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Effectiveness of Glycopyrronium Plus Formoterol Combination in Patients With Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation and chronic respiratory symptoms. Dual bronchodilator therapy with a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is recommended to improve lung function and symptom control.
Methods: This prospective interventional study included 104 patients with moderate to severe COPD diagnosed according to GOLD criteria. All patients received inhaled Glycopyrronium 25 µg plus Formoterol 12 µg twice daily for 12 weeks. Spirometry was performed at baseline, 6 weeks, and 12 weeks. Effectiveness was assessed by changes in forced expiratory volume in one second (FEV_1), while tolerability was evaluated by recording adverse events.
Results: Mean FEV_1 improved significantly from 61.08±13.25% predicted at baseline to 63.47±13.04% at 6 weeks and 65.24±12.76% at 12 weeks (p=0.001). The treatment was well tolerated, with only mild adverse events such as dry mouth, throat irritation, cough, and occasional tremors.
Conclusion: Glycopyrronium plus Formoterol significantly improved lung function and was well tolerated over 12 weeks, supporting its effectiveness and safety in the management of moderate to severe COPD.

Keywords: *Effectiveness, Glycopyrronium, Formoterol, Chronic, Pulmonary, Disease.*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous respiratory disorder characterized by persistent respiratory symptoms, including dyspnea, chronic cough, sputum production, and recurrent exacerbations, resulting from structural abnormalities of the airways and/or alveoli that cause persistent and usually progressive airflow limitation.[1] COPD is a major global public health problem and is one of the leading causes of morbidity and mortality worldwide.[2] It imposes a considerable socioeconomic burden owing to frequent hospitalizations, long-term pharmacotherapy, disability, and loss of productivity, particularly in low- and middle-income countries.[3] The global burden of COPD continues to increase because of population aging, continued exposure to tobacco smoke, biomass fuel, occupational pollutants, and ambient air pollution.[4] In India, COPD represents a significant public health challenge, highlighting the need for early diagnosis, prevention of risk-factor exposure, and evidence-based treatment strategies.[5]

The pathogenesis of COPD is strongly associated with prolonged exposure to noxious particles and gases. Cigarette smoking remains the most important risk factor worldwide.[6] In developing countries, indoor air pollution due to biomass fuel combustion is an important contributor, particularly among women.[7] Occupational exposure to dust, fumes, and

chemical agents also increases the risk of COPD.[8] Additional contributing factors include ambient air pollution, recurrent respiratory infections, impaired lung growth, and genetic susceptibility, particularly alpha-1 antitrypsin deficiency.[9]

Spirometry is the gold standard for the diagnosis of COPD and provides an objective assessment of airflow limitation. Important spirometric parameters include Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1), and the FEV_1/FVC ratio.[10] A post-bronchodilator FEV_1/FVC ratio of <0.70 confirms persistent airflow obstruction.[1] However, spirometric findings alone do not adequately reflect symptom burden or disease impact. Therefore, comprehensive assessment using validated tools such as the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale is recommended to guide treatment decisions.[11]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, pharmacological management is individualized based on symptom burden and exacerbation risk. Dual bronchodilator therapy with a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is the preferred treatment for symptomatic patients, particularly those in GOLD Groups B and E.[1] Glycopyrronium/Formoterol and Tiotropium/Formoterol are widely used LABA/LAMA fixed-dose combinations that provide complementary bronchodilation by targeting different pharmacological pathways, thereby improving lung function, relieving symptoms, reducing hyperinflation, and enhancing quality of life.[12]

Although several LABA/LAMA combinations are available for COPD management, evidence directly comparing their clinical effectiveness remains limited, particularly in the Indian population. Therefore, the present study was undertaken to evaluate the effectiveness of the fixed-dose Glycopyrronium/Formoterol combination in patients with moderate to severe COPD.

MATERIAL AND METHOD

Study Design and Setting

This prospective interventional study was conducted in the Department of TB and Respiratory Diseases at a tertiary care teaching hospital in North India from July 2024 to December 2025. Both outpatient and hospitalized patients were screened for eligibility. The study protocol was approved by the Institutional Ethics Committee (Ref. No. SGRD/IEC/2024-385), and written informed consent was obtained from all participants before enrollment.

Study Population

Patients diagnosed with moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were included. The diagnosis was based on clinical symptoms such as chronic cough, dyspnea, and sputum production, along with a history of exposure to relevant risk factors. Persistent airflow limitation was confirmed by post-bronchodilator spirometry demonstrating an FEV_1/FVC ratio of <0.70.

Inclusion Criteria

* Patients aged ≥40 years with moderate to severe COPD diagnosed according to GOLD criteria.
* Stable COPD confirmed by spirometry (post-bronchodilator FEV_1/FVC <0.70).
* Patients willing to provide written informed consent and comply with study follow-up.

Exclusion Criteria

Patients were excluded if they had:

* Bronchial asthma or asthma-COPD overlap.
* Pregnancy or lactation.
* Significant cardiovascular disease, including arrhythmias, coronary artery disease, or congestive heart failure.
* Hospitalization for pneumonia within the previous three months.
* Use of systemic corticosteroids within the preceding 6 weeks.
* Known hypersensitivity to Glycopyrronium, Formoterol, or any study medication.

Study Procedure

Previously diagnosed patients with moderate to severe COPD underwent a two-week run-in period during which their maintenance bronchodilator therapy was discontinued and replaced with salbutamol dry powder inhaler (DPI) as rescue medication. Newly diagnosed patients were enrolled after baseline clinical evaluation.

Detailed demographic data, smoking history, occupational exposure, symptom profile, and comorbidities were recorded. Clinical evaluation included measurement of height, weight, body mass index, and a complete general and respiratory system examination. Baseline investigations included complete blood count, fasting blood glucose, and chest radiography.

All enrolled patients received Glycopyrronium/Formoterol dry powder inhaler (25 µg/12 µg) administered twice daily for 12 weeks. Spirometry was performed at baseline (Day 1), 6 weeks (Day 42), and 12 weeks (Day 84). The primary outcome

measure was change in FEV_1 over the study period. Patients were monitored throughout follow-up for treatment adherence and adverse drug reactions to assess tolerability.

Statistical Analysis

Data were entered and analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Repeated measures ANOVA was used to compare spirometric parameters over time. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

Among the 104 participants, 53 (51.0%) were males and 51 (49.0%) were females, demonstrating a nearly equal gender distribution. The majority of patients belonged to the 51–60 years age group (Table 1).

TABLE 1 : SHOWING AGE AND SEX DISTRIBUTION OF COPD PATIENTS

AGE GROUP (in years)	FEMALES (%)	MALES (%)	Total(%)
< 20	1(2)	0(0)	1(0.9)
21-30	3(5.9)	3(5.7)	6(5.7)
31-40	8(15.7)	9(17)	17((16.3)
41-50	7(13.7)	7(13.2)	14(13.5)
51-60	17(33.3)	14(26.4)	31(29.8)
61-70	8(15.7)	13(24.5)	21(20.2)
> 70	7(13.7)	7(13.2)	14(13.5)
Total	51(100)	53(100)	104(100)

Clinical Presentation

Cough was the most common presenting symptom, reported by 72 (69.2%) patients, followed by shortness of breath in 67 (64.4%) patients. Expectoration was present in 43 (41.3%) patients. Thus, cough was the predominant presenting complaint, closely followed by dyspnea, while expectoration was reported in less than half of the study population. (Table 2)

TABLE 2 : SHOWING FREQUENCY OF SYMPTOMS AMONG COPD PATIENTS

Symptoms	No. of cases	Percentage
Cough	72	69.2
Shortness of breath (SOB)	67	64.4
Expectoration	43	41.3

Risk Factors

Exposure to biomass fuel smoke was the most common risk factor, identified in 68 (65.4%) patients. Smoking was reported by 17 (16.3%) patients, whereas a past history of pulmonary tuberculosis (PTB) was present in 2 (1.9%) patients. (Table 3)

TABLE 3 : SHOWING FREQUENCY OF RISK FACTORS AMONG COPD PATIENTS

Risk factors	No. of cases	Percentage
Biomass fuel exposure	68	65.4
Smoking	17	16.3
Past H/O PTB	2	1.9

Change in Pulmonary Function

The mean FEV_1 showed a progressive improvement during the 12-week treatment period with Glycopyrronium/Formoterol. The baseline mean FEV_1 was 61.08 ± 13.25, which increased to 62.34 ± 12.89 at 6 weeks and further improved to 65.24 ± 12.76 at 12 weeks. Repeated-measures ANOVA demonstrated that the improvement in FEV_1 over time was statistically significant ($F = 7.721$, $p = 0.001$), indicating that treatment with the Glycopyrronium/Formoterol combination was associated with significant improvement in lung function. (Table 4)

TABLE 4 : ASSOCIATION OF FEV1 VALUES ON FOLLOW UP PERIOD

	Mean	SD	f-value	p-value
FEV1 Baseline	61.08	13.25		
FEV1 at 6weeks	62.34	12.89		
FEV1 at 12 weeks	65.24	12.76	7.721	0.001

DISCUSSION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality worldwide, affecting nearly 300 million individuals. The Global Burden of Disease 2019 study highlighted that the highest burden of COPD is borne by low- and middle-income countries due to continued exposure to tobacco smoke, biomass fuel, occupational pollutants, and ambient air pollution.[13] In India, the prevalence of COPD among adults ranges from 4% to 10%, making it an important public health problem with substantial healthcare and socioeconomic implications.[14]

Dual bronchodilator therapy with a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is currently recommended as the preferred maintenance treatment for patients with moderate to severe COPD who remain symptomatic. The combination of Glycopyrronium and Formoterol provides complementary mechanisms of bronchodilation by inhibiting cholinergic bronchoconstriction and stimulating β_2-adrenergic receptors, resulting in sustained airway relaxation, improved airflow, and better symptom control. In addition, fixed-dose combination inhalers simplify treatment regimens, improve adherence, and may reduce the need for escalation to inhaled corticosteroid therapy.[15]

In the present study, the majority of patients were between 51 and 60 years of age, with an almost equal distribution of males and females. The substantial representation of female patients reflects the increasing contribution of non-smoking risk factors, particularly biomass fuel exposure, in the Indian population.[13] These findings are consistent with those reported by Salvi and Agarwal, who demonstrated that although COPD is more common in men, the disease burden among women is increasing because of prolonged exposure to biomass smoke.[14]

Cough was the most common presenting symptom, reported by 69.2% of patients, followed by shortness of breath (64.4%) and expectoration (41.3%). These findings are in agreement with previous studies, including that of Miravitlles et al., who identified chronic cough, dyspnea, and sputum production as the predominant clinical manifestations of stable COPD. Persistent cough and dyspnea significantly impair daily activities and quality of life, emphasizing the need for effective maintenance bronchodilator therapy.[16]

Biomass fuel exposure was the most frequently identified risk factor in the present study, followed by cigarette smoking, while only a small proportion of patients had a previous history of pulmonary tuberculosis. These findings support previous Indian studies demonstrating that biomass smoke is an important cause of COPD, particularly among women and individuals residing in rural areas.[17] In contrast, studies from Western countries, such as the COPDGene study, have consistently identified cigarette smoking as the predominant etiological factor, reflecting regional differences in environmental and occupational exposures.[18]

The principal finding of the present study was the significant improvement in pulmonary function following treatment with the Glycopyrronium/Formoterol combination. Mean FEV_1 increased from 61.08 ± 13.25% predicted at baseline to 62.34 ± 12.89% at 6 weeks and 65.24 ± 12.76% at 12 weeks, with the improvement being statistically significant ($F = 7.721$, $p = 0.001$). This progressive increase in FEV_1 indicates sustained bronchodilation and improvement in airflow limitation throughout the treatment period.

The observed improvement in lung function is biologically plausible because Glycopyrronium provides prolonged muscarinic receptor blockade, whereas Formoterol produces rapid-onset and sustained β_2-mediated bronchodilation. The complementary pharmacological actions of these agents reduce airway smooth muscle tone more effectively than either agent alone, thereby improving expiratory airflow and reducing lung hyperinflation.

Our findings are consistent with those of Gon et al.[19], who demonstrated significant improvements in trough FEV_1 with Glycopyrronium/Formoterol compared with placebo and monotherapy. Similarly, Martinez et al.[20] reported superior bronchodilation and clinically meaningful improvements in lung function with the Glycopyrronium/Formoterol fixed-dose combination, supporting its role as an effective maintenance therapy in patients with moderate to severe COPD.

The favorable response observed in the present study further supports current GOLD[1] recommendations advocating dual long-acting bronchodilator therapy as the cornerstone of pharmacological management in symptomatic COPD. Besides improving lung function, Glycopyrronium/Formoterol has the potential to reduce symptom burden, improve exercise tolerance, and enhance health-related quality of life, although these outcomes were not specifically evaluated in the present study.

CONCLUSION

Overall, the findings of the present study demonstrate that Glycopyrronium/Formoterol is an effective maintenance bronchodilator for patients with moderate to severe COPD, producing significant improvement in lung function over 12 weeks and supporting its use in routine clinical practice.

LIMITATIONS

The study was conducted at a single center with a relatively short follow-up period of 12 weeks. Patient-reported outcomes such as CAT score, mMRC dyspnea score, quality of life, exercise capacity, and exacerbation rates were not analyzed during follow-up. Larger multicenter studies with longer follow-up are required to evaluate the long-term effectiveness, safety, exacerbation prevention, and quality-of-life benefits of Glycopyrronium/Formoterol therapy.

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