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Original Research Article

A Comparative Study on the Efficacy of Formoterol-Budesonide, Salbutamol-Ipratropium and Formoterol- Glycopyrronium Nebulisations in Moderate to Severe Copd Patients by Using Clinical and Spirometric Parameters

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Conflict of interest: Nil

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation, resulting in significant morbidity, mortality, and healthcare burden worldwide. Nebulized bronchodilator combinations are widely used in the management of moderate-to-severe COPD, but comparative evidence regarding their efficacy remains limited. This study compared the effectiveness of Formoterol-Budesonide, Salbutamol-Ipratropium, and Formoterol-Glycopyrronium nebulization therapies in improving clinical symptoms and spirometric parameters in patients with moderate-to-severe COPD.

Aim: To compare the efficacy and safety of Formoterol-Budesonide, Salbutamol-Ipratropium, and Formoterol-Glycopyrronium nebulization in patients with moderate-to-severe COPD.

Materials and Methods: A prospective comparative study was conducted in the Department of Pulmonary Medicine, ACSR Government Medical College and Government General Hospital, Nellore, between May 2023 and April 2024. Seventy-five spirometry-confirmed moderate-to-severe COPD patients were equally allocated into three treatment groups (n=25 each): Group 1 received Formoterol-Budesonide, Group 2 received Salbutamol-Ipratropium, and Group 3 received Formoterol-Glycopyrronium nebulization. Clinical symptoms, oxygen saturation, respiratory rate, pulse rate, and spirometric parameters (FEV_1, FVC, and FEV_1/FVC ratio) were assessed before nebulization and at 15 and 45 minutes after treatment. Adverse events were also documented. Statistical analysis was performed using SPSS version 22 with $p<0.05$ considered statistically significant.

Results: The mean age of participants was 52.5±12.2 years, with males constituting 78.7% of the study population. All treatment groups demonstrated improvement in symptoms and lung function following nebulization. Formoterol-Glycopyrronium produced the greatest improvement in spirometric parameters, with 92% of patients demonstrating significant FEV_1 improvement at 45 minutes, comparable to Salbutamol-Ipratropium and significantly superior to Formoterol-Budesonide (68%; p=0.02). Salbutamol-Ipratropium achieved the highest rates of cough reduction (91.3%), complete dyspnea relief (100%), and sputum reduction (73.7%). All regimens were well tolerated, with only minimal adverse effects, including occasional tremors, tachycardia, dry mouth, and palpitations.

Conclusion: All three nebulization regimens significantly improved clinical symptoms and pulmonary function in moderate-to-severe COPD patients. Formoterol-Glycopyrronium demonstrated superior improvement in spirometric outcomes, while Salbutamol-Ipratropium provided greater symptomatic relief. Both regimens were safe and effective, supporting their use as preferred therapeutic options in the acute management of moderate-to-severe COPD.

Keywords: Chronic Obstructive Pulmonary Disease, Nebulization, Formoterol-Glycopyrronium, Salbutamol-Ipratropium, Spirometry.

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Introduction

COPD is regarded as a major public health issue in both developed and developing countries, characterized by the degeneration of lung tissue and restriction of airflow. The limitation of airflow in COPD is progressive and non-reversible [1]. COPD is estimated to have 3.5 million death in 2021, making it the fourth most common cause of death globally. Most of these were premature deaths, and majority (90%) occurred in nations with poor and moderate incomes. COPD ranks as the fifth largest cause of illness and death in the developed world. According to estimates, it is globally the eighth largest contributor to disability-adjusted life years [2].

It is projected that rising air pollution would increase the burden of COPD in the upcoming years and changing lifestyles [3]. The difficulty in diagnosing COPD further complicates the burden. In clinical settings, COPD is often underdiagnosed and diagnosed late. In resource-limited settings, the lack of access to spirometry delays diagnosis [4]. If left untreated, COPD leads to a gradual deterioration of lung function and a reduced overall quality of life. It also heightens an individual's susceptibility to other health issues like pneumonia, lung cancer, and heart disease. As symptoms worsen, patients face challenges in daily living due to breathlessness, which can limit productivity and impose an additional economic burden on families due to treatment and opportunity costs [5]

Changes in lifestyle brought about by globalization have raised the risk of COPD. Occupational exposure to noxious particles, dust, fumes, chemicals, air pollution, and deficiency of alpha-1 antitrypsin are additional significant risk factors of COPD besides exposure to cigarette smoke, with over 70% of COPD cases in affluent nations being caused by tobacco use. Exposure to other environmental air pollution, such as indoor air pollution, is especially important in the emergence of COPD in underdeveloped nations [6]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion uses spirometry in conjunction with symptoms and history to diagnose and stage COPD. The diagnosis of COPD is confirmed if the post-bronchodilator FEV1 (forced expiratory volume in 1 second)/FVC (forced vital capacity) ratio is less than 0.7. Further staging of the severity of COPD is done on the basis of FEV1, as shown in table 1 [7].

Table 1: GOLD Grades and Severity of Airflow Obstruction in COPD

In COPD patients (FEV1 / FVC < 0.7)		
GOLD Grade	**Severity**	**Post-Bronchodilator FEV1 (% predicted)**
GOLD 1	Mild	FEV1 > 80% predicted
GOLD 2	Moderate	50% ≤ FEV1< 80% predicted
GOLD 3	Severe	30% ≤ FEV1< 50% predicted
GOLD 4	Very Severe	FEV1 < 30 % predicted

The GOLD criterion also rates the COPD severity based on symptoms, using the Modified Medical Research Council (mMRC) dyspnea scale and the frequency of flare-ups to inform treatment strategies. This is called as the ABE classification. The details of the ABE classification is given in Figure 1 [(7)].

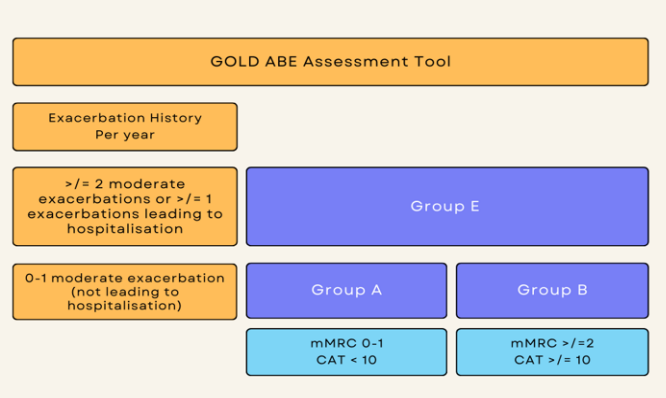

Figure 1: Gold Abe Assessment Tool

This dual classification helps in improved methods of management for moderate and severe COPD patients (8). The ABE criterion based on symptoms and frequency of exacerbations under the GOLD criterion is used as a guide for treatment. The treatment options mainly consist of bronchodilators and anti-inflammatories such as steroids. People in Group A are usually given short-acting

bronchodilators (SABA) like salbutamol or long acting bronchodilators (LABA). People in Group B are initiated on long-acting bronchodilators like salmeterol and long-acting muscarinic antagonists like tiotropium and glycopyrronium. For group E patients, long-acting muscarinic antagonists with long acting bronchodilators is the preferred initial therapy, inhaled corticosteroid is added to this combination, when the eosinophils count is more than 300 or there is a concomitant asthma are preferred. The overall treatment goal is to relieve symptoms, reduce exacerbations, and improve overall quality of life [7,8].

Previously researches has shown that formoterol-budesonide is more successful in lowering aggravation, alleviating symptoms, and enhancing quality of life in contrast to using single drug. Combined use of salbutamol with ipratropium bromide, which has been in vogue since the last 15 – 20 years, has significantly more bronchodilation as compared to the individual usage of the drugs. PINNACLE trails showed that the usage of formoterol-glycopyrronium among patients with moderate to severe COPD have significantly higher improvement in lung functions.

There are very few studies exist that compare the efficacy of formoterol-budesonide, salbutamol-ipratropium, and formoterol-glycopyrronium among patients with moderate to severe COPD. A study comparing the efficacy of three different combinations can aid clinicians in evidence-based decision-making, thereby leading to much better control of symptoms, a reduction in exacerbations, and an improvement in overall quality of life.

Therefore the purpose of this study is to compare the efficacy of Formoterol- Budesonide, Salbutamol-Ipratropium and Formoterol-Glycopyrronium Nebulisations in Moderate to Severe COPD Patients by assessing the improvement in clinical parameters like dyspnea, cough, and sputum production and also the improvement in Spirometric parameters like FEV1, FVC, FEV1/FVC in order to lessen exacerbations and enhance life quality.

Aim of the Study: To compare the efficacy of three nebulization treatments Formoterol-Budesonide, Salbutamol-Ipratropium, and Formoterol-Glycopyrronium in moderate to severe COPD patients using clinical and spirometric parameters.

Objectives of the Study: To evaluate and compare improvements in spirometric parameters (FEV1, FVC, FEV1/FVC) among the group. To document and compare clinical improvement among the three study groups. To document and compare side effects post-nebulization in each group.

Methodology

This was a comparative prospective study conducted on patients who attended Outpatient department and Wards in the Department of Pulmonary Medicine, ACSR Government Medical College and Government General Hospital, Nellore during the period from May 2023 to April 2024. The participants in the study included moderate to severe COPD patients aged 35–80 years who attended the Respiratory Medicine outpatient department and wards.

The study included patients with cough, dyspnea, and sputum production complaints who were known smokers, betel nut chewers, or had been passive smokers. Baseline Assessment like Chest X ray, ECG was performed and whose X rays shows only emphysematous changes without other significant lesions and normal ECG pattern were included. Sputum CBNAAT for Mycobacterium tuberculosis was done and those who are negative were included for the study. Participants were recruited based on Bronchodilator Reversibility Test. Spirometry was performed and after administration of short acting bronchodilator, reversibility check was done and those having <12 % improvement in measured FEV1 and FEV1/FVC < 0.7 were included for the study.

Inclusion Criteria: Patients diagnosed with moderate to severe COPD confirmed by spirometry (FEV1/FVC < 0.7). Chest X-ray showing emphysematous changes without other significant lesions. Patients capable of performing spirometry. Willingness to participate and provide informed consent.

Exclusion Criteria: Patients with cardiac disorders (e.g., ischemic heart disease, CCF). Active respiratory diseases other than COPD. Known allergy or hypersensitivity to study drugs. Recent surgeries (ophthalmic, thoracic, or abdominal).

Sample size was computed based on previously observed Comparative study of Single inhalation of LABA and LAMA versus Short acting Salbutamol plus Ipratropium on Comparison of Means of FEV with (29) with Confidence interval 95% and Power of study 80%. According to the calculation, 25 is the minimum sample size per category. Hence Total sample size of 75 for 3 groups.

Steps of data collection: Baseline Assessment: A Good history, Clinical evaluation, Sputum CBNAAT, Chest X ray, ECG were assessed. Pre nebulization Spirometry was performed. Patients were allocated to one of the three groups by Consecutive method:

- Group 1: Formoterol-Budesonide nebulization.
- Group 2: Salbutamol-Ipratropium nebulization.

- Group 3: Formoterol-Glycopyrronium nebulization.

Arformoterol which is an (R, R)- Enantiomer of Foromoterol was used as a substitute due to availability. Thus Arforomoterol-Glycopyrronium nebulization has been used in Group 3 patients.

Intervention: Nebulization was administered as per group allocation. Follow-up Assessments: Spirometry and clinical parameters were recorded at the 15th and 45th minutes post-nebulization. Data Recording: Clinical symptoms (cough, dyspnea, sputum) and spirometric values (FEV1, FVC, FEV1/FVC) were documented. Adverse effects (tremors, dry mouth, light-headedness, sweating) were noted.

The spirometric parameters includes FEV1/FVC, FEV1, FVC which were tabulated into Predicted values, Pre nebulization, and documented at 15th and 45th minute of Post nebulization and the clinical parameters includes oxygen saturation, pulse rate, and respiratory rate were noted for all the 3 groups at the same time points. The data was presented as numbers and percentages. Side effects of each group of patients like Tremor, Dry mouth, Tachycardia, Light headedness, Sweating, Palpitations were also recorded in number and percentages in each of the 3 groups.

Outcome Measures: Primary Outcomes: Improvement in Spirometric parameters (FEV1, FVC, FEV1/FVC). Clinical symptom relief (cough, dyspnea, sputum production). Secondary Outcomes: Incidence of side effects in each group. Time to symptomatic improvement (15th vs. 45th minute).

Statistical Analysis: The statistical analysis for this study was conducted using SPSS (Statistical Package for the Social Sciences), version 22. Descriptive statistics were used to compile the baseline characteristics of the participants in this study, including demographic details such as age, gender, smoking index, and comorbidities, with results presented as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. For comparisons of continuous variables across the three groups (Group 1, Group 2, and Group 3), the one-way analysis of variance (ANOVA) was used, assuming normal distribution. To compare categorical variables between the groups, the Chi-square test was applied. Fisher's exact test was applied if the expected cell count in any category was less than 5. Post-hoc Bonferroni tests were employed to evaluate pairwise differences between the groups when a significant result was found in the one-way ANOVA.

Frequency distributions and percentages were used to examine improvements in clinical symptoms (such as cough, dyspnea, and sputum production) prior to and following nebulization.

The change in spirometric parameters (FEV1, FVC, and FEV1/FVC ratio) at different time intervals (Pre-dose, 15 minutes, and 45 minutes) was analyzed using paired t-tests for comparisons within groups. For between- group comparisons, the one-way ANOVA was used. The p-values were considered statistically significant if they were less than 0.05.

Results

There were 75 participants enrolled in the present study. Three groups of study participants were formed based on the drug i.e. Group 1 nebulised with Formoterol- Budesonide, Group 2 nebulised with Salbutamol-Ipratropium, and Group 3 nebulised with Formoterol-Glycopyrronium. All the three groups had equal number of study participants i.e. 25 in each group.

Table 2: Age Distribution of the Study Participants (N=75)

AGE GROUP	Overall N (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)
35 to 44	25 (33.3)	8 (32.0)	11 (44.0)	6 (24.0)
45 to 54	14 (18.7)	4 (16.0)	5 (20.0)	5 (20.0)
55 to 64	21 (28.0)	9 (36.0)	7 (28.0)	5 (20.0)
65 to 74	13 (17.3)	4 (16.0)	2 (8.0)	7 (28.0)
75 to 80	2 (2.7)	0 (0.0)	0 (0.0)	2 (8.0)
Total	75 (100.0)	25 (100.0)	25 (100.0)	25 (100.0)
Mean (±SD) 52.5 (±12.2) years				

Table 3: Gender Distribution of the Study Participants (N=75)

GENDER	Number	Percentage
Male	59	78.7
Female	16	21.3

Table 4: Gold Staging of the Study Participants (N=75)

GOLD staging	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	p value by Chi^2
GOLD Stage 2	14 (56.0)	10 (40.0)	19 (76.0)	**0.03**
GOLD Stage 3	11 (44.0)	15 (60.0)	6 (24.0)	
Total	25 (100.0)	25 (100.0)	25 (100.0)	75 (100.0)

Table 6: Smoking Index and Pack Years of the Study Participants (N=75)

Variable	GROUP 1 (n=25)		GROUP 2(n=25)		GROUP 3(n=25)	
	Median	IQR	Median	IQR	Median	IQR
Smoking index	400	210 – 750	387.5	250 – 800	450	150 - 700
Pack year	20	10.5 – 37.5	19.4	12.5 – 40	22.5	7.5 - 35

Associated Comorbidities: There were 21 diabetic study participants (28%) and 13 study participants (17.3%) with hypertension. Among them, 7 study participants (9%) had both hypertension and diabetes mellitus.

Table 7: Clinical Symptoms across the Groups before Nebulisation

SYMPTOMS	GROUP 1 (n=25)		GROUP 2(n=25)		GROUP 3(n=25)	
	NUMBER	%	NUMBER	%	NUMBER	%
COUGH	24	34.3	23	32.9	23	32.9
DYSPNOEA	25	33.3	25	33.3	25	33.3
SPUTUM	17	32.7	19	36.5	16	30.8

Table 8: Improvement in Symptoms in Groups after Nebulisation (N=75)

Improvement of symptoms	Group 1 (N=25)		Group 2(N=25)		Group 3(N=25)	
	Number	%	Number	%	Number	%
Reduced cough	18	75.0	21	91.3	20	87.0
Improved with dyspnoea	24	96.0	25	100.0	25	100.0
Reduced sputum production	9	52.9	14	73.7	11	68.8

Table 9: Side Effects of Each Study Groups after Nebulisation (N=75)

Side Effects	Group 1		Group 2		Group 3	
	Number	%	Number	%	Number	%
Tremors	-	-	2	8%	-	-
Dry Mouth	-	-	-	-	1	4%
Light Headedness	-	-	-	-	-	-
Tachycardia	1	4%	-	-	1	4%
Palpitations	-	-	1	4%	-	-

Table 10: Assessment of Symptomatically Improvement with Oxygen Saturation Over Time (N=75)

Time interval	Oxygen			p value by Oneway ANOVA
	Group 1 Mean (±SD)	Group 2 Mean (±SD)	Group 3 Mean (±SD)	
Before nebulization	92.9 (±3.6)	93.4 (±3.9)	93.4 (±3.7)	0.86
At 15th min	93.7 (±3.4)	94.8 (±3.6)	94.6 (±3.3)	0.47
At 45th min	94.1 (±3.2)	95.4 (±3.3)	95.0 (±3.8)	0.38

Table 11: Assessment of Symptomatically Improvement with Respiratory Rate Over Time (N=75)

Time interval	Respiratory rate			p value by Oneway ANOVA
	Group 1 Mean (±SD)	Group 2 Mean (±SD)	Group 3 Mean (±SD)	
Before nebulization	23.1 (±1.7)	22.7 (±3.0)	22.3 (±3.1)	0.57
At 15th min	22.2 (±2.0)	21.5 (±2.6)	21.1 (±2.9)	0.32
At 45th min	21.8 (±1.8)	20.3 (±2.4)	20.4 (±2.6)	**0.04**

Table 12: Assessment of Symptomatically Improvement with Pulse Rate Over Time (N=75)

Time interval	Pulse rate			p value by Oneway ANOVA
	Group 1 Mean (±SD)	Group 2 Mean (±SD)	Group 3 Mean (±SD)	
Before nebulization	97.4 (±10.6)	96.5 (±12.4)	94.9 (±10.8)	0.74
At 15th min	99.7 (±11.3)	99.4 (±12.4)	98.5 (±13.7)	0.92
At 45th min	101.3 (±11.6)	100.4 (±13.1)	99.8 (±10.9)	0.90

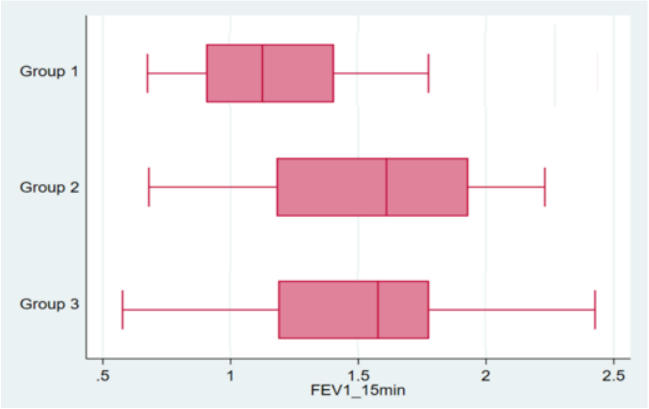

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Figure 2: Box-Whisker Plot Showing Fev1_Pre across Three Groups

The cases depicts FEV1 values of 3 Groups before Nebulization with Group 2 and Group 3 having Median FEV1 around 1.5 L/min and 1.4 L/min respectively and Group 1 having Lowest median around 1.2 L/min. Group 3, maximum and minimum values ranging from 0.4 to 2.5 and for Group 2, ranges from 0.3 to 2 and Group 1 ranges from 0.3 to 1.8 L/min, with Potential outliners above 2 in Group 1 and No visible outliners in Group 2.

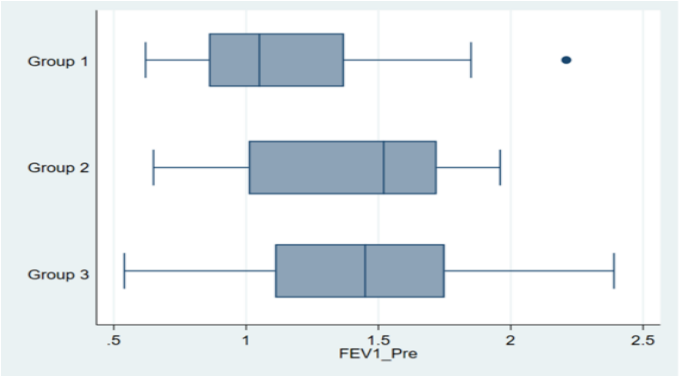

Figure 3: Box-Whisker Plot Showing Fev1_ at 15 Minutes across Three Groups

This plot compares the FEV1 values measured 15 minutes after Nebulization across 3 groups. Median for Group 1 remains stable (1.25 L/min) while Group 2 and Group 3 shows mild improvement in FEV1 when compared with Pre nebulisation values with Group 3 which had lowest baseline, shows a positive shift, suggesting stronger relative response (1.4 to 1.6 L/min)

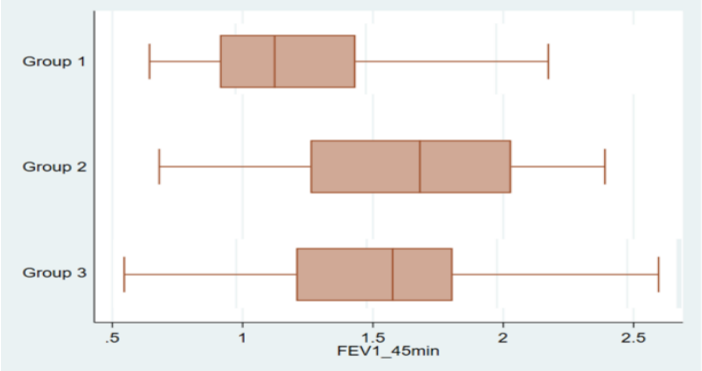

Figure 4: Box-Whisker Plot Showing Fev1 At 45 Minutes Across Three Groups

This follow up plot shows FEV1 measured at 45th minute following nebulisations across 3 groups with Group 2 shows good improvement over time (Median 1.5 to 1.7) and Group 3 shows a notable upward trend (Median 1.4 to 1.65) while Group 1 shows mild improvement (Median 1.2 to 1.3) when compared with median values of pre nebulization.

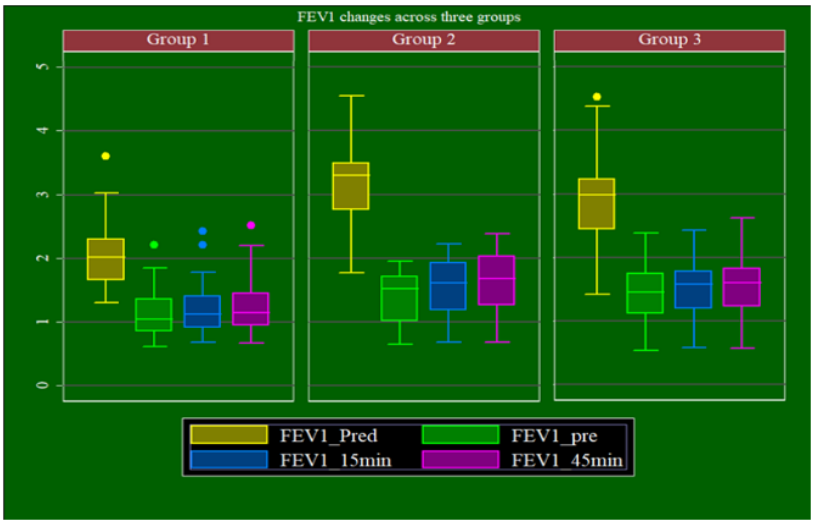

Figure 5: Assessment of improvement in FEV1 related to time (N=75)

Table 6: Assessment of improvement in FEV1 related to time after nebulisation across groups (N=75)

Spirometric Parameters	Group 1	Group 2	Group 3	p-value by Chi²
	Frequency (%)	Frequency (%)	Frequency (%)	
FEV1 (At 15th min)	18 (72.0%)	20 (80.0%)	22 (88.0%)	0.36
FEV1 (At 45th min)	17 (68.0%)	23 (92.0%)	23 (92.0%)	**0.02**

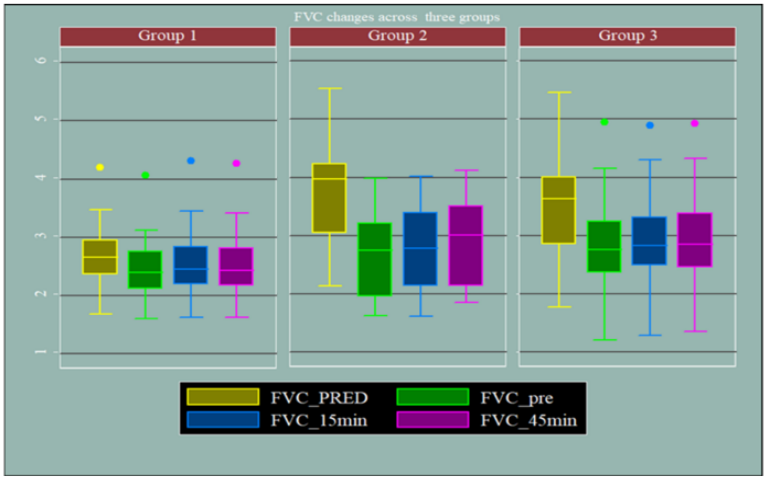

Figure 6: Assessment of improvement in FVC related to time (N=75)

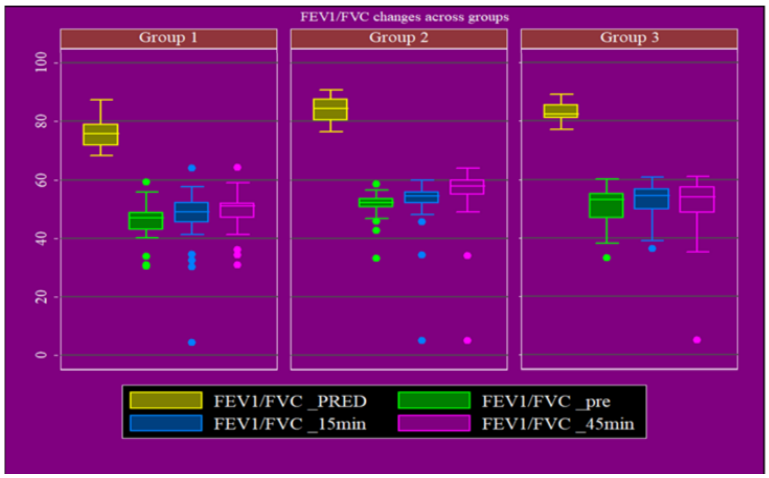

Figure 7: Assessment of improvement in FEV1/FVC related to time (N=75)

This Box and Whisker plot graph shows the improvement in FEV1/FVC across 3 groups with Group 1 showing less pronounced changes compared to Group 2 & Group 3. Illustrate the Temporal improvement in Spirometric parameters (FEV1, FVC, FEV1/FVC) across 3 groups with Group 3 and Group 2 showing Significant Improvement approaching predicted values compared to Group 1 across time intervals.

Discussion

This study aiming to systematically analyze the efficacy and safety profiles of three distinct dual combination nebulization therapies in patients with moderate to severe COPD (GOLD stages 2-3) compared Formoterol-Budesonide (LABA/ICS), Salbutamol-Ipratropium (SABA/SAMA), and Formoterol- Glycopyrronium (LABA/LAMA) combinations.

A total of 75 patients were enrolled with strict inclusion and exclusion criteria were followed, and 25 patients were randomly assigned to each therapy arm. Comprehensive baseline evaluations were performed on the patients that includes detailed clinical evaluation, symptom scoring using the COPD Assessment Test (CAT), and thorough spirometric testing. Spirometry was performed using a calibrated spirometer following ATS/ERS guidelines, with pre-nebulization measurements establishing baseline lung function. Post-nebulization assessments were conducted at precisely 15TH and 45TH minutes to capture both immediate and sustained treatment effects.

This rigorous temporal assessment protocol allowed us to evaluate not only the onset of action but also the duration of bronchodilation for each combination therapy. The study design incorporated washout periods for patients already on bronchodilator therapy to eliminate carryover effects.

Our results demonstrated distinct patterns of response across the three treatment arms. The LABA/LAMA combination (Formoterol-Glycopyrronium) showed superior improvement in both clinical parameters and spirometric values compared to the other regimens.

A significant mean improvement in FEV1 at 45th minute post-nebulization for Formoterol-Glycopyrronium (Mean FEV1 improvement 0.25) and Salbutamol-Ipratropium (Mean FEV1 improvement 0.20) when compared to Formoterol-Budesonide (Mean FEV1 improvement 0.10). Significant reduction in dyspnea scores.

Age Distribution: Our study population's mean age (52.5 years) was lower than Griffin et al study (69.2 years). [9] This could be due to inclusion of general practice database from UK. The mean age in Welte et al (2009) [10] Study was 62.5 years, which was greater than the mean in our study. This could be due to increased incidence of COPD patients in our study with the mean age of 52.5 years. In Larsson K et al (2013) [11] study had also noted higher mean age (67.6 years) than our study might be due to increased prevalence of COPD in their database which includes more diverse population and regional variations.

Gender Distribution: Our study has a larger male population, which is consistent with Griffin et al [9] and Welte et al. (2009) [10], where males constituted the majority of participants. This may be related to occupational exposures in specific industries and the higher incidence of smoking among men.

However, this contrasts with Larsson et al. (2013) [11] where 53% of the study population were females. The difference may be due to Larsson et al.'s inclusion of more diverse populations in the broader, multi-center study design, or regional variations in smoking habits and disease susceptibility between genders.

Further supporting the predominance of males, a study by Mannino et al. (2002) reported that males had a higher prevalence of smoking-related respiratory diseases, which may explain the gender disparity in our study. [12] Conversely, a more recent study by Tan et al. (2020) found an increasing trend of female smokers in Western countries, potentially influencing gender distribution in respiratory studies. [13]

Body Mass Index (BMI) Findings: The mean BMI in our study was 24.4, which falls within the normal range for Asian populations. This is comparable to Griffin et al. (2008), who reported a mean BMI of 25.4 [9]. The slightly higher BMI in Griffin's study may reflect differences in dietary habits and physical activity levels between Western and Asian populations. However, a research by Franssen et al. (2008) discovered that because of their increased metabolic needs and muscle atrophy, people with COPD frequently had lower BMIs. [14] Our findings indicate that most participants were not underweight, which aligns with the observations of Park et al. (2013), who reported that a normal BMI was common in early-stage respiratory disease patients. [15]

Smoking and Passive Smoking Exposure: In our study, 85.3% of the participants were active smokers and 24% of participants reported a history of passive smoking exposure. This contrasts sharply with Griffin et al. (2008), where 85% had exposure to active smoking but no history of passive smoking was noted. [9] Similarly, Larsson et al. (2013) found that 48% of their participants were current or former smokers. [11] These

variations could be due to regional smoking prevalence or differences in study inclusion criteria. Additionally, a meta-analysis by Oberg et al. (2011) emphasized that passive smoking contributes significantly to respiratory morbidity, supporting our findings on its prevalence accounting for 47% of deaths in women due to passive smoking, 28% in children and 26% in men. [16]

This study states as per the report of 2004, 40% of children, 33% of Male non-smokers, 35% of female non-smokers were exposed to second hand smoke worldwide.

Patterns of Comorbidities: In our study, diabetes and hypertension were the most prevalent chronic comorbidities among COPD patients. This is in contrast to research from Griffin et al. (2008), where asthma was the most common comorbidity, followed by cardiovascular disease (CVD) and diabetes (9). The disparity can result from variations in study populations—Griffin et al. relied on general practice databases, which may capture milder COPD cases with overlapping asthma.

Similarly, Larsson et al. (2013) reported a higher proportion of asthma (25%), depression (18%), and cancer (12%) in their COPD cohort, suggesting regional or methodological variations in comorbidity assessment [11].

A 2020 multinational cohort study by Divo et al. found that hypertension (52%), diabetes (22%), and CVD (18%) were the most frequent COPD comorbidities, aligning partially with our findings [17]. The higher prevalence of metabolic disorders in our study may reflect population-specific risk factors, such as dietary habits and genetic predisposition, as noted in Asian COPD studies by Yin et al. (2019) [18].

Treatment Efficacy:

Bronchodilators in COPD Our study observed significant improvement in FEV_1 and FVC with ipratropium/salbutamol combination therapy, corroborating the COMBIVENT Inhalation Aerosol Study Group (1994), which reported 24–25% FEV_1 improvement with ipratropium alone and increased effectiveness with combination treatment [19]. Conversely, a 2018 RCT by Mahler et al. found that short-acting ipratropium/salbutamol provided faster symptom relief in moderate COPD, aligning with our results [20]. These highlight the need for phenotype-specific treatment approaches, as emphasized in the 2025 GOLD guidelines [21]. Griffin et al. (2008) relied on analysis of retrospective databases that may lack spirometric rigor [9]. Our study and the COMBIVENT trial (1994) used prospective designs with spirometry, strengthening objective outcomes [19]. Larsson et al. (2013) included psychiatric comorbidities, often underrepresented in COPD studies [11].

Glow Phase 3: Phase 2 trials showed that Glycopyrronium provided 24 hour bronchodilation, rapid onset of action and sustained improvements in lung function i.e. FEV1. Phase 3 GLOW program ensured its long-term efficacy and reduction in dyspnoea, exacerbation risks and improved health status and exercise tolerance. This was comparable to the benefits provided by tiotropium. Even side effects were also minimal. Glycopyrronium is a viable alternative to tiotropium, having a single-dose need per day, faster action, and also provides sustained bronchodilation when combined with long- acting β_2-agonist (LABA). [22] This review was in favour of present study findings and had seen better clinical outcome in the group containing Formoterol-Glycopyrronium (LABA plus LAMA).

Di Marco F et al (2017) conducted a review on impact of symptom variability in COPD and the role of dual bronchodilation therapy (LABA/LAMA) in improving symptom control and reducing exacerbations. The review had found that LABA/LAMA combinations showed superior efficacy in terms of improved lung functions i.e. FEV1, reduced dyspnea, reduced use of rescue medication, and lower rate of moderate to severe exacerbations over monotherapies. [23] This was explained due to synergistic bronchodilation via complementary pathways i.e. β_2-agonism + anticholinergic effects. It was concluded that dual therapy is needed for symptomatic COPD patients to address the symptom variability and prevent exacerbations with once-a-day dosing. This combination was well- tolerated with low adverse effects similar to monotherapies.

Superiority of LABA/LAMA Combination in COPD: In our study, Group 3 (Formoterol-Glycopyrronium, LABA/LAMA) demonstrated significantly better clinical outcomes and spirometric improvements compared to Group 1 (Formoterol-Budesonide, LABA/ICS). Our study aligns with contemporary evidence from the FLAME trial (2016), which showed that LABA/LAMA reduced moderate-to-severe exacerbations by 11% compared to LABA/ICS in COPD patients, alongside superior lung function gains [24].

Similarly, the IMPACT trial (2018) reported that LABA/LAMA alone was non-inferior in many endpoints, supporting our findings (25). Mechanistically, glycopyrronium's prolonged M3-receptor antagonism provides sustained bronchodilation, while formoterol's rapid β2-agonism offers symptomatic relief, synergistically improving FEV_1 and symptom scores. In contrast,

ICS in COPD may only benefit a subset with eosinophilic inflammation, as highlighted in the GOLD 2023 guidelines.

The tolerability of ipratropium bromide (a SAMA) noted in Xu et al.'s study [26] extends to LAMAs like glycopyrronium in our cohort. Common AEs (e.g., dry mouth, cough) are typically mild and self-limiting. However, LAMAs exhibit better M3-receptor selectivity than SAMAs, minimizing systemic effects [27].

In PINNACLE-4 study (2020), formoterol/ glycopyrronium (LABA/LAMA) group showed similarly favorable outcomes, with dry mouth (4%) and tachycardia (4%) being the most common complaints. These results are in good agreement with the PINNACLE- 4 study (2020), which reported dry mouth in 6.2% of patients using glycopyrronium-containing regimens [28].

The DYNAGITO trial (2018) study showed a 15% reduction in hospitalization rates [29] The synergistic mechanism is well-established: LABAs activate β2-adrenergic receptors to relax airway smooth muscle, while LAMAs block acetylcholine-induced bronchoconstriction through M3 receptor antagonism. This dual pathway targeting provides more comprehensive bronchodilation than either class alone.

Mirror findings from the 5-year TORCH study extension (2021), which reported significantly better preservation of lung function with combination therapy [30]. The onset and duration of bronchodilatation was more for Glycopyrronium nebulization group than Salbutamol-Ipratropium which also favours the findings of our study signifying Glycopyrronium is seen to be superior to Salbutamol-Ipratropium. Additionally, this study is correlated with minimal to no side effects following nebulisations over the observation period.

Conclusion

Based on the present study, it can be concluded that all the three Nebulisation combinations, Group 1 nebulized with Formoterol-Budesonide, Group 2 nebulized with Salbutamol-Ipratropium, and Group 3 nebulized with Formoterol-Glycopyrronium improved clinical symptoms and spirometric parameters among Moderate to severe Chronic obstructive pulmonary disease patients. Yet, Formoterol-Glycopyrronium (Group 3) is seen to be more superior as far as spirometric values are concerned showing extremely good improvement in FEV1. However Salbutamol-Ipratropium (Group 2) shows the highest cough reduction, sputum reduction and dysponea relief in most of the patients. Formoterol-Budesonide (Group 1) is seen to be less efficacious than the other two Groups. Side effects were almost nonexistent to minimal with all three combination of nebulisations.

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