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SAFETY AND EFFICACY OF FORMOTEROL/TIOTROPIUM BROMIDE AND FORMOTEROL/GLYCOPYRRONIUM COMBINATION IN COPD WITH GOLD GRADE 3 PATIENTS

Jameel Ahmad [*1], Siraj Ahmad [1], Farida Ahmad [1], Zuber Ahmad [2], Diwan Israr Khan [3] and Vibhu Pandey [1]

Department of Pharmacology [1], Department of TB and Chest Diseases [2], Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh - 202001, Uttar Pradesh, India.
Ajmal Khan Tibbiya College and Hospital [3], AMU, Aligarh - 202002, Uttar Pradesh, India.

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Correspondence to Author:
Dr. Jameel Ahmad

Assistant Professor,
Department of Pharmacology,
Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh - 202001, Uttar Pradesh, India.

E-mail: ahmad.drjameel@gmail.com

ABSTRACT: An increasing airflow limitation that is not entirely reversible is a hallmark of chronic obstructive pulmonary disease (COPD). In patients with COPD, the present study investigated the effectiveness and safety of formoterol/tiotropium bromide vs formoterol/glycopyrronium in fixed combinations. In conjunction with formoterol, the long-acting anti-muscarinic drug glycopyrrolate has recently received approval for the maintenance treatment of chronic obstructive pulmonary disease. Studies on the combination of long-acting beta 2 agonist and glycopyrrolate, particularly in patients from India, are scarce. Therefore, it was thought interesting to compare the safety and effectiveness of formoterol/tiotropium fixed dose combinations to formoterol/glycopyrrolate fixed dose combinations in GOLD Grade 3 COPD patients. In the COPD patients of GOLD Grade 3, the efficacy and safety of formoterol/glycopyrrolate and formoterol/tiotropium was studied. A total of 68 patients was assessed by using the Spirometry, the COPD Assessment Test score, and the Symptom score. The assessment of the effectiveness of treatment was done on days zero (before the therapeutic intervention) and at intervals of two weeks up to 12 weeks. Spirometric variables like Forced Expiratory Volume (In one second), mean Symptom score and COPD Assessment score have shown an improvement following the therapy with the inhaled formoterol/glycopyrrolate and formoterol/tiotropium combination in GOLD Grade 3 COPD patients. The effectiveness and the patient safety profile of formoterol/glycopyrrolate combination was non-inferior to formoterol/tiotropium in the patients of GOLD Grade 3 COPD.

INTRODUCTION: COPD is defined by persistent obstruction of airflow and respiratory symptoms, resulting from abnormalities in the airways or alveoli typically caused by substantial exposure to harmful particles or gases [1].

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The Global Burden of Disease Study reported that approximately 251 million individuals globally have moderate to severe COPD. In 2010, COPD ranked as the 9th highest cause of Disability Adjusted Life Years (DALYs) lost worldwide. However, by 2013, COPD had climbed to the 5th position in terms of DALYs lost [2, 3].

According to a study by Verma *et al.* spanning from 2000 to 2020 and focusing on Indian patients aged 30 years and older, the prevalence of COPD was found to be 7% [4]. India significantly

contributes to the global mortality rate due to COPD, with estimates indicating the highest rate of 64.7 age-standardized deaths per 100,000 individuals in the Indian population [5]. There are several risk factors associated with the prevalence of COPD, including cigarette smoking, exposure to environmental toxins, occupational irritants, genetic factors, chronic bronchitis, and biomass fuel exposure. Among these, cigarette smoking stands out as the most significant risk factor [1]. The pharmacotherapy for COPD comprises three primary groups of drugs: anticholinergic drugs, inhaled beta-2 agonists, and inhaled corticosteroids. Presently, the Global Initiative for COPD recommends using long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) in combination for COPD patients [6].

The combination of LABA and inhaled corticosteroids has already demonstrated its benefits in patients with bronchial asthma [7]. Recent studies have highlighted that inhaled LABAs (such as salmeterol and formoterol) and LAMAs (like tiotropium, aclidinium, and glycopyrronium bromide) are the cornerstone of COPD treatment [8, 9]. A recent study conducted on Indian patients found that Indacaterol significantly improves FEV1 (forced expiratory volume in one second) and symptom scores, with safety and efficacy comparable to tiotropium in COPD patients [10]. Among anticholinergic drugs, tiotropium and glycopyrronium bromide are preferred agents due to their rapid onset of action and long duration of effect [11]. Glycopyrrolate, with its higher anticholinergic affinity for M3 receptors, was approved in 2015 for COPD maintenance therapy [12].

The combination therapy of formoterol/ glycopyrrolate has shown non-inferiority compared to formoterol/tiotropium in terms of efficacy and safety profiles in COPD patients [13]. Previous studies have primarily compared single LABA or LAMA treatments, such as formoterol vs. tiotropium or indacaterol vs. tiotropium, or evaluated two LAMA options like tiotropium vs. glycopyrrolate. However, there is limited data comparing the safety and efficacy of a LABA and LAMA combination, specifically formoterol/ glycopyrrolate, in India. Hence, the current study aims to assess the safety and efficacy of fixed-dose combinations of formoterol/ glycopyrrolate and formoterol/tiotropium in COPD patients.

METHODS: The present study was conducted at the tertiary centre of India from April 2018 to August 2019 on GOLD Grade 3 patients of COPD. The ethical clearance was obtained from the Institutional Ethics Committee of J.N. Medical College and Hospital, AMU, Aligarh (D. No. 295/FM/24-4-18) and the study was also registered with Clinical Trials Registry of India (CTRI Reference number REF/2018/05/019938). Informed and written consent of all patients was taken before enrolling them in the study. The study protocols were conducted in accordance with the principles outlined in the Declaration of Helsinki of the World Medical Association.

Study design: This was an observational, prospective, and open label study. The treatment was on the total discretion of the treating physician and at the end of enrolment period, 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 3 with COPD were included in the 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, FEV1 and Ratio of FEV1/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 FEV1, and ratio of FEV1/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 [14]. 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 intragroup 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 60 patients of GOLD Grade 3 with COPD were analyzed, out of which 33 (55%) patients were from treatment Group-1 (formoterol & glycopyrrolate) and 27 (45%) were from treatment Group-2 (formoterol & tiotropium).

Age Distribution and Baseline Parameters: The age of patients participating in this study varied between 25 to 70 years, with a mean age of 56.6 years observed among Grade 3 COPD patients. Among Grade 3 COPD patients, 6 (10%) were females and 54 (90%) were males **Table 1**. Additionally, patients were analyzed based on their cigarette smoking history (packs per year). The frequency of smoking, as measured by the number of packs smoked per year, indicated that the majority of smokers were consuming 10-19 packs per year. The baseline values of mean age, mean FEV1, mean symptom score, and mean CAT Score showed no statistically significant difference between the two Groups ($p>0.05$).

TABLE 1: DEMOGRAPHIC AND OTHER BASELINE PARAMETERS

Variables	Formoterol/ glycopyrrolate N=33 Frequency (%)	Formoterol/ tiotropium N=27 Frequency (%)
Age Group (years)		
20-34	1(100)	0
35-49	4(50)	4(50)
50-64	23(59)	16(41)
≥ 65	5(41.7)	7(58.3)
Gender distribution		
Males	32(59.3)	22(40.7)
Females	1(16.7)	5(83.3)
Smoking status		
Smokers	27(57.4)	20(42.6)
Nonsmoker	6(46.2)	7(53.8)

Safety Assessment: During this study, the reported adverse events were mild in nature (Naranjo grade 1-4) in the 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, and nasopharyngitis are seen in both the treatment groups. However, the adverse events were statistically not significant ($p>0.05$) between the groups. 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 acts as a long-acting beta-2 agonist, and Tiotropium functions as a muscarinic (M3) receptor antagonist, both working to achieve bronchodilation by relaxing the smooth muscles of the airways. Glycopyrrolate, when used alone as a monotherapy, received FDA approval in 2017 and is administered via a dry powder inhaler (DPI). Moreover, inhaled glycopyrrolate is also available in a fixed-dose combination with formoterol/indacaterol [15].

Glycopyrrolate has been the subject of comparative studies with other long-acting muscarinic antagonists medications, demonstrating its higher relative affinity for M3 receptors. Additionally, various studies have confirmed the safety and effectiveness of once-daily long-acting beta-2 agonists, such as formoterol and salmeterol, in patients diagnosed with COPD [16].

As per the National Institute for Health and Care Excellence (NICE) guidelines, the combination therapy of LABA and LAMA has been shown to enhance the quality of life for patients with COPD. Furthermore, a review of the existing evidence supports the use of inhaled long-acting bronchodilators, including LABA and LAMA, as the mainstay of treatment for COPD [7]. In a comprehensive Cochrane review consisting of 22 studies, Tiotropium demonstrated significant improvements in quality of life and a reduction in exacerbations compared to placebo. On the other

hand, another Cochrane review, which included seven studies, found that Tiotropium showed similar efficacy to long-acting beta 2 agonists in terms of improving quality of life and lung function. However, Tiotropium was found to be more effective than LABA in preventing exacerbations and disease-related hospital admissions [17]. A study involving 773 patients found that once-daily administration of LAMA (either Glycopyrrolate or Tiotropium) as an add-on therapy to a combination of LABA and fluticasone inhalation for 12 weeks resulted in similar improvements in lung function, health status, and rescue medication use when compared to LABA/ICS combination therapy. The comparable efficacy of add-on therapy with inhalational corticosteroids (ICS) prompted further investigation into a combination therapy involving LABA and LAMA [18].

TABLE 2: COMPARISON OF PRE-TREATMENT (DAY 0) AND POST TREATMENT (WEEK 12) IN FEV1 (L) VALUE IN GOLD GRADE 3 COPD PATIENTS

Drug treatment	FEV1 (Pre-treatment) Mean±SD	FEV1 (Post treatment) Mean±SD	P value
Formoterol/Glycopyrrolate	1.32 ± 0.48	1.60 ± 0.57***	< 0.001
Formoterol/Tiotropium	1.47 ± 0.71	1.85 ± 0.70***	< 0.001

*** Highly significant ($p < 0.001$). Mean FEV1 values are expressed in litres (L)

The results of our study are consistent with the findings of Chapman *et al.* in 2014, as both therapies (formoterol plus tiotropium and formoterol/glycopyrrolate combination) showed improved FEV1 after 12 weeks of treatment. Although formoterol plus tiotropium demonstrated slightly better efficacy, statistical tests confirmed the non-inferiority ($p>0.05$) of the formoterol/ glycopyrrolate combination [19]. Glycopyrrolate exhibited rapid bronchodilation on day 1, but its effect became comparable to the Tiotropium Group in subsequent visits and at week 12 ($p>0.05$), which aligns with the findings of the GLOW5 study. The GLOW5 study demonstrated that Glycopyrronium 50 mcg once daily provided similar efficacy and safety to tiotropium 18 mcg once daily, with Glycopyrrolate showing a faster onset of action on day 1 compared to tiotropium [19].

At week 12, both treatment Groups (formoterol/ glycopyrrolate and formoterol/ tiotropium) showed comparable improvements in symptom score, CAT score, rescue medication use, and the rate of COPD exacerbations ($p>0.05$). There were no significant differences in adverse events between the two Groups, and they also exhibited a similar number of exacerbations (10 in the formoterol/ glycopyrrolate Group and 9 in the formoterol/tiotropium Group). Overall, both treatment Groups demonstrated an acceptable safety and tolerability profile, with a comparable incidence of adverse events. The GLOW2 (Glycopyrronium bromide in COPD airways) and GLOW5 studies also reported similar findings, with glycopyrrolate compared to tiotropium, and adverse events were comparable in both treatment Groups (glycopyrronium 40.4% vs. tiotropium 40.6%), with a slightly higher frequency in the tiotropium Group [20]. The current study's results concerning the effects of glycopyrrolate on patients with GOLD Grade 3 with COPD, such as improvements in lung function, reduced risk of exacerbations, alleviation of breathlessness, and enhanced quality of life, were found to be comparable to Tiotropium. Although glycopyrrolate demonstrated similar effects on lung function compared to tiotropium, it exhibited a more rapid onset of action.

In Grade 3 COPD patients of Group 1, the mean FEV1 increased by 280 ml (from 1.32 ± 0.48 to 1.60 ± 0.57 liters), while in Group 2, this increase in FEV1 was 380 ml (from 1.47 ± 0.71 to 1.85 ± 0.70 liters) from the baseline values to 12 weeks of treatment **Table 3**. Additionally, in Grade 3 COPD patients, there was a highly significant improvement ($p < 0.001$) observed in the intragroup comparison at each follow-up, but the inter-group comparisons between the two groups at every follow-up were not statistically significant ($p > 0.05$) **Table 3**. These findings from the present study are consistent with the reports of previous studies which have also demonstrated the non-inferiority of LABA/LAMA combinations like Formoterol/ Glycopyrrolate and Formoterol/ Tiotropium. Health status was assessed using the COPD Assessment Test (CAT score), which is an 8-item questionnaire designed to evaluate health

status impairment in COPD. The CAT score ranges from 0 to 40, and a score of 10 or higher indicates the need to start therapy. In our study involving Grade 3 COPD patients, the mean CAT score decreased by 3.66 in treatment Group 1 (Formoterol/ Glycopyrrolate) from the baseline score of 14.81 to 11.15 at week 12. In treatment Group 2 (Formoterol/Tiotropium), the mean CAT score decreased by 3.26 from the baseline value of 14.33 to 11.07 at week 12 in intragroup comparisons. However, the decrease in CAT score between the two treatment groups in Grade 3 COPD patients was not statistically significant (p>0.05).

TABLE 3: INTRAGROUP COMPARISON OF FEV1 COMPARED TO BASELINE AND INTERGROUP COMPARISON OF FEV1 AT SUBSEQUENT FOLLOW UP IN GOLD GRADE 3 COPD PATIENTS

Time	Group 1 (Formoterol/ Glycopyrrolate) n=33 (Mean±SD)	Group 2 (Formoterol/ Tiotropium) n=27 (Mean±SD)	Group 1 vs Group 2 (P value)
Baseline	1.32 ±0.48	1.47 ±0.71	> 0.05#
1 week	1.47 ±0.55**	1.70 ±0.69**	> 0.05#
2 week	1.47 ±0.56**	1.74 ±0.68**	> 0.05#
4 week	1.51 ±0.48***	1.78 ±0.71***	> 0.05#
8 week	1.51 ±0.52***	1.80 ±0.72***	> 0.05#
12 week	1.60 ±0.57***	1.85 ±0.70***	> 0.05#

Note: Values are expressed in mean ± S.D; ** 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 FEV1 values are expressed in litres (L).

Clinical improvement was evaluated based on a symptom score encompassing cough, breathlessness, chest tightness, and nighttime awakening. In both treatment Groups (intragroup comparison), there was a significant improvement in the symptom score from baseline to 12 weeks of treatment ($p < 0.001$) **Table 4**. A higher symptom score indicates a poorer patient condition, so a decrease in the symptom score indicates clinical improvement. Among GOLD Grade 3 COPD patients in Group 1 (Formoterol/Glycopyrrolate), the mean symptom score decreased by 6.57 (from a baseline of 9.72 to 3.15 at week 12), while in Group 2 (Formoterol/Tiotropium), it decreased by 6.27 after 12 weeks of therapy (from a baseline value of 10.07 to 3.80 at week 12) **Table 5**. The improvement in symptom score within both treatment Groups (intragroup comparison) was statistically significant ($p < 0.001$). However, the improvement in symptom score between Group 1 and Group 2 (intergroup comparison) was not statistically significant ($p > 0.05$).

TABLE 4: INTRAGROUP COMPARISON OF CAT SCORES COMPARED TO BASELINE AND INTERGROUP COMPARISON OF CAT SCORE AT WEEK 12 OF FOLLOW UP IN GOLD GRADE 3 COPD PATIENTS

CAT score	Grade 3 (n=60)		Group 1 *vs* Group 2 (P value)
	Group 1 (Formoterol/ Glycopyrrolate) n=33 (55%) (Mean±SD)	Group 2 (Formoterol/ Tiotropium) n=27 (45%) (Mean±SD)	
Baseline	14.81 ±2.69	14.33 ±2.68	> 0.05#
12 Week	11.15 ±2.57***	11.07 ±2.57***	> 0.05#

Note: Values are expressed in mean ± S.D; *** values were highly significant ($p < 0.001$) when compared with their baseline values. #: Not significant ($p > 0.05$). Standard Error (S.E.) denoted by bar in graph.

TABLE 5: INTRAGROUP COMPARISON OF SYMPTOM SCORE COMPARED TO BASELINE AND INTERGROUP COMPARISON OF SYMPTOM SCORE AT WEEK 12 OF FOLLOW UP IN GOLD GRADE 3 COPD PATIENTS

Symptom score	Group 3 (n=60)		Group 1 vs Group 2 (P value)
	Group 1 (Formoterol/ Glycopyrrolate) n=33 (55%) (Mean±SD)	Group 2 (Formoterol/ Tiotropium) n=27 (45%) (Mean±SD)	
Baseline	9.72 ± 1.30	10.07 ± 1.23	> 0.05#
12 Week	3.15 ± 1.43***	3.8 ± 1.64***	> 0.05#

Note: Values are expressed in mean ± S.D; *** values were highly significant ($p < 0.001$) when compared with their baseline values. #: Not significant ($p > 0.05$). Standard Error (S.E.) denoted by bar in graph.

Both treatments were effective and comparable, showing statistical significance in the intragroup comparison (from baseline to 12 weeks of follow-up). However, there was no significant difference

in the intergroup analysis (Group 1 vs. Group 2). Previous studies comparing the fixed-dose combination of Indacaterol/Glycopyrronium and Formoterol/Tiotropium have demonstrated improvements in lung function and dyspnea, and they suggest that the combination of Indacaterol/Glycopyrronium may have the potential to be more effective than the combination of Formoterol/Tiotropium [21]. In both treatment Groups, 9 patients in each (Formoterol/Glycopyrrolate and Formoterol/ Tiotropium), reported experiencing adverse drug reactions. Adverse events such as cough immediately after Tiotropium and Formoterol inhalation have been previously documented. Additionally, patients in both Groups reported other adverse reactions, including tremor, dry mouth, palpitation, and headache, but there was no statistically significant difference ($p > 0.05$) between the two Groups.

As both treatment Groups involved combination therapy of LABA and LAMA, the occurrence of adverse events was similar in both Groups. Side effects such as dry mouth, tremor, headache, tachycardia, and nasopharyngitis were observed in both Groups. The Formoterol/Tiotropium Group reported these adverse events more frequently compared to the Formoterol/Glycopyrrolate Group, but the difference was not statistically significant ($p > 0.05$) and aligned with the findings of Buhl et al [21]. Both treatment Groups exhibited clinically significant improvement in lung function, demonstrating comparable efficacy and safety profiles, which are consistent with the current treatment guidelines for GOLD Grade 3 COPD patients.

Limitations: The study had certain limitations, such as a small sample size and relied solely on spirometry to evaluate airflow limitation in some patients which could potentially underestimate clinically significant physiologic impairment.

CONCLUSION: The findings of the study suggest that the combination of Formoterol/Tiotropium is equally effective as the combination of formoterol/glycopyrrolate in terms of FEV1 (forced expiratory volume in one second), CAT score (COPD Assessment Test score), and symptom score. Both combination therapies, Formoterol/ Glycopyrrolate and Formoterol/Tiotropium, were well tolerated, with no safety concerns identified in patients with GOLD Grade 3 COPD. Although glycopyrrolate demonstrated similar effects on lung function compared to tiotropium, it exhibited a more rapid onset of action.

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