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EFFECTIVENESS OF TRIPLE THERAPY WITH SINGLE AND MULTIPLE INHALERS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Introduction: *Exacerbations of chronic obstructive pulmonary disease (COPD) contribute to 3 million annual deaths worldwide. Triple therapy (ICS + LABA + LAMA) helps reduce symptoms and exacerbation risk.*
Objective: *To assess the effectiveness and clinical response of single versus multiple inhaler therapy in managing COPD.*
Methods*: A pre-post study was conducted on two groups of COPD patients over 8 weeks. Group 1 (n=47) used a single inhaler, while Group 2 (n=45) used multiple inhalers. Outcomes were measured using the mMRC scale, blood eosinophil levels, and spirometry at weeks 2 and 8.*
Results: *The single-inhaler group significantly reduced mMRC scores, with a median decrease from 4.00 to 2.00 ($p<0.05$). Eosinophil levels also decreased significantly in both groups, with a larger reduction in the single-inhaler group ($p<0.05$). Lung function improved in both groups, but no significant differences were found ($p>0.05$) in terms of time or between-group comparisons.*

Conclusion: *Single-inhaler therapy reduced dyspnea and eosinophil levels more effectively than multiple inhalers. The clinical implications of these findings emphasize the potential benefits of simplifying inhaler regimens for COPD management.*

Keywords: COPD; Triple Therapy; Eosinophils; Single Inhaler; mMRC.

ABSTRAK

Pendahuluan: Eksaserbasi penyakit paru obstruktif kronik (PPOK) menyebabkan 3 juta kematian setiap tahun di seluruh dunia. Terapi triple (ICS + LABA + LAMA) membantu mengurangi gejala dan risiko eksaserbasi.
Tujuan: Menilai efektivitas dan respons klinis terapi inhaler tunggal dibandingkan dengan beberapa inhaler dalam penanganan PPOK.
Metode: Studi pre-post dilakukan pada dua kelompok pasien PPOK selama 8 minggu. Kelompok 1 (n=47) menggunakan inhaler tunggal, sementara Kelompok 2 (n=45) menggunakan beberapa inhaler. Hasil diukur menggunakan skala mMRC, kadar eosinofil darah, dan spirometri pada minggu ke-2 dan ke-8.
Hasil: Kelompok inhaler tunggal menunjukkan penurunan skor mMRC yang signifikan, dengan median menurun dari 4,00 menjadi 2,00 ($p<0,05$). Kadar eosinofil juga menurun secara signifikan pada kedua kelompok, dengan penurunan lebih besar pada kelompok inhaler tunggal ($p<0,05$). Fungsi paru meningkat pada kedua kelompok, tetapi tidak ditemukan perbedaan signifikan ($p>0,05$) terkait waktu maupun perbandingan antar kelompok.
Kesimpulan: Terapi inhaler tunggal lebih efektif dalam mengurangi dispnea dan kadar eosinofil dibandingkan dengan beberapa inhaler. Implikasi klinis dari temuan ini menekankan manfaat potensial dari penyederhanaan regimen inhaler untuk manajemen COPD.

Kata kunci: PPOK; Terapi trilegi; Eosinofil; Inhaler Tunggal; mMRC.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) was the third leading cause of death globally in 2016, with approximately 3 million deaths reported that year.(Hurst et al., 2020) Recent studies have shown that the prevalence of COPD, defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (a forced expiratory volume in one second [FEV1] to forced vital capacity [FVC] ratio < 0.7), is between 9% and 12%. This translates to around 300–400 million individuals worldwide affected by COPD as of 2018–2019.(Boers et al., 2023) The rate of COPD exacerbations is also notably high; more than 50% of COPD patients experience exacerbations during their lifetime, with 23% experiencing ≥2 moderate-to-severe exacerbations annually, and 14% experiencing ≥3 exacerbations per year. COPD exacerbations significantly strain healthcare systems and pose substantial socioeconomic challenges—a burden expected to increase in the coming years.(Hurst et al., 2020; Miravitlles & Ribera, 2017)

The recommended pharmacological management for newly diagnosed COPD patients includes long-acting bronchodilators for Group A based on the modified Medical Research Council Dyspnea Questionnaire (mMRC), such as long-acting muscarinic antagonists (LAMA), long-acting β2 agonists (LABA), or their combination for Group B.(Agustí et al., 2023) For continued management, dual combinations (LAMA-LABA and LABA-ICS) and triple therapy (LAMA-LABA-ICS) are advised when initial treatment becomes less effective.(Khan et al., 2023; Suissa, 2023) However, the precise parameters for escalating to triple therapy remain a key question for clinicians.

Eosinophil counts have emerged as a key biomarker for guiding COPD therapy, as higher eosinophil levels are associated with increased exacerbation risk and response to corticosteroids.(Agustí et al., 2023; Benson et al., 2019; Singh, 2020) GOLD 2020 guidelines set thresholds at >300 cells/μL and <100 cells/μL to identify individuals more and less likely, respectively, to benefit from ICS treatment.(Singh, 2020) In the GOLD 2023 update, patients with persistent exacerbations (with or without dyspnea) on monotherapy with a blood eosinophil count ≥300 cells/μL may be escalated directly to LABA+LAMA+ICS. Similarly, patients with ongoing exacerbations on LABA+LAMA therapy are recommended for LABA+LAMA+ICS if their blood

eosinophil count is ≥100 cells/μL.(Agustí et al., 2023) This approach emphasizes the importance of eosinophil monitoring as a key factor in determining optimal treatment options.(Cui & Chen, 2023)

While the use of eosinophil biomarkers aids in tailoring appropriate therapy, debate remains over single versus multiple inhalers for administering triple therapy. Single inhaler therapy offers simplicity and convenience, whereas multiple inhalers provide greater flexibility and customization.(Cazzola et al., 2024) Some researchers believe that poor inhalation technique correlates with poorer health outcomes in COPD patients, with a higher likelihood of misuse among patients using multiple inhalers that involve various inhaler types compared to those using a single inhaler.(Cho & Gershon, 2022) A systematic review by Zhang et al. (2020) analyzed 24 randomized clinical trials and one prospective study on asthma, finding no significant differences in effectiveness between single and multiple inhaler use.(S. Zhang et al., 2020) However, another systematic review and meta-analysis by Zhang et al. (2022) found that single-inhaler therapy significantly improved FEV1 change from baseline compared to multiple inhalers (mean difference = 0.02 L; 95% CI, 0.00–0.05 L; $P < 0.01$).(L. Zhang et al., 2022)

The variability in research findings highlights the need for further studies to comprehensively evaluate this comparison. The aim of this study is to assess the effectiveness of triple therapy using either a single or multiple inhalers, based on laboratory and clinical parameters in COPD patients.

METHODS

Participant characteristics and research design

The study was conducted at our local health center. The study population consisted of patients diagnosed with COPD who met the inclusion criteria: aged 40 years or older and with blood eosinophil levels above 300 cells/μL, or between 100–300 cells/μL with a history of recurrent moderate exacerbations. Exclusion criteria included a diagnosis of acute respiratory failure at baseline, cystic fibrosis, certain medications that impact inhaler use (such as systemic corticosteroid therapy within the last 3 months), pregnancy or breastfeeding, inability to follow study protocols, severe allergic reactions to any therapy component, and severe heart disease or other medical conditions that could limit participation in the study.

This study utilized a pre-post trial design with two groups of subjects receiving a combination of LAMA+LABA+ICS therapy once a day over 8 weeks. Group 1 consisted of COPD patients using a single inhaler consisted of fluticasone furoate, umeclidinium (as bromide) and vilanterol (as trifenatate), while Group 2 comprised COPD patients using multiple inhalers, either a combination of budesonide + formoterol fumarate dihydrate and tiotropium bromide or a combination of luticasone propionate + salmeterol xinafoate and tiotropium bromide. The use of this option is due to the fact that National Health Insurance Program in Indonesia only provides those as the available coverage. The study aimed to compare the effectiveness and clinical response of these inhaler types in managing COPD. Monitoring was conducted by measuring mMRC dyspnea scale scores and blood eosinophil levels at the beginning and end of the intervention period to evaluate changes in patients' conditions.

Sampling procedures

This study was conducted from October to December 2023. All participants provided informed consent prior to the study. Subjects were randomly assigned to two groups: single inhaler and multiple inhalers. All patients received a triple therapy regimen consisting of LABA, LAMA, and ICS. Each subject was educated on inhaler use, recommended once daily with two puffs per use. The study aimed to evaluate treatment effectiveness, monitored through several variables, including mMRC scores, serum eosinophil levels, and the FEV1/FVC percentage from spirometry. Measurements were taken at three-time points: before treatment, 2 weeks after treatment, and 8 weeks post-treatment. Additionally, all participants underwent a thorough health assessment before treatment to ensure no medical conditions could influence study outcomes.

Data analysis

Data were collected and tabulated in Microsoft Excel. Subject characteristics were presented as mean ± standard deviation for normally distributed data and median (Q1, Q3) if non-normal distribution. The Liliefors test was used for normality testing to determine the appropriate data distribution. Outcome measures included changes in eosinophil counts and mMRC scores over 12 weeks. Statistical analyses were conducted to assess changes within each treatment group using repeated measures ANOVA for normally distributed data, and the Friedman rank test for non-normal data. Post-hoc testing was performed to compare differences between groups. Inter-group differences were analyzed using the independent T-test for normal data distribution, and the Mann-Whitney test for non-normal data distribution. Statistical significance was set at $p < 0.05$, and all analyses were performed using SPSS version 26.0.

RESULTS AND DISCUSSION

The study included 92 subjects, with 47 receiving single-inhaler treatment and 45 receiving multiple-inhaler treatment, of which 19 receiving a combination of budesonide + formoterol fumarate dihydrate and tiotropium bromide, and 26 receiving combination of luticasone propionate + salmeterol xinafoate and tiotropium bromide. The median age of participants was 66.5 years (Q1 = 56.5; Q3 = 73.75). Baseline mMRC scores had a median of 4.00 (Q1 = 3.00; Q3 = 4.00), indicating a high level of dyspnea. After 2 weeks, mMRC scores decreased to a median of 2.00 (Q1 = 2.00; Q3 = 3.00) and remained at a median of 2.00 (Q1 = 1.00; Q3 = 2.00) after 8 weeks, showing a significant improvement in dyspnea. Baseline eosinophil levels had a median of 483.50 cells/µL (Q1 = 305.75; Q3 = 918.00), which decreased to a median of 369.00 cells/µL (Q1 = 211.00; Q3 = 725.50) after 2 weeks and reached a median of 308.50 cells/µL (Q1 = 267.50; Q3 = 308.50) after 8 weeks, indicating a downward trend in eosinophil levels throughout the study period.

Table 1
Subject Characteristics and Response to Triple Therapy Based on Inhaler Type

Characteristics	Triple therapy		N (%)	P value*
	Single-inhaler	Multiple inhaler		
Sex [n (%)]				
Male	46 (52.27)	42 (47.72)	95.65%	
Female	1 (25)	3 (75)	4.34%	
Age [Mean ± SD]	65.51 ± 12.47	64.44 ± 10.36		0.492
mMRC [Median (Q1,Q3)]				
Baseline	4.00 (3.00, 4.00)	3.00 (2.00, 4.00)		0.000
2 weeks	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)		0.907
8 weeks	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)		0.044
Eosinophil (cells/ µL) [Median (Q1,Q3)]				
Baseline	410 (282, 612)	638 (368, 1263.50)		0.007
2 weeks	261 (162, 401)	646 (340.5, 946)		0.000
8 weeks	295 (274, 317)	452 (222, 805)		0.005
Spirometry (FEV1/FVC; %) [Median (Q1,Q3)]				
Baseline	71.15 (66.67, 77.06)	67.79 (54.31, 73.70)		0.009
2 weeks	80.25 (75.01, 84.28)	71.83 (68.56, 75.13)		0.000
8 weeks	85.32 (79.63, 90.87)	79.65 (72.06 – 86.58)		0.001

**Mann-Whitney, p< 0.05 significant*

The mMRC score exhibited a significant baseline difference, where subjects using a single inhaler had a median mMRC score of 4.00 (3.00, 4.00), higher than the multiple-inhaler group with a score of 3.00 (2.00, 4.00) ($p=0.000$, $p < 0.05$). After 2 weeks, no significant difference was observed between the two groups ($p=0.907$, $p > 0.05$). However, by 8 weeks, the mMRC score continued to

show improvement in both groups, with a significantly greater reduction in the single-inhaler group compared to the multiple-inhaler group (p=0.044, p < 0.05).

Serum eosinophil levels also showed significant differences between the groups. At baseline, the median eosinophil count in the single-inhaler group was 410 (282, 612) cells/µL, lower than in the multiple-inhaler group, which had 638 (368, 1263.50) cells/µL (p=0.007, p < 0.05). After 2 and 8 weeks, the single-inhaler group showed a greater reduction in serum eosinophils compared to the multiple-inhaler group (p<0.05).

For spirometry based on FEV1/FVC percentage, both groups showed improvements in lung function. The single-inhaler group had a median baseline spirometry of 71.15% (66.67, 77.06), higher than the multiple-inhaler group at 67.79% (54.31, 73.70) (p=0.009, p < 0.05). After 2 and 8 weeks, the single-inhaler group continued to demonstrate a significant improvement in lung function compared to the multiple-inhaler group (p<0.05 at both times). The study observed a notable improvement in lung function in the single inhaler group (+20%, p<0.05), compared to the multiple inhaler group (+17%, p>0.05).

Table 2
Comparison of Rankings and Measurements for Single and Multiple Inhalers

Variable	Median (Q1, Q3)	Ranks	P *value**
mMRC – Single Inhaler			0.000
Baseline	4.0 (3.00, 4.00)	2.99	
2 weeks	2.00 (2.00, 3.00)	1.82	
8 weeks	2.00 (1.00, 2.00)	1.19	
mMRC – Multiple Inhaler			0.000
Baseline	3.00 (2.00, 4.00)	2.53	
2 weeks	2.00 (2.00, 3.00)	1.91	
8 weeks	2.00 (1.00, 2.00)	1.56	
Eosinophil - Single Inhaler			0.000
Baseline	410 (282, 612)	2.60	
2 weeks	261 (162, 401)	1.60	
8 weeks	295 (274, 317)	1.81	
Eosinophil – Multiple Inhaler			0.000
Baseline	638 (368, 1263.50)	2.33	
2 weeks	646 (340.5, 946)	2.16	
8 weeks	452 (222, 805)	1.51	
Spirometry - Single Inhaler			0.918
Baseline	71.15 (66.67, 77.06)	2.04	
2 weeks	80.25 (75.01, 84.28)	2.00	
8 weeks	85.32 (79.63, 90.87)	1.96	
Spirometry - Multiple Inhaler			0.701
Baseline	67.79 (54.31, 73.70)	2.09	
2 weeks	71.83 (68.56, 75.13)	1.91	
8 weeks	79.65 (72.06 – 86.58)	2.00	

* Friedman *Rank*, p < 0.05 significant

In this analysis, the Friedman Rank test was performed to assess median differences in mMRC, eosinophil, and spirometry variables between the single and multiple-inhaler groups at three-time points: baseline, 2 weeks, and 8 weeks. For mMRC, both the single- and multiple-inhaler groups showed p values of 0.000 (p < 0.05), indicating significant differences in median mMRC scores across measurement times. The mean rank for the single-inhaler group decreased from 2.99 at baseline to 1.82 at 2 weeks and 1.19 at 8 weeks, indicating significant improvement in mMRC symptoms with the single-inhaler therapy. In the multiple-inhaler group, mean ranks also showed a downward trend, from 2.53 at baseline to 1.91 at 2 weeks and 1.56 at 8 weeks, indicating similar improvement.

Significant differences were also observed in serum eosinophil levels (p = 0.000, p < 0.05). The mean rank for the single-inhaler group showed a decrease in median eosinophil levels from 2.60 at baseline to 1.60 at 2 weeks and a slight increase to 1.81 at 8 weeks. For the multiple-inhaler group,

mean ranks decreased from 2.33 at baseline to 2.16 at 2 weeks and 1.51 at 8 weeks, indicating a significant reduction in eosinophil levels after treatment.

However, in the spirometry assessment, the p value for the single-inhaler group was 0.918 ($p > 0.05$), and for the multiple-inhaler group, it was 0.701 ($p > 0.05$), indicating no significant differences across measurement times. Although there was an increase in median spirometry values for both inhaler types from baseline to 8 weeks, the increase was not statistically significant. This analysis suggests that both single and multiple inhalers effectively reduced mMRC scores and eosinophil levels but did not show a significant change in spirometry results.

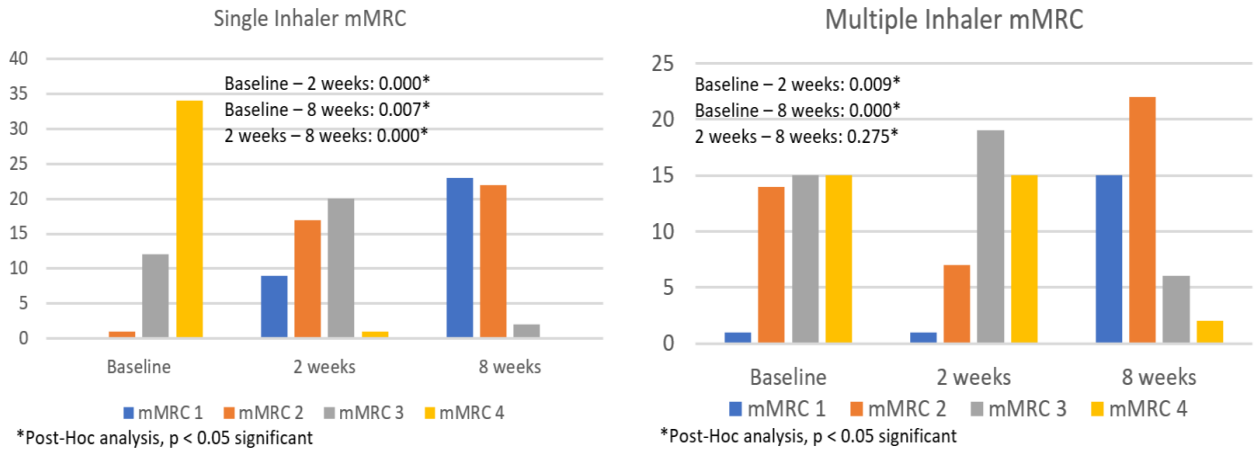

Figure 1. Post-hoc analysis for mMRC and eosinophil variables.

Post-hoc analysis was conducted to compare differences in mMRC and eosinophil levels at different measurement times after the Friedman test indicated significant results. For mMRC with the single-inhaler therapy, significant differences were found between 8 weeks and 2 weeks ($p = 0.007$, $p < 0.05$), as well as between 8 weeks and baseline ($p < 0.001$, $p < 0.05$). Additionally, there was a significant difference between 2 weeks and baseline ($p < 0.001$, $p < 0.05$). For the multiple-inhaler group, there was no significant difference between mMRC scores at 8 weeks and 2 weeks ($p = 0.275$, $p > 0.05$). However, significant differences were found between mMRC scores at 8 weeks and baseline ($p < 0.001$) and between 2 weeks and baseline ($p = 0.009$, $p < 0.05$).

The analysis for serum eosinophils with single-inhaler therapy showed a significant difference between eosinophil levels at 2 weeks and baseline ($p = 0.000$, $p < 0.05$), and between 8 weeks and baseline ($p = 0.001$), but no significant difference between eosinophil levels at 2 weeks and 8 weeks ($p = 0.907$, $p > 0.05$). For the multiple-inhaler therapy, there were significant differences between eosinophil levels at 8 weeks and 2 weeks ($p = 0.007$, $p < 0.05$), and between 8 weeks and baseline ($p = 0.000$, $p < 0.05$), while no significant difference was found between eosinophil levels at 2 weeks and baseline ($p = 1.000$, $p > 0.05$).

This study aimed to evaluate the effects of single and multiple inhalers in COPD patients, specifically in assessing the improvement of dyspnea symptoms measured using the mMRC score, as well as changes in serum eosinophil levels and spirometry results. The study involved 92 subjects, with 47 using a single inhaler and 45 using multiple inhalers. The median age of participants was 66.5 years, indicating that most subjects were in the elderly age group, commonly affected by COPD. Advanced age is a proven risk factor for COPD, partly due to its gradual progression. Most exposures, such as smoking, vehicle emissions, or occupational exposure, take time to cause COPD.(Kukrety et al., 2018) The prevalence of COPD is also 2 to 3 times higher in individuals over 60 compared to younger age groups.(MacNee, 2016)

The results of this study showed a significant improvement in mMRC scores in both treatment groups, both single and multiple inhalers. Before treatment, the median mMRC score indicated a high

level of dyspnea, at 4.00 (Q1 = 3.00; Q3 = 4.00) in the single inhaler group and 3.00 (Q1 = 2.00; Q3 = 4.00) in the multiple inhaler group. After 2 weeks of treatment, there was a significant reduction in mMRC scores in both groups, with the median remaining at 2.00 (Q1 = 2.00; Q3 = 3.00). This reduction indicates that the treatment effectively reduced dyspnea symptoms significantly, leading to noticeable improvements in patients' quality of life. This finding aligns with Cheng et al. (2020), which showed that triple therapy significantly improved lung function and symptoms.(Cheng et al., 2020) The mMRC score is thought to play an essential role in FEV1 improvement and patients' overall condition. In a study by Ohtsuka et al. (2023), a combination of triple therapy significantly improved FVC and FEV1 inspiratory capacity compared to pre-intervention values. This improvement was associated with higher mMRC scores, suggesting that patients with more severe dyspnea symptoms (higher mMRC scores) tend to experience a greater FEV1 increase (OR 2.36, $P < .01$) with triple therapy.(Ohtsuka et al., 2023)

However, at the 8-week measurement, although both groups still showed the same median mMRC score (2.00), the single inhaler group experienced a more significant reduction than the multiple inhaler group ($p = 0.044$). Based on this result, we suggest that single inhalers may be more effective in reducing long-term dyspnea symptoms due to differences in patient compliance and treatment adherence. A retrospective cohort study by Halpin et al. (2022) supports this argument, noting that single inhaler users have significantly higher compliance rates than multiple inhaler users over 6, 12, and 18 months ($p < 0.001$).(Halpin et al., 2022) The dosing regimen complexity required for multiple inhaler use (e.g., multiple inhalers with different daily frequencies or inhalation techniques) is often associated with lower real-world compliance and treatment persistence. Conversely, a simpler single inhaler makes it easier for patients to consistently maintain therapy use, which is critical for achieving optimal clinical outcomes.(Beeh et al., 2024; Halpin et al., 2021)

In this study, a significant decrease in serum eosinophil levels was observed in both the single and multiple inhaler groups. This aligns with the clinical improvements reflected by improved lung function and reduced dyspnea symptoms. Eosinophils are an essential biomarker in airway inflammation, especially in COPD, often linked to the response to inhaler therapy.(David et al., 2021; Tashkin & Wechsler, 2018) Under normal conditions, eosinophils remain inactive in the blood; after exposure to pro-inflammatory mediators, some become active before migrating to the site of inflammation. After reaching the lungs, pro-inflammatory mediators—including major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin, cytokines, chemokine ligands/CCL, tumor necrosis factor (TNF), and transforming growth factor [TGF]α/β)—released by eosinophils contribute to sustained inflammation and tissue damage.(Tashkin & Wechsler, 2018) This inflammatory state also plays a role in the increased risk of exacerbations. A systematic review and meta-analysis by Harries et al. (2020) showed that the independent effect of ICS on reducing COPD exacerbation risk is 20% at serum eosinophils ≥2% (RR, 0.80; 95% CI, 0.74–0.85), 35% at serum eosinophils ≥150 cells/μL (RR, 0.65; 95% CI, 0.52–0.79), and 39% at serum eosinophils ≥300 cells/μL (RR, 0.61; 95% CI, 0.44–0.78).(Harries et al., 2020)

Spirometry analysis results showed no significant difference in lung function improvement between the single and multiple inhaler groups over the measurement period (p-value > 0.05). Although there was an increase in median spirometry values from baseline to 8 weeks in both groups, this increase was not statistically significant to indicate that one inhaler method was superior in improving lung function. This does not align with previous theories and studies, which generally show significant lung function improvement from triple therapy use.(Kerstjens et al., 2021; Zheng et al., 2018) The findings are more similar to a retrospective study by Lin et al. (2023), which found higher mean scores on the COPD Assessment Test (CAT), more patients with mMRC >1, but lower mean FEV1% and FEV1/FVC values in single inhaler patients compared to multiple inhaler patients.(Lin et al., 2023) These findings may reflect that both single and multiple inhalers can provide relatively similar effects in improving lung function, although other factors such as patient compliance with therapy or individual variability may play a role in determining the final outcomes.

The findings align with recent studies highlighting the importance of inhaler regimen simplicity in improving patient adherence. Previous research has demonstrated that complex inhaler regimens

contribute to improper usage, leading to suboptimal disease control. Although there was no significant difference in spirometry results, improvements in dyspnea symptoms and reduced eosinophilic inflammation in both groups demonstrate the effectiveness of therapy in improving patients' overall clinical condition. Spirometry may not be the only parameter to consider when assessing treatment success in COPD or asthma patients, especially when clinical and inflammatory improvements are more apparent.

LIMITATIONS OF THE STUDY

This study has some limitations that should be considered. First, the relatively small sample size may limit the generalization of these results to a broader population. Another limitation is the inability to control external variables, such as patient adherence to inhalation therapy, which may affect the results. Furthermore, this study did not include further analysis of other factors that may contribute to different outcomes, such as health history and environmental factors.

The findings of this study have significant implications for clinical practice, particularly in selecting appropriate inhalation therapy based on patient profiles. Physicians may consider recommending a single inhaler as an initial treatment strategy for patients with high mMRC scores and increased eosinophil levels to improve patients' quality of life and reduce dyspnea symptoms. Additionally, it is essential to conduct continuous monitoring of patients to evaluate the effectiveness of therapy and make necessary adjustments.

CONCLUSION

This study suggests that single inhalers are more effective in reducing dyspnea symptoms based on mMRC and eosinophil levels compared to multiple inhalers within 8 weeks. These findings highlight the need for further studies with larger sample sizes and longer follow-up durations to confirm these results and explore other potential variables that may affect the effectiveness of inhalation therapy. This study contributes to a better understanding of therapeutic options that can improve the quality of life for patients with respiratory diseases.

ETHICAL CONSIDERATIONS

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Conflict of Interest
The authors declare no conflict of interest.

REFERENCES

Agustí, A., Celli, B. R., Criner, G. J., Halpin, D., Anzueto, A., Barnes, P., Bourbeau, J., Han, M. L. K., Martinez, F. J., de Oca, M. M., Mortimer, K., Papi, A., Pavord, I., Roche, N., Salvi, S., Sin, D. D., Singh, D., Stockley, R., López Varela, M. V., … Vogelmeier, C. F. (2023). Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *The European Respiratory Journal*, *61*(4). https://doi.org/10.1183/13993003.00239-2023

Beeh, K. M., Rothnie, K. J., Claussen, J., Hardtstock, F., Knapp, R. K., Wilke, T., Czira, A., Compton, C., & Ismaila, A. S. (2024). Characteristics of Users and New Initiators of Single- and Multiple-Inhaler Triple Therapy for Chronic Obstructive Pulmonary Disease in Germany. *International Journal of Chronic Obstructive Pulmonary Disease*, *19*, 945–956. https://doi.org/10.2147/COPD.S431291

Benson, V. S., Pascoe, K. C., Siddall, J., Small, M., & Müllerová, H. (2019). Exacerbation Frequency And Eosinophil Counts Among Patients With COPD Currently Prescribed Triple Therapy.

International Journal of Chronic Obstructive Pulmonary Disease, *14*, 2711. https://doi.org/10.2147/COPD.S217503

Boers, E., Barrett, M., Su, J. G., Benjafield, A. V., Sinha, S., Kaye, L., Zar, H. J., Vuong, V., Tellez, D., Gondalia, R., Rice, M. B., Nunez, C. M., Wedzicha, J. A., & Malhotra, A. (2023). Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. *JAMA Network Open*, *6*(12), E2346598. https://doi.org/10.1001/JAMANETWORKOPEN.2023.46598

Cazzola, M., Ora, J., Maniscalco, M., & Rogliani, P. (2024). A clinician's guide to single vs multiple inhaler therapy for COPD. *Expert Review of Respiratory Medicine*, *18*(7), 457–468. https://doi.org/10.1080/17476348.2024.2384702

Cheng, W. C., Wu, B. R., Liao, W. C., Chen, C. Y., Chen, W. C., Hsia, T. C., Tu, C. Y., Chen, C. H., & Hsu, W. H. (2020). When to Use Initial Triple Therapy in COPD: Adding a LAMA to ICS/LABA by Clinically Important Deterioration Assessment. *International Journal of Chronic Obstructive Pulmonary Disease*, *15*, 3375. https://doi.org/10.2147/COPD.S279482

Cho, E. E., & Gershon, A. S. (2022). Single vs Multiple Inhaler Triple Therapy in the COPD Population. *Chest*, *162*(5), 947–948. https://doi.org/10.1016/j.chest.2022.09.004

Cui, Y., & Chen, Y. (2023). Blood eosinophils in chronic obstructive pulmonary disease: A potential biomarker. *Journal of Translational Internal Medicine*, *11*(3), 193. https://doi.org/10.2478/JTIM-2023-0096

David, B., Bafadhel, M., Koenderman, L., & De Soyza, A. (2021). Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. *Thorax*, *76*(2), 188–195. https://doi.org/10.1136/THORAXJNL-2020-215167

Halpin, D. M. G., Rothnie, K. J., Banks, V., Czira, A., Compton, C., Wood, R., Tritton, T., Massey, O., Wild, R., Snowise, N., Nikitin, K., Sharma, R., Ismaila, A. S., & Vogelmeier, C. F. (2022). Comparative Adherence and Persistence of Single- and Multiple-Inhaler Triple Therapies Among Patients with Chronic Obstructive Pulmonary Disease in an English Real-World Primary Care Setting. *International Journal of Chronic Obstructive Pulmonary Disease*, *17*, 2417. https://doi.org/10.2147/COPD.S370540

Halpin, D. M. G., Worsley, S., Ismaila, A. S., Beeh, K. M., Midwinter, D., Kocks, J. W. H., Irving, E., Marin, J., Martin, N., Tabberer, M., Snowise, N. G., & Compton, C. (2021). INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. *ERJ Open Research*, *7*(2). https://doi.org/10.1183/23120541.00950-2020

Harries, T. H., Rowland, V., Corrigan, C. J., Marshall, I. J., McDonnell, L., Prasad, V., Schofield, P., Armstrong, D., & White, P. (2020). Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: Systematic review and meta-analysis. *Respiratory Research*, *21*(1), 1–15. https://doi.org/10.1186/S12931-019-1268-7/FIGURES/9

Hurst, J. R., Skolnik, N., Hansen, G. J., Anzueto, A., Donaldson, G. C., Dransfield, M. T., & Varghese, P. (2020). Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *European Journal of Internal Medicine*, *73*, 1–6. https://doi.org/10.1016/J.EJIM.2019.12.014

Kerstjens, H. A. M., Abbott, C., Boulet, L.-P., Chang, S., Chupp, G., Crawford, J., Hanania, N. A., Nathan, R., Oppenheimer, J., Pizzichini, E., Sagara, H., & Busse, W. (2021). CAPTAIN: Effects of triple therapy on FEV1 response in patients with inadequately controlled asthma on ICS/LABA. *European Respiratory Journal*, *58*(suppl 65), PA3386. https://doi.org/10.1183/13993003.CONGRESS-2021.PA3386

Khan, K. S., Jawaid, S., Memon, U. A., Perera, T., Khan, U., Farwa, U. E., Jindal, U., Afzal, M. S., Razzaq, W., Abdin, Z. U., & Khawaja, U. A. (2023). Management of Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in Hospitalized Patients From Admission to Discharge: A Comprehensive Review of Therapeutic Interventions. *Cureus*, *15*(8). https://doi.org/10.7759/CUREUS.43694

Kukrety, S. P., Parekh, J. D., & Bailey, K. L. (2018). Chronic obstructive pulmonary disease and the hallmarks of aging. *Lung India : Official Organ of Indian Chest Society*, *35*(4), 321.

https://doi.org/10.4103/LUNGINDIA.LUNGINDIA_266_17
Lin, L., Liu, C., Cheng, W., Song, Q., Zeng, Y., Li, X., Deng, D., Liu, D., Chen, Y., Cai, S., & Chen, P. (2023). Comparison of treatment persistence, adherence, and risk of exacerbation in patients with COPD treated with single-inhaler versus multiple-inhaler triple therapy: A prospective observational study in China. *Frontiers in Pharmacology*, *14*, 1147985. https://doi.org/10.3389/FPHAR.2023.1147985/FULL
MacNee, W. (2016). Is Chronic Obstructive Pulmonary Disease an Accelerated Aging Disease? *Annals of the American Thoracic Society*, *13 Suppl 5*, S429–S437. https://doi.org/10.1513/ANNALSATS.201602-124AW
Miravitlles, M., & Ribera, A. (2017). Understanding the impact of symptoms on the burden of COPD. *Respiratory Research*, *18*(1), 1–11. https://doi.org/10.1186/S12931-017-0548-3/FIGURES/3
Ohtsuka, K., Harada, N., Horiuchi, A., Umemoto, S., Kurabatashi, R., Yui, A., Yamamura, H., Shinka, Y., & Miyao, N. (2023). Therapeutic Response to Single-Inhaler Triple Therapies in Moderate-to-Severe COPD. *Respiratory Care*, *68*(3), 330. https://doi.org/10.4187/RESPCARE.10188
Singh, D. (2020). Blood Eosinophil Counts in Chronic Obstructive Pulmonary Disease: A Biomarker of Inhaled Corticosteroid Effects. *Tuberculosis and Respiratory Diseases*, *83*(3), 185. https://doi.org/10.4046/TRD.2020.0026
Suissa, S. (2023). Triple therapy in COPD: understanding the data. *ERJ Open Research*, *9*(1). https://doi.org/10.1183/23120541.00615-2022
Tashkin, D. P., & Wechsler, M. E. (2018). Role of eosinophils in airway inflammation of chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease*, *13*, 335. https://doi.org/10.2147/COPD.S152291
Zhang, L., Wang, X., Zhang, Y., & Chen, W. (2022). Efficacy and Safety of Single Inhaler Triple Therapy Versus Separate Triple Therapy in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. *Clinical Therapeutics*, *44*(6), 859–873. https://doi.org/10.1016/J.CLINTHERA.2022.04.004
Zhang, S., King, D., Rosen, V. M., & Ismaila, A. S. (2020). Impact of Single Combination Inhaler versus Multiple Inhalers to Deliver the Same Medications for Patients with Asthma or COPD: A Systematic Literature Review. *International Journal of Chronic Obstructive Pulmonary Disease*, *15*, 417. https://doi.org/10.2147/COPD.S234823
Zheng, Y., Zhu, J., Liu, Y., Lai, W., Lin, C., Qiu, K., Wu, J., & Yao, W. (2018). Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis. *The BMJ*, *363*. https://doi.org/10.1136/BMJ.K4388