Kirkuk Journal of Medical Sciences

ORIGINAL ARTICLE

# Optimization of Bronchodilator Treatment in COPD: A Comparison of the Glycopyrrolate/Formoterol Combination vs. Formoterol Alone

Hiwa Fateh Saber [1,*] and Ahmed Duraid Abdullah [2]

[1]*Anesthesia and Intensive Care Department, Hawler Teaching Hospital, Erbil, IRAQ*
[2]*Anesthesia and Intensive Care Department, Tala'afar Hospital, Nineveh City, IRAQ*

[*]*Corresponding author email: hiwasaber1976@gmail.com*

***Received:*** 04 January 2025
***Accepted:*** 03 April 2025
***First published online:*** 03 July 2025

**How to cite this article:**

Saber HF, Abdullah AD. Optimization of bronchodilator treatment in COPD: a comparison of the glycopyrrolate/formoterol combination vs. formoterol alone. *Kirkuk Journal of Medical Sciences*. 2025;13(2):6-11.
DOI: 10.32894/kjms.2025.156364.1137

## ABSTRACT

**Background:** Using a glycopyrrolate/formoterol combination to manage COPD patients is considered a new method. The objectives of this study are to evaluate the effectiveness of the glycopyrrolate/formoterol combination against formoterol alone in optimizing lung function in moderate and severe COPD patients.

**Methods:** Twenty patients with chronic obstructive pulmonary disease were of class II and III according to the ASA classification. Patients were prospectively divided into two groups: group 1 was given glycopyrrolate and formoterol metered dose inhalers, and group 2 was given a formoterol nebulizer alone. Optimization of treatment was assessed on the first day, at the second week, and at the fourth week by lung function tests (FEV1 and FVC).

**Results:** Formoterol alone and a combination of formoterol with glycopyrrolate were well tolerated and optimized lung function. FEV1, FVC, and FEV1/FVC ratio significantly increased (p-value<0.001). However, the combination of glycopyrrolate and formoterol had a better effect on lung function (FEV1 and FVC) in comparison to formoterol alone (p-value<0.001) in 4 weeks of use.

**Conclusion:** Glycopyrrolate/formoterol metered dose inhaler is more effective in the optimization of the condition of patients with COPD disease than a formoterol nebulizer alone.

**Key words**: Bronchodilator; Chronic Obstructive Pulmonary Disease; Formoterol; Glycopyrrolate; Spirometry


ISSN: 2790-0207 (Print), 2790-0215 (Online).

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common preventable lung diseases, which has a partially reversible obstruction in the airflow [1, 2].

There was a mixture of diseases causing airway obstruction, including large airways like chronic bronchitis, small airways like bronchiolitis, and parenchymal destruction like emphysema caused by noxious particles or gases [2, 3].

A lot of anatomical lesions can cause expiratory airflow obstruction, like the narrowing of small airways, fibrosis, and loss of elastic recoil of the lung. Secretions, edema, and inflammation may also be the cause of airflow obstruction [4].

Symptoms of COPD include cough, sputum production, and dyspnea [1]. Spirometry can be used for the diagnosis of COPD. The result of a post-bronchodilator forced expiratory volume in one second (FEV1) 80% of the predicted value and forced expiratory volume in one second/ forced vital capacity ratio (FEV1/FVC) 70% indicates the presence of obstructions of the airflow which is not fully reversible [5].

The treatments are often based on the stages of the COPD, short or long-acting bronchodilators are used depending on their effects on the dyspnea and should be continued if symptomatic benefits are detected. If the patients have persistent or severe symptoms or have exacerbation after management by the long-acting muscarinic antagonist (LAMA) or long-acting beta-agonist (LABA) alone, a combination of LAMA/LABA can be used as treatment. In some patients, long-acting beta-agonist/ inhaled corticosteroid (LABA/ICS) may be the first choice like in patients with a history of asthma [5, 6].

One of the long-acting muscarinic antagonists (LAMA) is a glycopyrrolate, which antagonizes muscarinic receptors in the airway smooth muscles, preventing the acetylcholine action on the muscarinic receptors and leading to bronchodilatation [7]. It is ready-made in by-mouth, intravenous, topical, and inhalator forms. Glycopyrrolate differs from other LAMAs in that it mainly acts on the M3 muscarinic receptors rather than M2 muscarinic receptors which are present in the airway smooth muscles and are the primary cause of bronchoconstriction in patients with COPD [8, 9]. However, glycopyrrolate has many side effects such as blurred vision, loss of visual focus, dry eyes, dry mouth, dry skin, constipation, flushing, dizziness, drowsiness, and palpitations [10].

Formoterol is the fumarate salt form of formoterol. It is a long-acting $\beta_2$ agonist (LABA), and it has a longer duration of action than, for example, salbutamol, which is a short-acting $\beta_2$ agonist, formoterol acts for up to 12 hours while salbutamol acts for 4 to 6 hours. Formoterol can be used for the treatment of asthma and COPD, leading to bronchodilatation of the obstructed airways. Formoterol has 200-fold greater agonist activity at $\beta_2$ receptors than at $\beta_1$ [11], but it has a lot of dangerous side effects like asthma-related death [12], deterioration of disease and acute episodes, paradoxical bronchospasm, cardiovascular effects (increases in pulse rate, systolic and/or diastolic blood pressure), hypokalemia, hyperglycemia, and immediate hypersensitivity reactions (anaphylactic reactions) [11, 13].

This study aims to evaluate the effectiveness of the glycopyrrolate/formoterol combination against formoterol alone in the optimization of lung function in moderate and severe COPD patients.

## MATERIAL AND METHODS

This study is a prospective randomized comparative study, conducted at Rizgary and Hawler teaching hospitals in Erbil/ Iraq between the period of January 2019 and June 2019.

Inclusion criteria: include patients between 45-75years old, and COPD patients of stages 3 and 4 according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 criteria and admitted to the respiratory care unit (R.C.U.) and put on non-invasive continuous positive airway pressure (CPAP) and the study started after two weeks of resolving of acute exacerbation of the disease.

Exclusion criteria: include lung diseases that need long-term oxygen therapy for more than twelve hours/day other than COPD, lung operations like lobectomy, and patient refusal were excluded.

This study included 20 patients (Figure 1), who were randomly distributed into two groups: group 1 (n=10) for a combination of glycopyrrolate/formoterol and group 2 (n=10) for formoterol alone. The patients of group 1 were given a glycopyrrolate/formoterol by metered dose inhaler and learned how to use it at home, each patient received 18/9.6μg in divided doses by inhaler. In the second group (group 2), the patients received 20 μg of formoterol fumarate by nebulizer twice daily.

Three visits were arranged to be done with the patients of both groups, 1st visit was done two weeks after the resolution of the acute exacerbation of the disease (before drug administration), the second visit was two weeks later, and the third visit 4th week after the first visit (after the drug administration). At the time of the visit, it should be assured that the patients ceased the medications for the last 6 hours, with the studied medications also stopped. Spirometry tests (FEV1,

FVC, and FEV1/FVC ratio) were done before and after the drug administration at each visit.

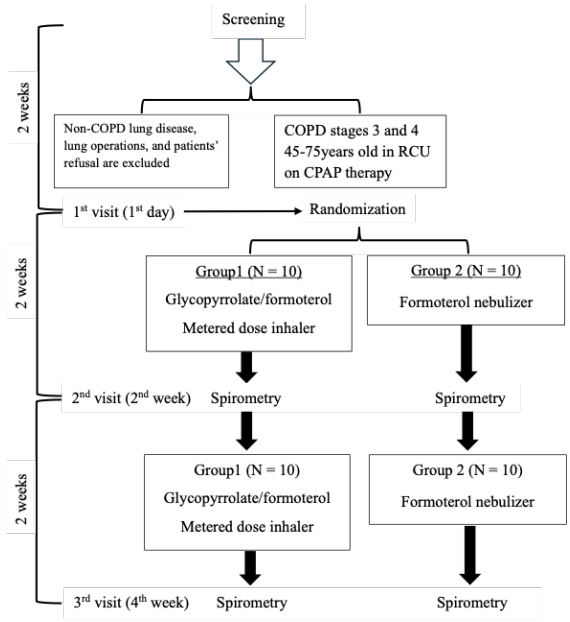


**Figure 1.** Study design

The data were analyzed using the Statistical Package for Social Sciences (SPSS, version 22). To compare the means of the respiratory parameters measured before treatment and those measured two weeks and four weeks after treatment, a paired t-test was employed in each of the study groups. The means of the two study groups were compared using a student's t-test for two independent samples. Any p-value less than or equal to 0.05 was considered to indicate statistical significance. A 95% Confidence Interval (CI) was calculated for the mean differences, and lack of overlap between the groups considered statistically significant.

## RESULTS

Both groups had nonsignificant differences regarding age, sex, weight, and COPD severity (p-value > 0.05). As shown in (Table 1) the means of the respiratory parameters in different periods of the study. In Group 1, the mean force expiratory volume in one second (FEV1) was 1.98 liters before the drug administration, but it increased significantly two weeks after the drug administration and four weeks after the drug administration with a p-value of < 0.001 for both. The same is true for forced vital capacity (FVC) which also significantly increased in the different study periods with a p-value of < 0.001. The ratio of FEV1/FVC also increased significantly from 55.06% to 56.80% to 60.17% in different periods of the study (p < 0.001). The same pattern was also observed among patients of Group 2 who took formoterol only, where it is evident that there was a statistically significant increase in the means of all the respiratory parameters after the drug administration, whether two weeks or four weeks after the drug administration.

The increase in the means of all the respiratory parameters was more in Group 1 than in Group 2, two and four weeks after the drug administration. As presented in (Figure 2), the difference between the values measured two and four weeks after the drug administration minus the values measured before the drug administration was calculated. All the differences were significant except for the FVC after two weeks (p-value = 0.622).

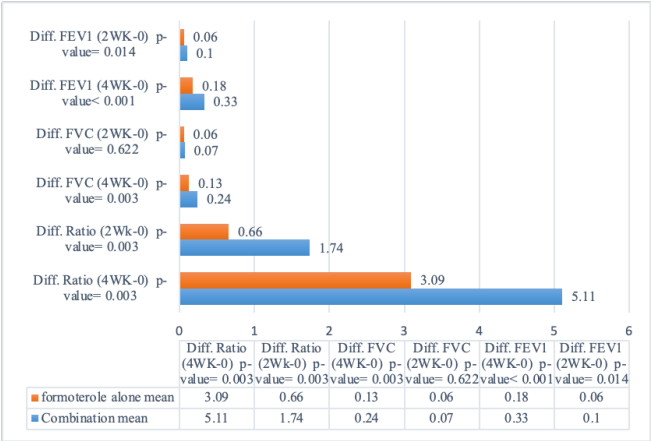


**Figure 2.** Means of the difference in readings of the two study groups.

In Table 2, the 95% confidence interval was calculated for all mean differences between the two study groups. In the Combination group, the mean difference in FEV1 after 2 weeks minus baseline indicates that we can be 95% confident that the true mean improvement in FEV1 after 2 weeks lies between 0.069 and 0.137. This improvement is greater than the mean difference observed in the formoterol-alone group, which ranges from 0.043 to 0.071. Additionally, all other mean differences in the combination group exceed those in the formoterol-alone group, as demonstrated by the results of the 95% confidence interval. The lack of overlap in the confidence intervals for the mean difference in FEV1 (4th week minus 0 week), the mean difference in FVC (4th week minus 0 week), the mean difference in FEV1/FVC Ratio (2nd week minus 0 week), and mean difference in FEV1/FVC Ratio (4th week minus 0 week) suggest statistically significant differences between the combination group and the formoterol alone group, which is greater in the combination group. The results are consistent over both 2-week and 4-week intervals, reinforcing the reliability of the findings.

**Table 1. Means of the respiratory parameters at different times**

| Group | Parameter | First Day | 2 Weeks | 4 Weeks | p-value (0 vs 2wk)* | p-value (0 vs 4wk)* |
|---|---|---|---|---|---|---|
| Combination (n = 10) | FEV1 (L) | 1.98 (0.24) | 2.08 (0.25) | 2.31 (0.28) | **< 0.001** | **< 0.001** |
| | FVC (L) | 3.59 (0.33) | 3.66 (0.33) | 3.83 (0.36) | **< 0.001** | **< 0.001** |
| | FEV1/FVC (%) | 55.06 (4.11) | 56.80 (3.80) | 60.17 (3.30) | **< 0.001** | **< 0.001** |
| Formoterol (n = 10) | FEV1 (L) | 1.88 (0.19) | 1.93 (0.20) | 2.06 (0.20) | **< 0.001** | **< 0.001** |
| | FVC (L) | 3.54 (0.36) | 3.60 (0.37) | 3.67 (0.38) | **< 0.001** | **< 0.001** |
| | FEV1/FVC (%) | 53.20 (3.98) | 53.87 (4.23) | 56.30 (4.59) | **< 0.001** | **< 0.001** |

* *p*-value by paired t-test. Values are expressed as mean (±SD).
FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; SD = Standard Deviation; WK = Week.

**Table 2. Means of the difference in readings of the two study groups**

| | Combination | | | Formoterol alone | | |
|---|---|---|---|---|---|---|
| | Mean | (±SD) | 95% CI | Mean | (±SD) | 95% CI |
| Diff. FEV1 (2WK–0)* | 0.103 | (0.048) | 0.069 - 0.137 | 0.057 | (0.020) | 0.043 - 0.071 |
| Diff. FEV1 (4WK–0)* | 0.330 | (0.095) | 0.262 - 0.398 | 0.180 | (0.035) | 0.155 - 0.205 |
| Diff. FVC (2WK–0)* | 0.070 | (0.035) | 0.045 - 0.095 | 0.063 | (0.032) | 0.040 - 0.086 |
| Diff. FVC (4WK–0)* | 0.240 | (0.084) | 0.180 - 0.300 | 0.130 | (0.059) | 0.088 - 0.172 |
| Diff. Ratio (2WK–0)* | 1.744 | (0.891) | 1.107 - 2.381 | 0.661 | (0.452) | 0.338 - 0.984 |
| Diff. Ratio (4WK–0)* | 5.114 | (1.603) | 3.967 - 6.261 | 3.085 | (0.905) | 2.438 - 3.733 |

*Diff. is the difference between the values measured two or four weeks after drug administration and the value measured before administration.
FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; SD = Standard Deviation; CI = Confidence Interval; WK = Week.

## DISCUSSION

This study shows that long-acting beta-agonists (formoterol fumarate) were effective and well tolerated by the patients; it significantly improved all the pulmonary function tests (FEV1, FVC, and FEV1/FVC) with a p-value < 0.001. However, the use of the combination of LAMA/LABA (Glycopyrrolate/formoterol fumarate) is more beneficial than using them alone in improving lung functions, which is clear in the results of this study where the usage of formoterol alone increases the FEV1 and FVC, especially after 4 weeks of treatment but at the same time the usage of combination therapy shows a greater benefit and more improvement of lung functions. This is supported by the lack of overlap in the 95% confidence interval results for the following mean differences: a mean differences in FEV1 (after 4 weeks minus baseline), a mean difference in FVC (after 4 weeks minus baseline), a mean difference in the FEV1/FVC ratio (after 2 weeks minus baseline), and a mean difference in the FEV1/FVC ratio (after 4 weeks minus baseline).

In an article published in the International Journal of Chronic Obstructive Pulmonary Disease 2018, D'Urzo et al. [14] investigated new developments in optimizing bronchodilator treatment of COPD: a focus on glycopyrrolate/formoterol combination formulated by co-suspension delivery technology, the study has documented that the combination of LAMA/LABA in a fixed dose was useful in improving the symptoms (transition dyspnea index [TDI] score), get better pulmonary function tests (especially FEV1), and better life quality (SGRQ score) comparing to the LAMA or LABA monotherapies. Horita et al. [15] describe in their study comparing the usage of LAMA/LABA versus LABA plus inhaled corticosteroid, they found that the LAMA/LABA combination caused greater improvement of lung functions (FEV1), with decreased risk of infection (pneumonia) and lesser exacerbations. Martinez et al [16] 2020 studied the Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Improves Lung Function versus Monotherapies they concluded that glycopyrrolate/formoterol fumarate metered dose inhaler 18/9.6μg demonstrated superiority over placebo and mono-component metered dose inhalers, fully tolerated by the patients, and therefore can be used as another line of treatment in a moderate to severe COPD patients. Maqsood et al. [17] examined the use of once-daily LABA and LAMA in a combined inhaler versus placebo for COPD patients, showing that the use of a combination of LABA/LAMA as a single daily dose inhaler in mild-to-moderate COPD patients causes better life quality and greater improvement of pulmonary functions. Reisner et al [18] studied the safety and efficacy of 4 doses of glycopyrrolate/formoterol fumarate given through a metered dose inhaler versus the mono-components in a COPD

patient (moderate-to-severe) for 7 days, they confirmed the superiority of the use of glycopyrrolate/formoterol fumarate metered dose inhaler over mono-component with a higher dose in the improvement of pulmonary function.

This study aligns with the aforementioned studies in that the use of a combination of LAMA/LABA is superior to the use of formoterol alone in COPD patients, with more beneficial effects on pulmonary function, particularly FEV1. Limitations of this study include a follow-up duration of only 4 weeks, the inability of patients to produce acceptable and reproducible spirometry, and, due to the small sample size, a relatively high margin of error for the 95% confidence interval, indicating some degree of uncertainty around our estimate. To improve the precision of our estimate, we might consider increasing the sample size in future studies.

## CONCLUSION

The use of a glycopyrrolate/formoterol metered dose inhaler is more effective in the optimization of the condition of patients with COPD disease than a formoterol nebulizer alone. However, it is suggested that researchers in other studies select higher sample sizes and follow up the patients for longer periods.

## ETHICAL DECLARATIONS

- **Ethics Approval and Consent to Participate**

  All subjects gave informed consent for inclusion before participating in the study. The study was approved by the Ethics Committee of the Scientific Council of the Arabic Board for medical specialization (anesthesia and intensive care).

- **Consent for Publication**

  Non.

- **Availability of Data and Material**

  The datasets are available from the corresponding author upon reasonable request.

- **Competing Interests**

  The authors declare that there is no conflict of interest.

- **Funding**

  Self funded.

- **Use of Generative Artificial Intelligence**

  The authors declare that no generative AI was used in the creation or language editing of this manuscript.

- **Authors' Contributions**

  All authors contributed significantly, directly, and intellectually to the work and consented to its publication.

## REFERENCES

[1] Kacmarek RM, Stoller JK, Heuer A. Egan's Fundamentals of Respiratory Care. 12th ed. St. Louis, MO: Elsevier, Health Professions 2019 . eBook, ISBN: 9780323597982.

[2] Ritchie AI, Wedzicha JA, Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. Clinics in chest medicine 2020;41(3):421–438. https://doi.org/10.1016/j.ccm.2020.06.007.

[3] Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. European Respiratory Journal 2019;53(5). https://doi.org/10.1183/13993003.00164-2019.

[4] Agustí A, Hogg JC, Update on the pathogenesis of chronic obstructive pulmonary disease. New England Journal of Medicine 2019;381(13):1248–1256. https://doi.org/10.1056/NEJMra1900475.

[5] Stolz D, Barandun J, Borer H, Bridevaux PO, Brun P, Brutsche M, et al., Diagnosis, prevention and treatment of stable COPD and acute exacerbations of COPD: the Swiss recommendations 2018. Respiration 2018;96(4):382–398. https://doi.org/10.1159/000490551.

[6] Zatloukal J, Brat K, Neumannova K, Volakova E, Hejduk K, Kocova E, et al., Chronic obstructive pulmonary disease–diagnosis and management of stable disease; a personalized approach to care, using the treatable traits concept based on clinical phenotypes. Position paper of the Czech Pneumological and Phthisiological Society. Biomedical Papers of the Medical Faculty of

Palacky University in Olomouc 2020;164(4):325–356. https://doi.org/10.5507/bp.2020.056.

[7] Melani AS, Long-acting muscarinic antagonists. Expert review of clinical pharmacology 2015;8(4):479–501. https://doi.org/10.1586/17512433.2015.1058154.

[8] Tashkin DP, Gross NJ, Inhaled glycopyrrolate for the treatment of chronic obstructive pulmonary disease. International Journal of Chronic Obstructive Pulmonary Disease 2018;13:1873–1888. https://doi.org/10.2147/COPD.S162646.

[9] Bhattacharyya P, Saha D, Chatterjee M, Sengupta S, Dey D, Banerjee R, COPD and glycopyrronium responsiveness assessment: An appraisal. Lung India 2023;40(3):227–234. https://doi.org/10.4103/lungindia.lungindia_376_22.

[10] Gallanosa A, Stevens JB, Hendrix JM, Quick J. Glycopyrrolate. In: StatPearls [Internet] Treasure Island (FL): StatPearls Publishing 2025. Updated 2025 Jan 19. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526035/.

[11] Tashkin DP, Formoterol for the treatment of chronic obstructive pulmonary disease. International Journal of Chronic Obstructive Pulmonary Disease 2020;15:3105–3122. https://doi.org/10.2147/COPD.S273497.

[12] Ray SD. Side Effects of Drugs Annual: A Worldwide Yearly Survey of New Data in Adverse Drug Reactions, vol. 44 of Book series, ScienceDirect. United States: Elsevier 2022 . 1–531.

[13] Hanania NA, Sethi S, Koltun A, Ward JK, Spanton J, Ng D, Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD. International Journal of Chronic Obstructive Pulmonary Disease 2019;14:117–127. https://doi.org/10.2147/COPD.S173595.

[14] D'Urzo A, Cazzola M, Hanania N, Buhl R, Maleki-Yazdi MR, New developments in optimizing bronchodilator treatment of COPD: a focus on glycopyrrolate/formoterol combination formulated by co-suspension delivery technology. International Journal of Chronic Obstructive Pulmonary Disease 2018;13:2805–2819. https://doi.org/10.2147/COPD.S113306.

[15] Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, et al., Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews 2017;(2). https://doi.org/10.1002/14651858.CD012066.pub2.

[16] Martinez FJ, Rabe KF, Lipworth BJ, Arora S, Jenkins M, Martin UJ, et al., Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Improves Lung Function versus Monotherapies in GOLD Category A Patients with COPD: Pooled Data from the Phase III PINNACLE Studies. International Journal of Chronic Obstructive Pulmonary Disease 2020;15:99–106. https://doi.org/10.2147/COPD.S229794.

[17] Maqsood U, Ho TN, Palmer K, Eccles FJR, Munavvar M, Wang R, et al., Once daily long-acting beta2-agonists and long-acting muscarinic antagonists in a combined inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2019;(3). https://doi.org/10.1002/14651858.CD012930.pub2.

[18] Reisner C, Pearle J, Kerwin EM, St Rose E, Darken P, Efficacy and safety of four doses of glycopyrrolate/formoterol fumarate delivered via a metered dose inhaler compared with the monocomponents in patients with moderate-to-severe COPD. International Journal of Chronic Obstructive Pulmonary Disease 2018;13:1965–1977. https://doi.org/10.2147/COPD.S166455.