Original Article

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Comparative Efficacy of Formoterol Combined with Glycopyrronium versus Budesonide in Managing Chronic Obstructive Pulmonary Disease: A Randomised Clinical Trial

Internal Medicine Section

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a leading global health issue, often resulting from prolonged exposure to harmful particles or gases. The 2022 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest using combinations of Long-acting Beta Agonist plus Inhaled Corticosteroid (LABA+ICS), Long-acting Beta Agonist plus Long-Acting Muscarinic Antagonist (LABA+LAMA) or LAMA for treatment, but do not specify which combination is most effective. Studies have shown mixed results regarding the superiority of LABA+ICS over LABA+LAMA, with some suggesting better outcomes for LABA+ICS, while others report similar or even better efficacy for LABA+LAMA.

Aim: To compare the effects of Formoterol+Glycopyrronium (LABA+LAMA) versus Formoterol+Budesonide (LABA+ICS) in COPD patients by evaluating changes in spirometry, 6-minute walk test performance, side-effects and Quality Of Life (QOL).

Materials and Methods: This double-blinded Randomised Clinical Trial (RCT) included 70 COPD patients visiting the Department of Respiratory Medicine at BLDE (Deemed to be University) Shri BM Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka, India. The study compared two treatment regimens: LABA+LAMA (Formoterol+Glycopyrronium) FM-GP group and LABA+ICS (Formoterol+Budesonide) FM-PD group. The study's sample size was 70 patients, with 35 in each group. Inclusion criteria included patients aged over 40, of either sex and willing to provide informed consent. Several tools were used to assess the severity and prognosis of COPD, including spirometry, the Six-minute Walk Test (6MWT), the Body Mass Index, Airflow Obstruction, Dyspnoea and Exercise Capacity (BODE) index, the COPD Assessment Test (CAT), the Clinical COPD Questionnaire (CCQ) and the modified Medical Research Council (mMRC) scale. Follow-up assessments took place after three months. The data were analysed using Statistical Package for the Social Sciences (SPSS) version 20.0 and the results are presented as mean±SD, median, interquartile range and percentages.

Results: The mean age was 64.41 years in the FM-BD group and 64.75 years in the FM-GP group, respectively. In a study of 70 COPD patients, both the Formoterol-Budesonide (FM-BD) and Formoterol-Glycopyrronium (FM-GP) groups showed improvements in various parameters over three months. The FM-GP group exhibited a significant improvement in predicted Forced Expiratory Volume in One Second (FEV1) (p=0.001) and a more substantial reduction in the BODE index (p=0.04). Both groups showed significant improvements in mMRC scores, with the FM-GP group showing a slightly better outcome (p=0.019). The FM-BD group had more adverse effects and hospitalisations, including higher rates of exacerbations and Intensive Care Unit (ICU) admissions.

Conclusion: The FM-GP group showed significant improvement in mMRC and BODE Index and reduced adverse effects and rates of exacerbations compared to the FM-BD group. The mean change in post-bronchodilator FEV1 was significant in the FM-BD group compared to the FM-GP group.

Keywords: Adverse effects, Airflow obstruction, Inhalers, Quality of Life

INTRODUCTION

The COPD is a significant global health issue, projected to become the third leading cause of death by 2022 [1]. COPD is characterised by lasting respiratory symptoms and airflow limitations caused by damage to the airways and alveoli from harmful exposures. The severity of COPD is frequently assessed using Forced Expiratory Volume in One Second (FEV1). However, more than this measure is needed to fully capture the disease's systemic effects. To better predict outcomes, a multidimensional grading system evaluates Body Mass Index (BMI) (B), airflow obstruction (O), Dyspnoea (D) and Exercise capacity (E), the latter assessed by the 6MWT [2].

The COPD treatment follows a systematic approach to enhance patients' QOL, utilising various bronchodilators. Long-acting bronchodilators, such as LABA and LAMA, are crucial in managing COPD, with ICS used for more severe cases despite associated risks. The GOLD 2022 guidelines suggest various drug combinations without specifying preferences between LABA+ICS and LABA+LAMA [3]. Research into the efficacy of LABA+ICS versus LABA+LAMA has yielded mixed results, highlighting the need for further investigation [4,5]. Thus, the present study aimed to compare the effects of Formoterol+Glycopyrronium (LABA+LAMA) versus Formoterol+Budesonide (LABA+ICS) in terms of spirometry changes, 6MWT results, side-effects and QOL.

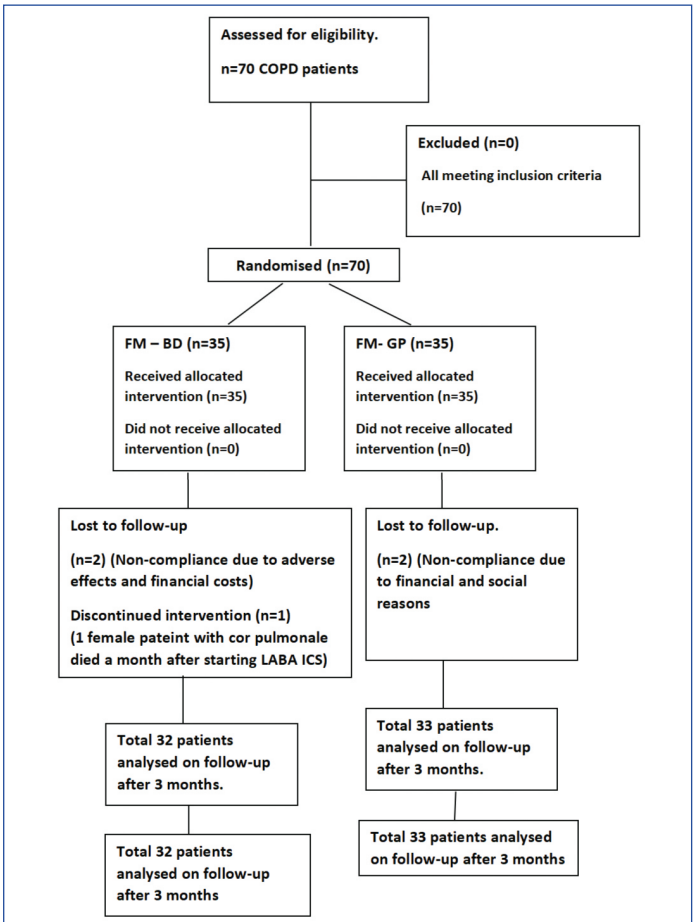
MATERIALS AND METHODS

The present Randomised Clinical Trial involved COPD patients from the Department of Respiratory Medicine at BLDE (Deemed to be University) Shri B. M. Patil Medical College, Vijayapura, Karnataka, India. It was conducted as a double-blinded, RCT over two years. The study was initiated in August 2022 and concluded in August 2024. Ethical clearance was obtained, with the Institutional Ethics Committee (IEC) number BLDE (DU)/IEC/735/2022-23 and the CTRI registration number CTRI/2023/07/054973.

Inclusion and Exclusion criteria: The present study included patients over 40 years of age, regardless of gender, who provided informed consent. Patients who were unwilling to consent, pregnant

or breastfeeding women and those who were not willing to use inhalational treatment or undergo spirometry were excluded from the study.

Sample size calculation: Based on the expected exacerbation rates of 19.45% for + or - and 74.14% for LABA-ICS [6], the study required 35 participants per group (a total of 70) to achieve over 98% power for detecting a significant difference between groups at a two-sided p-value of 0.02. Randomisation was conducted using a lottery system and the study included 70 patients, with 35 receiving LABA-LAMA (Formoterol+Glycopyrronium) and 35 receiving LABA-ICS (Formoterol+Budesonide). Formoterol was administered at a dosage of 6 mcg, Budesonide at 200 mcg and Glycopyrronium at 25 mcg [Table/Fig-1] [7,8].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) flowchart [7,8].

Study Procedure

Demographic data included age, gender, BMI, mean pack years (calculated as the product of the average number of packs of cigarettes smoked per day and the duration of smoking in years) [9] and mean biomass exposure years (the average hours spent cooking per day multiplied by the number of years of cooking) [10].

Several tools were used to assess the severity and prognosis of COPD, including spirometry, the 6MWT, the BODE index, the CAT, the CCQ and the mMRC scale. Together, these tools provided comprehensive insights into COPD severity, guiding treatment decisions and predicting patient outcomes.

Spirometry is a reliable, non invasive tool for diagnosing airflow obstruction in symptomatic patients; however, it is not intended for screening asymptomatic individuals. A FEV1/FVC ratio of less than 0.7 confirms the diagnosis of COPD. It also helps assess COPD severity, guide treatment decisions and monitor disease progression during follow-up evaluations [11]. The 6MWT was performed in our general ward over a flat, straight 30-m hard surface. Patients were advised to walk for six minutes and were encouraged throughout the process. If a patient became tired, they were advised to slow down or stop, but the timer continued. Patients were encouraged to start walking again once they regained their energy and to continue until the six minutes were complete. If a patient's saturation dropped below 80%, or they developed symptoms such as chest pain, intolerable dyspnoea, leg cramps, diaphoresis, or a pale appearance, the test would be halted [12].

The BODE index evaluates BMI, airway obstruction, dyspnoea and exercise capacity, predicting mortality risk, with higher scores linked to increased mortality. Research has shown that the BODE index is a more accurate indicator of mortality risk among COPD patients than the FEV1 [12].

The CAT evaluates both respiratory and non respiratory symptoms, classifying patients into low or high-symptom groups to guide treatment based on the GOLD classification. The CAT consists of eight items that focus on respiratory symptoms such as cough, sputum production, chest tightness and dyspnoea, as well as non respiratory symptoms like fatigue or sleep disturbances and additional indicators such as difficulty performing tasks at home or a lack of confidence in leaving the house [13].

The CCQ, which includes ten items covering symptoms, function and mental health, categorises severity based on the total score, with higher scores indicating poorer health-related QOL [14]. The mMRC scale provides a simple and subjective assessment of dyspnoea, which is essential for evaluating the severity of COPD, tracking disease progression and guiding treatment decisions, particularly in conjunction with other measures like the Global Initiative for GOLD grading system. The mMRC dyspnoea scale assesses breathlessness on a scale of 0 to 4, ranging from breathlessness only during strenuous exercise to being too breathless to leave the house [15]. The mMRC grade of patients was assessed at both visits and the difference in mMRC grades for each patient was calculated. The mean of these differences was then computed and compared between the two groups.

Follow-up assessments occurred three months after the initial visit, during which QOL questionnaires, spirometry tests and evaluations of side-effects were reassessed.

STATISTICAL ANALYSIS

The data were analysed using Statistical Package for the Social Sciences (SPSS) (version 20.0) and the results are presented as mean±SD, median, interquartile range and percentages. Statistical tests included t-tests, Mann-Whitney U tests and Chi-square or Fisher's-exact tests, with significance set at $p<0.05$.

RESULTS

In the present study, 70 patients were examined, primarily aged between 60 and 69 years, with a mean BMI of 21.5±0.56 kg/m^2 and significant exposure to smoking and biomass fuels. The demographic details of both groups were comparable [Table/Fig-2].

Demographic data	FM-BD group	FM-GP group	p-value
Number of patients (first visit)	35	35	0.156
Number of patients (second visit)	32	33	0.268
Mean age (in years)	64.41±0.45	64.75±0.73	0.116
Mean BMI (kg/m^2)	21.28±0.32	21.57±0.89	0.345
Number of male patients	25	23	0.848
Number of female patients	10	12	0.946
Mean pack years	24.5±0.25 years	25.2±0.36 years	0.565
Mean biomass exposure years	20.8±0.14 years	20.3±0.05 years	0.248

[Table/Fig-2]: Demographic characteristics of patients in both the groups at baseline.

Among the spirometry parameters, significant improvement was observed in post-bronchodilator FEV1% predicted in the FM-GP group (p=0.01) and in post-bronchodilator change in FEV1% in the FM-BD group (p=0.01). Both treatments positively impacted the mean 6MWT, mean BODE index, mean CAT Score and Mean CCQ Score (p=0.01) [Table/Fig-3].

Parameters	FM-BD group		p-value	FM-GP group		p-value
	First visit	Second visit		First visit	Second visit	
Post bronchodilator FEV1% predicted	34±11.68	33.59±13.3	0.24	39.53±16.33	40.08±19.53	0.01
Post bronchodilator FVC%	50.94±13.12	47.5±17.86	0.53	53.3±15.7	50.83±20.57	0.66
Post bronchodilator change in FEV1%	14.75±10.8	8.50±7.22	0.01	11.11±15.7	7.50±6.13	0.66
Mean MMRC grading	3.625±.25	3.15±.12	0.01	3.75±.36	2.84±.37	0.01
Mean 6MWT (in meters)	169.71±56.12	200.00±87.97	0.01	182.72±47.48	226.94±86.36	0.01
Mean bode index	7.88±1.80	6.53±2.22	0.01	7.78±1.80	5.06±2.21	0.01
Mean CAT score	29.47	23.47	0.01	28.58	21.81	0.01
Mean CCQ score	3.336±0.94	2.650±0.76	0.01	3.153±0.33	2.45±0.80	0.01

[Table/Fig-3]: Spirometric and QOL questionaries in both groups in both visits and its significance.

The improvement in post-bronchodilator change in FEV1% was more remarkable in the FM-BD group (p=0.008). Both treatments positively affected the MMRC scores, with FM-GP displaying a significant advantage (p=0.019). While the results for 6MWT were similar, FM-GP resulted in a notable reduction in the BODE index (p=0.04) [Table/Fig-4].

Parameters	FM-BD group	FM-GP group	p-value
Spirometry data			
Mean change in post bronchodilator FEV1% predicted	3.18±2.05	4.06±2.48	0.103
Mean change in post bronchodilator FVC%	4.476±5.55	2.72±2.008	0.150
Mean change in post bronchodilator change in FEV1	8.71±7.705	4.06±2.48	0.008
Mean change in MMRC grading	0.56±0.61	0.89±0.75	0.019
Mean change in 6MWT (in meters)	50.15±27.47	57.22±30.94	0.400
Mean change in bode index	0.91±0.965	1.97±1.108	0.04
Mean change in CAT score	4.21±2.26	4.17±2.02	0.72
Mean change in CCQ score	1.05±0.9	0.49±0.24	0.93

[Table/Fig-4]: Mean change in difference of various parameters compared in both groups.

The FM-BD group experienced more adverse effects and hospitalisations, while CAT and CCQ scores showed no significant differences (p=0.72 and p=0.93, respectively) [Table/Fig-5].

Adverse effects	FM-BD	FM-GP
Dry mouth	2 (6.25%)	5 (15.1%)
Dysphonia	4 (12.5%)	2 (6%)
Oral candidiasis	5 (15.6%)	0
Tachycardia	5 (15.6%)	3 (9.09%)
Tremors	6 (18.75%)	4 (12.5%)
Headache	5 (15.6%)	2 (6.25%)
Anxiety	3 (9.3%)	0
Hoarseness	6 (18.75%)	1 (3.12%)
Number of patients with exacerbations within 3 months	6 (18.75%)	2 (6.25%)
Number of ward admissions	4 (12.5%)	1 (3.12%)
Number of ICU admissions	2 (6%)	1 (3.12%)
Number of deaths	1 (3.12%)	0

[Table/Fig-5]: Adverse effects and rate of exacerbations and deaths in both the groups.

DISCUSSION

The present study compared the effects of FM-BD and FM-GP in 70 COPD patients, randomised after PFT evaluation. Both groups had similar baseline characteristics, with higher pack-years or biomass exposure linked to more severe COPD. Initial assessments included spirometry, CAT score, CCQ score and BODE index. Within three months, 18.75% of patients in the FM-BD group experienced exacerbations, compared to 6.25% in the FM-GP group. The FM-BD group had more ward admissions (4 vs. 1) and ICU admissions (2 vs. 1). One death occurred in the FM-BD group, while the FM-GP group had no deaths.

Around 69% of the patients enrolled in this trial were male, reflecting a common trend in COPD demographics. Both groups had a similar age distribution centered around 60-69 years, which is typical for COPD patients. The mean age was 64.41 years in the FM-BD group and 64.75 years in the FM-GP group, respectively. The mean BMI was 21.28 in the FM-BD group and 21.57 in the FM-GP group, respectively. Tashkin DP et al., reported similar mean ages in the FM-BD (63.8 years) and FM-GP (61.8 years) groups, while the present study found mean ages of 64.41 and 64.75 years, respectively [16]. Singh CV et al., reported a slightly higher mean BMI (27.6 vs. 27.2) compared to the present study (21.28 vs. 21.57) and observed similar trends in COPD severity among patients with higher pack years, a trend also seen in Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS), which reported average pack years of 47 for FM-BD and 48 for FM-GP and in Singh CV et al., which found averages of 39 and 40, respectively [17,18].

When evaluating lung function, the present study showed that the FM-BD group had no significant change in predicted FEV1 (p=0.24), while the FM-GP group showed a significant improvement (p=0.001). This is consistent with the findings of Rabe KF et al., which indicated no significant difference in FEV1 changes between the FM-BD and FM-GP groups [19]. Conversely, Aziz MIA et al., reported noteworthy improvements in FEV1 and overall lung function for the LABA/ICS and LABA/LAMA groups [20]. Regarding FVC%, this study observed a decline in both groups; however, this change was not statistically significant (FM-BD: p=0.53, FM-GP: p=0.066). This observation aligns with the results from the FlowTriever for Acute Massive Pulmonary Embolism (FLAME) trial [21], which did not emphasise FVC% differences, although both treatment regimens resulted in improved lung function. Interestingly, the FM-BD group significantly improved FEV1% from 14.85% to 7.88% (p=0.01). In contrast, the FM-GP group showed a minor, non significant change (p=0.066), though the Mann-Whitney test revealed a significant difference between groups (p=0.008). This finding is consistent with Rodrigo GJ et al., and Tashkin DP et al., which found improvements with both LABA-ICS and LABA-LAMA, but the latter's meta-analysis suggested no significant difference in FEV1 improvements between treatments [22,23]. Additionally, the 6MWT results showed significant improvements in both groups (FM-BD: p=0.001, FM-GP: p=0.001), but there was no significant difference between groups (p=0.4), which is consistent with the FLAME trial [21], which showed LAMA/LABA as superior to LABA/ICS in improving 6MWT distance. The BODE index revealed a significant improvement in both groups (p=0.001), with the FM-GP group showing a significantly greater improvement (p=0.04). This aligns with Singh CV et al., which also found better outcomes with LABA/LAMA compared to LABA/ICS for the BODE index; however, differences in improvements between studies were noted [17].

Regarding adverse effects, the FM-BD group in the present study had higher rates of dysphonia, oral candidiasis, tachycardia,

tremors, headache, anxiety and hoarseness compared to the FM-GP group, which aligns with findings from Rabe KF et al., and Sharafkhaneh A et al., who also reported increased adverse events with LABA/ICS. Interestingly, the FM-GP group had a higher incidence of dry mouth than the FM-BD group [19,24]. These findings are consistent with Singh CV et al., who observed higher incidences of nasopharyngitis, oral candidiasis and tachycardia with LABA-ICS and Rabe KF et al., who found everyday adverse events associated with LABA-ICS [17,19]. The present study also found that the FM-BD group had more exacerbations (18%) and higher rates of hospital admissions and ICU admissions, along with one death, compared to the FM-GP group (6% exacerbations, fewer admissions and no deaths). The ETHOS [18] trial reported similar findings, showing lower exacerbation rates in the FM-GP group but noted slightly higher death rates with FM-BD. The FINE registry [25] reported a 10.6% adverse event rate with FM-GP, similar to our findings. The FLAME trial found that LABA/LAMA was associated with fewer moderate-to-severe exacerbations than LABA/ICS [21].

Regarding dyspnoea, the FM-GP group showed a statistically significant improvement in the MMRC score (0.89 vs. 0.56 for FM-BD, p=0.019), suggesting better management of dyspnoea. This aligns with the findings from the FLAME [21] and SPARK [26] trials, which demonstrated improvements in dyspnoea with both treatments; however, the improvements in the MMRC scale were not consistently emphasised. Both treatment groups showed enhancements in the CAT scores, with the FM-BD group decreasing from 29.47 to 23.47 and the FM-GP group decreasing from 28.58 to 21.81. However, the Mann-Whitney test indicated no significant difference between the groups, with a p-value of 0.72. Rabe KF et al., also found no significant difference in CAT scores between the groups [19]. Lastly, the CCQ scores improved significantly in both groups (FM-BD: 3.336 to 2.650, FM-GP: 3.153 to 2.45, both p=0.001), but no significant difference was observed between groups (p=0.93), which is consistent with findings from Jiang Y et al., [27]. In conclusion, while both treatment regimens showed benefits, the FM-GP group had fewer adverse effects, fewer exacerbations and better lung function improvement.

Limitation(s)

A larger dataset could provide more robust conclusions and reduce the impact of outliers or anomalies. The follow-up period was limited to three months, which may not be long enough to fully evaluate the long-term effects of treatments on lung function, exacerbation rates and overall patient outcomes. A longer follow-up period would provide a clearer understanding of the sustainability of treatment effects. Although validated questionnaires such as the CCQ and CAT were employed to assess respiratory health, they may have limitations in sensitivity or specificity when detecting changes over time. Moreover, subjective measures like the MMRC may be influenced by patient perceptions, leading to variability in reported outcomes. Inherent biases in patient reporting and clinician assessments of symptoms, exacerbations and QOL could impact the validity of the findings. Despite the statistical insignificance of some compared data, monitoring these changes over time is essential for evaluating respiratory health and treatment efficacy in these groups.

CONCLUSION(S)

The study predominantly involved patients aged 60-69 years, with a mean BMI of 21.5 kg/m^2, showing a male dominance and significant smoking and biomass exposure in severe COPD cases. The FM-GP group showed significantly more improvement in the MMRC and BODE Index, as well as reduced adverse effects and rates of exacerbations compared to the FM-BD group. The mean change in post-bronchodilator FEV1% was significantly higher in the FM-BD group than in the FM-GP group. Although there were similar improvements in respiratory health and QOL measures, FM-BD was linked to a higher frequency of exacerbations, hospitalisations and mortality. Further investigations should focus on the long-term efficacy and safety of FM-GP versus FM-BD, the mechanisms of exacerbations and mortality, the impact of smoking and biomass exposure, QOL outcomes, subgroup analyses, cost-effectiveness, personalised treatment approaches and an understanding of the causes of higher mortality in FM-BD patients.

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