International Journal of Research in Medical Sciences
Ahmad S et al. Int J Res Med Sci. 2023 Apr;11(4):1239-1245
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20230868

Original Research Article

Safety and efficacy of formoterol/tiotropium bromide and formoterol/glycopyrronium combination in patients with chronic obstructive pulmonary disease

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Received: 31 January 2023
Revised: 04 March 2023
Accepted: 10 March 2023

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ABSTRACT

Background: Chronic obstructive pulmonary disease is characterized by a progressive development of airflow limitation that is not fully reversible. The study investigated the efficacy and safety of formoterol/tiotropium bromide and formoterol/glycopyrronium combination in patients with chronic obstructive pulmonary disease. Glycopyrrolate, a long-acting anti-muscarinic agent is recently approved for the maintenance therapy of chronic obstructive pulmonary disease in combination with formoterol. However, the studies on glycopyrrolate along with long-acting beta 2 agonist, particularly in Indian patients are limited. Hence it was considered worthwhile to determine safety and efficacy of fixed dose combinations of formoterol/ tiotropium vs. formoterol/glycopyrrolate in grade-2 patients of chronic obstructive pulmonary disease patients.
Methods: Efficacy and safety of formoterol/glycopyrrolate and formoterol/tiotropium were compared in Grade-2 patients. Total 68 patients were analysed and the efficacy of treatment was determined by Spirometry, Chronic Obstructive Pulmonary Disease Assessment Test score and Symptom score at day zero (before therapeutic intervention) and at two weeks of interval till 12 weeks.
Results: The treatment with inhaled combination of formoterol/glycopyrrolate and formoterol/tiotropium has shown an improvement in spirometric variable Forced Expiratory Volume (in one second) decrease in mean Symptom score and COPD Assessment Test score among the grade-2 Chronic Obstructive Pulmonary Disease patients.
Conclusions: Combination therapy of formoterol/glycopyrrolate is non-inferior to formoterol/tiotropium in terms of efficacy and safety profile of patients with chronic obstructive pulmonary disease.

Keywords: Tiotropium, Glycopyrrolate, Formoterol, Symptom score, COPD assessment test

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and respiratory symptoms that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world and estimated to be the 3rd leading cause of death by 2020.[2] According to Global Burden of Disease Study nearly 251 million people are affected with moderate to severe COPD worldwide and COPD was the 9th leading cause of loss of DALY (Disability Adjusted Life Year) globally in 2010 but by 2013, COPD was

ranked as 5th leading cause of DALYs lost.[3,4] As of 2016, three out of five leading causes of mortalities constitute non-communicable diseases whereas COPD is the second largest cause of death in India.[5] Among COPD related mortalities, India contributes a significant percentage in world, which is estimated to be the highest i.e., 64.7 estimated age standardized death per 100,000 among the Indian population.[6]

There are various risk factors for prevalence of COPD like cigarette smoking, exposure to environmental toxins, occupational irritants, genetic factors, chronic bronchitis, biomass fuel exposure etc. Out of all this risk factors, cigarette smoking is by far the strongest risk factor.[1] Pharmacotherapy of COPD includes three main groups of drugs namely: anti cholinergic drugs, inhaled beta-2 agonist and inhaled corticosteroids. Currently the Global initiative for COPD suggests the use of long-acting beta agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) in combination, for patients with COPD.[7] The combination of LABA and inhaled corticosteroid have already been shown its benefit in patients of bronchial asthma.[8] In another study it was found that inhaled LABA (e.g.; salmeterol and formoterol) and LAMA (e.g.; tiotropium, aclidinium and glycopyrronium bromide) are the mainstay of treatment of COPD.[9,10] In very recently published data from Indian patients, Indacaterol has shown significant improvement in FEV_1 variable and symptom score, and its safety and efficacy are comparable to tiotropium in COPD.[11] Among anticholinergic drugs tiotropium and glycopyrronium bromide (glycopyrrolate) are amongst the preferred agents as they have faster onset of action in addition to their long duration of action.[12] Glycopyrrolate having higher anticholinergic affinity for M_3 receptors was approved in 2015 for the maintenance therapy of COPD.[13,14] The previous studies have been found to compare single LABA and LAMA like formoterol vs tiotropium or indacaterol vs. tiotropium or comparative evaluation of two LAMA like tiotropium vs glycopyrrolate but data to compare the safety and efficacy of a combination of LABA and LAMA (Glycopyrrolate) are limited in India. Therefore, the present study has been designed to determine safety and efficacy of fixed dose combination of formoterol/glycopyrrolate and formoterol/tiotropium in patients of COPD.

METHODS

The present study was conducted at the tertiary centre of India from April 2018 to August 2019 on GOLD Grade-2 patients of COPD. The study was also registered with clinical trials registry-India. Informed and written consent of all patients was taken before enrolling them in the study.

Study design

This was an observational, prospective, and open label study. The treatment was prescribed by treating physician and at the end of study the patients were divided into two groups, Group-1 (administered with formoterol 12 mcg & glycopyrrolate 50 mcg in the form of dry powder inhaler once a day in the morning) and Group-2 (administered with formoterol 12 mcg & tiotropium 18 mcg in the form of dry powder inhaler once a day in the morning). Patients having age more than 18 years of GOLD Grade-2 COPD were included in study. The sample size of the study was 154 patients.

Efficacy assessments

Efficacy was determined by assessment of pulmonary function test (PFT), symptom score and CAT score (COPD assessment test). In spirometry, FEV_1 and Ratio of FEV_1/FVC were recorded at day zero (before therapeutic intervention) and at 2, 4, 8, 12 weeks of drug treatment. After three acceptable spirograms had been taken, the best values of FEV_1, and ratio of FEV_1/FVC were recorded.

The complaints of patients were assessed by symptom score and CAT score. Symptom score included major complaints of COPD i.e., cough, shortness of breath, chest tightness and nighttime awakening. For example, the Shortness of breath is graded as follows: None (unaware of any difficulty), mild, moderate, marked, and severe (almost constant, present even when resting). Health status was assessed by COPD Assessment test (CAT) score.

Safety assessment

All adverse events experienced by a patient or observed by the treating physician/investigator were recorded at each visit. Adverse drug reactions were assessed on Naranjo's ADR Probability Scale and onset and severity classification[15]. Additional laboratory tests were performed wherever required.

Statistical analysis

The data of the two groups were compared and analyzed by using SPSS software (version-20). For intra-group comparison paired t-test and for intergroup comparison unpaired t-test was used. Fisher's exact test is used for comparison of adverse events in both the groups.

RESULTS

A total of 68 patients of GOLD Grade-2 COPD were analyzed, out of which 33 (48.5%) patients were from treatment Group-1 (formoterol & glycopyrrolate) and 35 (51.5%) were from treatment Group-2 (formoterol & tiotropium).

Age distribution

The age of patients in this study ranges from 25-70 years. Mean age of Grade II COPD patients was 56.2. Among grade 2 COPD patients, 5 (7%) were females and 63 (93%) were males (Table1). Patients were also analyzed on the basis of cigarette smoking (pack per year). Frequencies of

smoking according to pack per year shows that majority of the smokers were smoking 10-19 pack per year.

Table 1: Demographic and other baseline parameters.

Variables	Formoterol/ glycopyrrolate N=33 Frequency (%)	Formoterol/ tiotropium N= 35 Frequency (%)
Age group (years)		
20-34	0	0
35-49	6 (85.7)	1 (14.3)
50-64	24 (49)	25 (51)
≥ 65	3 (25)	9 (75)
Gender distribution		
Males	32 (50.8)	31 (49.2
Females	1 (20)	4 (80)
Smoking status		
Smokers	25 (48.1)	28 (50)
Nonsmoker	8 (50)	7 (51.9)

There was no statistically significant difference between the two groups in the baseline values of mean age, mean FEV_1, mean symptom score, mean CAT Score ($p>0.05$).

Safety assessment

During this study, the reported adverse events were mild in nature (Naranjo grade 1-4) in majority of patients. Adverse events were not continuous data; therefore, Fisher's exact test was used to compare the events in both the treatment groups. These adverse events include dry mouth, tremors, palpitation, headache, nasopharyngitis are seen in both the treatments groups were statistically not significant ($p>0.05$) (Table 6). The number of adverse drug reactions in treatment Group-1 and Group-2 are 9 and 11, respectively. Although treatment Group-2 had number of adverse drug events more than treatment Group-1 yet this difference was statistically insignificant ($p>0.05$). Number of exacerbations in treatment Group-1 is 6 (18%), whereas in treatment Group-2 it was 5 (14%). Though there were slightly a greater number of exacerbations in treatment group 1, this difference was statistically not significant ($p>0.05$). Rescue medications like oral and inhaled form of steroids were given to these patients who had exacerbation.

DISCUSSION

Formoterol is long-acting beta-2 agonist and Tiotropium is muscarinic (M_3) receptor antagonist, produces bronchodilation by relaxation of airway smooth muscles. Glycopyrrolate as monotherapy via dry powder inhaler (DPI) was approved by FDA in 2017. Inhaled glycopyrrolate is also available as fixed dose combination with formoterol/indacaterol.[16] Based on comparative studies of other LAMA with Glycopyrrolate, it was found that glycopyrrolate show higher relative affinity for M_3 receptors. The studies have established the safety and efficacy of once daily long-acting beta-2 agonists like formoterol and salmeterol in patients of COPD.[17]

NICE guidelines also state that, combination therapy of LABA and LAMA provide benefit in quality of life in COPD. In a review it was also concluded that inhaled long-acting bronchodilators like LABA and LAMA are the mainstay of treatment of COPD.[8] NICE guidelines and Vestbo et al 2013 both recommended that a long-acting bronchodilator as monotherapy (LABA or LAMA) should be given initially in symptomatic patients with $FEV_1 \geq 50\%$ predicted.[18,19] If symptoms persist thereafter, both classes i.e., LABA and LAMA may be used in either two separate devices or more conveniently in a LABA/LAMA combination.[18]

In a Cochrane review of 22 studies, Tiotropium was associated with significant improvement in quality of life and reduction in exacerbation compared to placebo.[20] However, in another Cochrane review across seven studies, it was found that Tiotropium was like LABA in improving quality of life and lung function, although the former was more effective than LABA in preventing exacerbations and disease related hospital admissions.[21] This reduction in exacerbation with LAMA is possibly due to attenuating the cholinergic pro-inflammatory effects.[22] In a study on 773 patients who were given once daily LAMA Glycopyrrolate, Tiotropium, or placebo as an add on therapy to a combination of LABA and fluticasone (an ICS) for 12 weeks show comparable improvements in lung function, health status and rescue medication by LABA/LAMA combination, compared to LABA/ICS combination.[23] This insignificant action of add-on therapy with ICS, also prompted us to proceed with a combination therapy of LABA and LAMA. The result of our study in terms of FEV_1 improvement is consistent with findings of Chapman et al., 2014 after 12 weeks of therapy with slightly better efficacy using formoterol plus tiotropium, but statistical tests established non-inferiority ($p>0.05$) of formoterol/glycopyrrolate combination.[24] Glycopyrrolate demonstrated rapid bronchodilation after first dose on day 1 but the effect was comparable to Tiotropium group at subsequent visits and at week 12 ($p>0.05$) which was consistent with findings of GLOW5 study, which demonstrate that in patients with moderate to severe COPD, Glycopyrronium 50 mcg once daily provided similar efficacy and safety to tiotropium 18 mcg once daily, with Glycopyrrolate providing a faster onset of action on day 1 compared with tiotropium.[24] Treatment group 1 (formoterol/glycopyrrolate) shows improvements comparable to group 2 (formoterol/tiotropium) in symptom score, CAT score, rescue medication uses and rate of COPD exacerbations at week 12 ($p>0.05$). Adverse events were also not significantly different in both the treatment groups. Both the treatment groups show comparable number of exacerbations, 6 in group 1 (formoterol/glycopyrrolate) and 5 in group 2 (formoterol/tiotropium) (Table 6). Both the treatment groups had acceptable safety and tolerability profile, with a comparable overall incidence of adverse events.

Table 2: Comparison of pre-treatment (day 0) and post treatment (week 12) in FEV_1 (L) value in Grade-2 COPD patients.

Drug treatment	FEV_1 (Pre-treatment) Mean±SD	FEV_1 (Post treatment) Mean±SD	P value
Formoterol/Glycopyrrolate	1.36±0.63	1.64±0.64***	< 0.001
Formoterol/Tiotropium	1.35±0.57	1.65±0.55***	< 0.001

*** Highly significant (p<0.001). Mean FEV_1values are expressed in liters (l)

Table 3: Intra group comparison of FEV_1 compared to baseline and intergroup comparison of FEV_1 at subsequent follow up in Grade-2 COPD patients.

Time (weeks)	Formoterol/ Glycopyrrolate Group 1, N=33	Formoterol/ Tiotropium Group 2, N=35	Group 1 vs. Group 2
	Mean±SD	Mean±SD	
Baseline	1.36±0.63	1.35±0.57	> 0.05#
1	1.52±0.63**	1.57±0.55**	> 0.05#
2	1.53±0.63**	1.56±0.55**	> 0.05#
4	1.54±0.62**	1.61±0.58***	> 0.05#
8	1.52±0.68**	1.67±0.59***	> 0.05#
12	1.64±0.64***	1.65±0.55***	> 0.05#

Values are expressed in mean±SD; ** values were significant (p<0.05); *** values were highly significant (p<0.001) when compared with their baseline values. # Not significant (p>0.05). Mean FEV_1 values are expressed in Liters (L).

Table 4: Intragroup comparison of CAT scores compared to baseline and intergroup comparison of CAT score at week 12 of follow up in Grade-2 COPD patients.

CAT score	Grade-2 (n=68)		P value (Formoterol/Glycopyrrolate vs. Formoterol/Tiotropium)
	Formoterol/ Glycopyrrolate N=33 (48.5%)	Formoterol/tiotropium N=35 (51.5%)	
	Mean±SD	Mean±SD	
Baseline	13.00±2.42	12.71±2.03	>0.05#
12 Weeks	10.09±2.36***	9.4±2.14***	>0.05#

Values are expressed in mean±SD; *** values were highly significant (p<0.001) when compared with their baseline values. #: Not significant (p>0.05). Standard Error (SE)

Similar finding was also observed in GLOW2 (GLycopyrronium bromide in COPD airways) and GLOW 5 studies, where glycopyrrolate was compared with tiotropium and adverse events were comparable in both the treatment groups (Glycopyrronium 40.4% vs tiotropium 40.6%), with slightly frequent in tiotropium group.[25] The finding of the present study about effect of glycopyrrolate on patients of moderate COPD in terms of improvement of lung function, reduced risk of exacerbation, alleviation of breathlessness was comparable to Tiotropium. The study concludes that glycopyrrolate improves lung function, reduces the risk of exacerbations, and alleviates the symptoms of breathlessness and improves quality of life. Glycopyrrolate has comparable effects on lung function to tiotropium, and it showed more rapid onset of action than tiotropium. In the intragroup comparison (within group 1 as well as within group 2), the improvement in FEV_1 was highly significant in subsequent follow-ups from the baseline values to 12 weeks of treatment (Table 1) (p < 0.001). In the Formoterol/Glycopyrrolate group (Group 1) of GOLD grade 2 patients, the increase in mean FEV_1 from the baseline pre-treatment value till 12 weeks of treatment was 280 ml (1.36±0.63 to 1.64±0.64 liter) while in Formoterol plus Tiotropium group (group 2), the increase in mean FEV_1 was 300 ml (1.35±0.57 to 1.65±0.55 liter). Though there was highly significant improvement (p<0.001) seen in the intra-group comparisons, but the inter-group comparisons (between the two treatment groups) were not significant (p>0.05) (Table 2). Health status was also assessed by CAT score (COPD Assessment Test). It is an 8-item questionnaire for health status impairment in COPD, and closely correlates to SGRQ.[26] Questionnaire has score 1 to 5 from no symptom or no limitation in activity (score 1) to severe symptoms and excessive limitation in daily activities (score 5). The score ranges from 0-40 and the cut-off to start the therapy in CAT score is 10[27]. In this questionnaire, questions are asked on symptoms, activity limitation due to disease, sleeping pattern & sleep interference due to disease. In our study on grade 2 COPD patients, the decrease in mean CAT score in treatment group 1 (Formoterol/ Glycopyrrolate) was 3 (from 13 baseline score to 10 at week 12) and in treatment group 2 (Formoterol/ Tiotropium) was 3.31 (from 12.71 baseline values to 9.4 at

week 12) upon intragroup comparison (Table 3). However, decrease in CAT score between both the treatment groups (inter-group comparison) in grade 2 COPD patients was statistically not significant (p>0.05).

Table 5: Intragroup comparison of symptom score from the baseline and intergroup comparison of symptom score at week 12 follow up in Grade-2 COPD patients.

Symptom score	Grade-2, (n=68)		P value (Formoterol/ Glycopyrrolate vs. Formoterol/Tiotropium)
	Formoterol/Glycopyrrolae N=33 (48.5%)	Formoterol/tiotropium N=35 (51.5%)	
	Mean±SD	Mean±SD	
Baseline	7.09±0.91	7.28±0.85	>0.05#
12 weeks	1.97±0.63 ***	1.80±0.75***	>0.05#

Values are expressed in mean±SD; ***values were highly significant (p<0.001) when compared with their baseline values. #: Not significant (p>0.05). Standard Error (SE).

Table 6: Incidence of adverse events in treatment group 1 and 2.

Adverse reactions	Formoterol/Glycopyrrolate N=33, Frequency (%)	Formoterol/Tiotropium N=35, Frequency (%)	P value
Cough	2 (6)	2 (6.5)	>0.05
Dry mouth	2 (6)	3 (9.7)	>0.05
Headache	1 (3)	1 (3)	>0.05
Tremor	2 (6)	3 (9)	>0.05
Palpitation	1 (3)	1 (3)	>0.05
Nasopharyngitis	1 (1.5)	1 (1.6)	>0.05

Table 7: Number of exacerbations in treatment Group-1 and Group-2.

Observations			Number of exacerbations			Total
			0	1.0	2.0	
Groups	Group 1	Count	27	5	1#	33
		% Within Group	81.8	15.2	3.0	100.0
	Group 2	Count	30	5	0	35
		% Within Group	85.7	14.3	0.0	100.0
Total		Count	57	10	1	68
		% Within Group	83.8	14.7	1.5	100.0

Exacerbation between treatment group, #statistically not significant.

Clinical improvement was assessed on the basis of symptom score that included cough, breathlessness, chest tightness and nighttime awakening. There was an improvement in the symptom score in both the treatment groups (intragroup comparison) from the baseline till 12 weeks of treatment and this difference was statistically highly significant (p <0.001) (Table 4). Higher is the symptom score poorer is patient condition. Therefore, clinical improvement is assessed by decrease in symptom score. Among grade 2 COPD patients of group 1 (Formoterol/Glycopyrrolate), the mean symptom score was decreased by 5.12 (from 7.09 baseline value to 1.97 at week 12), while in group 2 (Formoterol/Tiotropium) it was decreased by 5.48 after 12 weeks of therapy (from 7.28 baseline value to 1.80 at week 12) (Table 4). The improvement in symptom score (from baseline to 12 weeks) among both the treatment groups (intra-group comparison) is statistically highly significant (p<0.001). However, improvement in symptom score between group 1 and 2 (inter-group comparison) was statistically not significant (p>0.05).

It was observed that both treatments were effective and comparable reaching a statistical significance in intragroup comparison (from baseline to 12 weeks of follow up), but there was no significant difference in intergroup (group 1 vs group 2) analysis. The previous studies which compared the fixed dose combination of Indacaterol/ Glycopyrronium and Formoterol/tiotropium have shown improvement in lung function and dyspnea and concluded that the combination of Indacaterol/Glycopyrronium has the potential to be more effective than the combination of Formoterol/Tiotropium[28]. In another study on COPD patients using fixed dose combination of aclidinium bromide (LAMA) and formoterol (LABA), it was found that this LABA/LAMA combination controls the symptoms of stable moderate to severe COPD with significant lung function improvement.[29] Adverse drug reactions are reported by 9 patients in treatment group 1 (Formoterol/Glycopyrrolate) and by 11 patients in treatment group 2 (Formoterol/Tiotropium) (Table 5). Adverse events like cough, immediately after Tiotropium and Formoterol inhalation has also been previously

reported by Rennard et al.[30] Other adverse reactions like tremor, dry mouth, palpitation, and headache were also reported by patients in both the treatment groups but there was no significant difference (p>0.05) between them.

Since both the treatment group contains combination therapy of LABA and LAMA, adverse events in both groups were similar. Side effects like dry mouth and tremor were more frequently reported among both the treatment groups. These adverse events were usually mild, often transient and did not lead to any significant patient withdrawal to therapy. Headache, tachycardia and nasopharyngitis were also observed in both groups (Table 5). These adverse reports were frequent with Formoterol/tiotropium group as compared to Formoterol/Glycopyrrolate but were statistically not significant (p>0.05) and was consistent with studies of Buhl et al.[27] Both the treatment groups provide clinically significant improvement in lung function with comparable efficacy and safety profile and these findings are consistent with the current treatment guidelines of grade 2 and grade 3 COPD patients.

Limitations

The limitation of this studies was small sample size and lost to follow up of the patients. In some patients, reliance on spirometry exclusively for airflow limitation may result in underestimation of clinically important physiologic impairment.

CONCLUSION

This study shows that Formoterol/tiotropium combination is non-inferior to combination of Formoterol/Glycopyrrolate in terms of FEV_1, CAT score, Symptom score or in terms of adverse drug reaction and exacerbations. The combination therapies of Formoterol/Glycopyrrolate and Formoterol/tiotropium were well tolerated, and no safety concerns were raised in patients with GOLD stage II COPD.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ahmad S, Ahmad J, Ahmad F, Ahmad Z. Safety and efficacy of formoterol /tiotropium bromide and formoterol/glycopyrronium combination in patients with chronic obstructive pulmonary disease. Int J Res Med Sci 2023;11:1239-45.