment, small airway function parameters FEF25, FEF25-75 and FEF75 levels of observation group were significantly higher than those of control group.

In the present study, there was no significant (p>0.05) difference in FEV1/FVC between the groups at all the time periods. Wang et al[18] compared the efficacy and safety of tiotropium bromide inhalation powder (spiriva) and doxofylline oral tablet (doxofylline) in the treatment of chronic obstructive pulmonary disease and found that $FEV_1/FVC\%$ was significantly higher than those before the medication.

This study showed that there was no significant (p>0.05) difference in PEFR between the groups at all the time periods. MVV was found to be significantly higher in Group II compared to Group I at 6 weeks (p=0.03) and 12 weeks (p=0.04). Mariana et al[19] reported that patients who received tiotropium bromide, had better clinical and laboratory dynamics and a full recovery of surface-active fraction of the pulmonary surfactant system, which clearly correlates with the prolongation of treatment.

One of the limitations of this study was small sample size. The studies with larger sample size long term follow-up are required to have robust findings.

5 CONCLUSION

Once-daily GLY demonstrated similar effects to TIO when combined with SAL/FP in patients with moderate and severe COPD. [1–19]

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