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Research Article

ASSESSMENT OF THE EFFECTIVENESS OF TRIPLE-DRUG THERAPY OVER DUAL-DRUG THERAPY IN COPD PATIENTS – A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Objectives: The current study aimed to determine the efficacy of triple-drug combination therapy over double-drug combination therapy.

Methods: A retrospective cohort observational study was conducted on a total number of 240 patients at Medicover Hospitals. The study encompassed 240 subjects suffering from chronic obstructive pulmonary disease (COPD), and parameters such as demographics, symptoms, comorbid conditions, and forced expiratory volume (FEV1)/forced vital capacity (FVC) ratio were assessed. The data were compiled and analyzed by applying unpaired t-tests and Chi-square tests using software.

Results: Male patients with 61–70 years of age were prone to suffer from COPD as compared to the other age groups. With regard to the symptoms associated with COPD, shortness of breath and cough were more remarkable in >100 and >90 patients, followed by fever symptoms. In the COPD patients with dual therapy, FEV1:FVC ratio of over 3 months, 30% (n=36) of patients had a FEV1:FVC ratio of <0.7, which increased to 90% (n=108) in the post-treatment, whereas those with a ratio >0.7 decreased from 70% (n=84) to 10% (n=12). 16.67% of patients had a FEV1:FVC ratio of <0.7, which was raised to 93.33% after treatment. This significant shift (**p<0.001) demonstrated a substantial improvement in lung function following triple-drug therapy.

Conclusion: The study demonstrated that triple-drug therapy was effective over dual-drug therapy in the management of COPD by marked improvement in lung function and, thereby reduction in exacerbation rates.

Keywords: Chronic obstructive pulmonary disease, Retrospective, Cohort study, Triple therapy, Dual therapy.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by escalated airflow accompanied with respiratory symptoms such as cough, sputum production, and dyspnea. It also presents a significant global health issue attributed to substantial morbidity and mortality worldwide [1]. COPD has historically gotten insufficient attention from medical professionals and academics despite its prevalence and severity. This underscores an urgent need for increased awareness and efficient management options. Globally, COPD affects millions of individuals that leads to chronic morbidity worldwide. Globally, a study of the Global Burden of Disease revealed that an estimated 210 million people suffered from COPD, with the disease being blamed for almost 3 million fatalities per year [2]. Unbelievably, COPD is becoming more commonplace and is expected to overtake all other causes of death globally by 2030 [3]. Alarmingly, the prevalence of COPD is on the rise, and by 2030, it is projected to become the third leading cause of mortality worldwide [3]. These figures highlight a critical need for all-encompassing preventative and therapeutic approaches to lessen the growing COPD burden.

COPD is manifested by chronic inflammation and structural changes in the airways and lungs that lead to limit airflow and impairment of gaseous exchange [4]. The pathophysiology of COPD involves chronic obstructive bronchiolitis, characterized by airway inflammation and fibrosis, together with emphysema, distinguished by destruction of lung parenchyma and loss of elasticity [4]. However, exposure to environmental tobacco smoke, indoor and outdoor pollution, occupational dust and chemicals, socioeconomic factors, and respiratory infections also contribute to the development and progression of COPD smoking is the primary risk factor for COPD, accounting for the majority of the cases.

Globally, the prevalence of COPD varies; higher rates are seen in areas where smoking is more common and there is more pollution in the air [5]. According to estimates, more than 1% of people globally may be affected by COPD, with prevalence rates greater in those 40 years of age or older [6].

The range of incidence rates is 2–6/1,000 person-years, contingent upon the diagnostic criteria and demographics of the population. A higher percentage of men, elderly people, and smokers are affected by COPD. However, COPD is becoming more common in women, and there have been documented sex-specific variations in symptoms and prognoses [7]. The financial toll that COPD takes is high, and hospital stays and outpatient visits are major contributors to the overall expense of treating the disease. COPD presents an extensive variety of symptoms, such as cough, sputum production, dyspnea, wheezing, and chest tightness [8]. Dyspnea, being progressive and exertional, showed a significant impact on patients' quality of life and functional capacity. The disease also follows variables punctuated by exacerbations, which contribute to the progression of disease, decline in lung function, and increased mortality risk [9].

Acute exacerbation of COPD (AECOPD) can be treated pharmacologically with systemic corticosteroids, rapid-acting bronchodilators, and, in certain cases, antibiotics. Resuming baseline clinical status and quality of life, preventing abrupt respiratory failure and mortality, preventing hospitalization or shortening hospital stays, and resolving exacerbation symptoms are the objectives of treatment. In the therapy, bronchodilators, including long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), form a cornerstone of COPD treatment, improving airflow and controlling symptoms [10]. Recent evidence suggested that triple therapy, combining LABAs, LAMAs,

and inhaled corticosteroids (ICS), may provide further advantages for specific COPD patient subgroups, especially for those who have a severe illness or recurrent exacerbations. Triple therapy aims to reduce the risk of exacerbation and improve lung function by addressing both inflammation and bronchodilation.

In the assessment of COPD, Spirometry is a fundamental diagnostic technique that offers vital information about the lung function of those who are afflicted. There are two vital parameters: Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), both of which play crucial roles in evaluating the severity and progression of COPD. The FEV1 is the amount of air that is forcibly expelled after the maximal inhalation [11]. This measure reflects the level of blockage in the airways and acts as a direct indicator of airflow limitation. In COPD, reduced FEV1 values are indicative of significant airflow limitation stemming from bronchoconstriction, inflammation, and structural changes within the lungs. Moreover, the FEV1 values that are expressed as a percentage of predicted values for factors such as age, sex, height, and ethnicity, assist in classifying the severity of COPD, directing medical professionals in choosing courses of action and prognostic evaluations [11].

FVC provides essential insights into overall lung capacity and the strength of respiratory muscles. In COPD, diminished FVC values often result from factors such as air trapping, reduced lung elasticity, and impaired respiratory function. These values serve as crucial markers for the assessment of the severity of COPD and for monitoring disease progression over time [12]. The ratio of FEV1 to FVC, known as the FEV1/FVC ratio, emerges as a key diagnostic parameter in COPD evaluation. This ratio reflects the proportion of the vital capacity forcefully exhaled in the first second, with a reduced FEV1/FVC ratio indicative of airflow obstruction. In COPD diagnosis, a FEV1/FVC ratio below the established threshold (commonly 0.70 or 70%) signifies airflow limitation that is characteristic of the disease [12]. Furthermore, the severity of airflow obstruction is often stratified based on the magnitude of this ratio, aiding in the classification of COPD into distinct stages ranging from mild to very severe [13]. The present study was taken up to evaluate the effectiveness of triple-drug therapy over dual-drug therapy in COPD patients with respect to the exacerbation rates and improvements in lung function measured by the FEV1:FVC ratio.

METHODS

Study area, period and design

The study was observational and retrospective which was conducted in Hospitals, Hyderabad. It was carried out for a period of 6 months from January 2023 to June 2023.

Determination of sample size

The study encompassed 240 subjects suffering from COPD, divided equally into two groups, each comprising 120 subjects. Group A denoted (n=120) patients who underwent dual therapy for COPD, whereas Group B (n=120) consisted of patients who underwent triple therapy.

Study criteria

Inclusion criteria

The study included both male and female patients ≥18 years of age diagnosed with COPD who have been prescribed either triple-drug therapy or dual-drug therapy over a specified period.

Exclusion criteria

The study excluded patients with other respiratory conditions, pediatric, pregnant, and breastfeeding mothers.

Ethics statement

Patient privacy and anonymity were guaranteed by the study's adherence to ethical standards. The appropriate institutional review board or ethics committee of the KIMS Foundation and Research Centre, Secunderabad, Telangana, granted ethical approval.

Data collection and Study procedure

The data were collected from electronic medical records and pharmacy databases were used to identify the eligible patients and extract the relevant data. The key variables that were collected include demographic information, smoking history, COPD severity, medication use, exacerbation history, and lung function tests (including FEV1:FVC ratio).

Statistical analysis

The collected data were entered into Microsoft Excel Worksheet and was taken into IBM SPSS Statistic for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) software for calculation of frequency, percentage, mean, standard deviation, and probability value. Unpaired and Chi-Square Tests were applied to analyze the data. A $p<0.001$ was deemed statistically significant.

RESULTS

The present observational study was conducted on 240 subjects in the Department of Pulmonology bearing protocol number KFRC/SRC/APR/0012/2015 at the KIMS Foundation and Research Centre. This study was carried out to compare the efficacy of triple combination over dual combination in patients with COPD. In Group A, 76 subjects (63.33%) were male, and 44 subjects (36.67%) were female. Similarly, in Group B, 85 subjects (70.83%) were male, and 35 subjects (29.17%) were female. Statistical analysis, indicated by the $p=0.999$, demonstrated no significant difference in gender distribution between the two groups, ensuring demographic comparability for subsequent analysis (Table 1).

Age groups from 41 to 90 years with 5-year intervals were considered; statistical analysis indicated no significant age distribution difference between groups ($^{ns}p=0.999$), ensuring demographic comparability for subsequent analysis. Age groups with 61–70 years suffered from COPD in both groups A and B as compared to the other age groups (Table 2).

In Group A, 73 male subjects (60.83%) were smokers, whereas 47 (39.17%) were non-smokers. Similarly, in Group B, 85 male subjects (70.83%) were smokers, and 35 (29.17%) were non-smokers. Statistical analysis, with a $p=0.9633$, reveals no significant difference in the distribution of male smokers and non-smokers between the two groups (Table 3).

In Group A, 76.67% of the patients reported cough, whereas 85% experienced shortness of breath, 45% had a fever, and 15% suffered from hemoptysis (Fig. 1). Corresponding percentages for Group B were 81.66, 95, 50, and 20%, respectively. Statistical analysis revealed no significant difference in symptoms between the groups ($p=0.269$), displayed in Table 4.

Hypertension was present in 70% of Group A and 76.66% of Group B patients. Heart disease was reported by 40% of Group A and 45% of Group B, whereas diabetes affected 60% of Group A and 56.66% of Group B, respectively. Pneumonia occurred in 25% of Group A and 30% of Group B. GIT conditions were noted in 10% of Group A and 13.33% of Group B. Statistical analysis revealed no significant difference in comorbidities in COPD patients between the two groups ($p=0.834$) as displayed in Table 5 and Fig. 2.

The study evaluated the effect of dual drug therapy on the FEV1:FVC ratio in COPD patients over 3 months. Initially, 30% of patients had a FEV1:FVC ratio of <0.7, which increased to 90% in the post-treatment, while those with a ratio >0.7 decreased from 70% to 10%. This significant change ($p<0.0001$) indicated that dual drug therapy had refinement in lung function (Table 6 and Fig. 3).

The study assessed the impact of triple-drug therapy on the FEV1:FVC ratio in COPD patients over 3 months. Before medication, 16.67% of patients had a FEV1:FVC ratio of <0.7, which was raised to 93.33% after treatment. Conversely, patients with a ratio of >0.7 were decreased

Table 1: Gender-wise distribution of subjects suffering from COPD

Gender	Group A n (%)	Group B n (%)
Male	76 (63.33)	85 (70.83)
Female	44 (36.67)	35 (29.17)
Mean ($\bar{x}$) 60		Mean ($\bar{x}$) 60
SD-16		SD-25
95% CI; P>0.999; df=2; t=0 (Student t test)		

Data were expressed in Mean±SD; values in the groups were in n (%),
COPD: Chronic obstructive pulmonary disease

Table 2: Age-wise distribution of subjects suffering from COPD

Age groups (years)	Group A n (%)	Group B n (%)
41–50	30 (25)	32 (26.67)
51–60	34 (28.33)	38 (31.67)
61–70	42 (35)	40 (33.33)
71–80	8 (6.66)	6 (5)
81–90	6 (5)	4 (3.33)
	Mean ($\bar{x}$) 24	Mean ($\bar{x}$) 24
	SD-14.4	SD-15.7
	95% CI; P>0.999; df=8; t=0 (Student t test)	

Data were expressed in Mean±SD; values in the groups were in n (%).
COPD: Chronic obstructive pulmonary disease

Table 3: Distribution of male subjects based on the percentage of smokers and non-smokers

Male subjects	Group A n (%)	Group B n (%)
Smokers	73 (60.83)	85 (70.83)
Non-smokers	47 (39.17)	35 (29.17)
	Mean ($\bar{x}$) 60	Mean ($\bar{x}$) 60
	SD-13	SD-25
	95% CI; ^{ns}p=0.9633; df=2; t=0.05 ns-Non-significant (Unpaired t-test)	

Data were expressed in Mean±SD; values in the groups were in n (%)

Table 4: Distribution based on the presence of symptoms in COPD patients

Symptoms	Group A n (%)	Group B n (%)
Cough	92 (76.67)	98 (81.66)
Shortness of breath	102 (85)	114 (95)
Fever	54 (45)	60 (50)
Hemoptysis	18 (15)	24 (20)
	Mean ($\bar{x}$) 66.5	Mean ($\bar{x}$) 74
	SD-33.23	SD-34.89
	95% CI; ^{ns}p=0.7965; df=6; t=0.269 ns-Non-significant (Student's t-test)	

Data were expressed in Mean±SD; values in the groups were in n (%).
COPD: Chronic obstructive pulmonary disease

from 83.33% to 6.67%. This significant shift (**p<0.001) demonstrated a substantial improvement in lung function following triple drug therapy (Table 7 and Fig. 4).

DISCUSSION

Globally, 384 million people were projected to have COPD in 2010.

Table 5: Distribution based on their comorbidities in COPD patients

Comorbidities	Group A n (%)	Group B n (%)
Hypertension	84 (70)	92 (76.66)
Heart disease	48 (40)	54 (45)
Diabetes	72 (60)	68 (56.66)
Pneumonia	30 (25)	36 (30)
GIT related disorders	12 (10)	16 (13.33)
	Mean ($\bar{x}$) 49.2	Mean ($\bar{x}$) 26.09
	SD-26.4	SD-53.2
	95% CI; ^{ns}p=0.834; df=8; t=0.2155 ns-Non-significant (Unpaired t-test)	

Data were expressed in Mean±SD; values in the groups were in n (%).
COPD: Chronic obstructive pulmonary disease

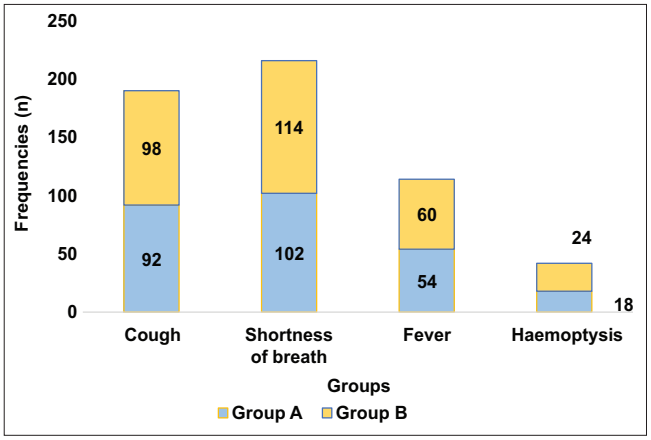

Fig. 1: Distribution based on the presence of symptoms in chronic obstructive pulmonary disease patients. (Data were expressed in Mean±SD; values in the groups were in n [%])

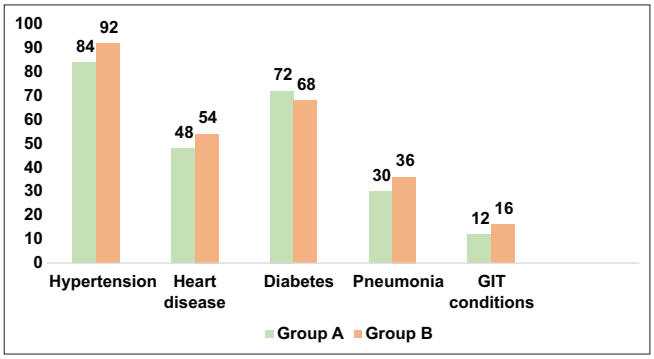

Fig. 2: Distribution based on their comorbidities in chronic obstructive pulmonary disease patients. (Data were expressed in Mean±SD; values in the groups were in n [%])

Approximately 5 lakh deaths in India are linked to the disease annually, which translates to one fatality every minute [14]. Transitioning from two- to three-drug regimens, the latter have only lately shown superior efficacy over previous drug combinations [15].

The current study aimed to evaluate the comparative effectiveness of triple-drug therapy over dual-drug therapy in the management of COPD, thus focusing on the exacerbation rates and improvements in lung function that can be measured by the FEV1/FVC ratio. The results provided valuable insight into the efficacy of these therapeutic approaches and highlighted the significant impact of triple-drug therapy on the clinical outcomes of COPD patients. In addition, the

Table 6: Distribution of patients based on their FEV1:FVC ratio pre- and post-treatment with dual therapy

Indices	Number of patients – Pre-medication, n (%)	Number of patients – Post-medication (After 3 months), n (%)
FEV1:FVC ratio of <0.7	36 (30)	108 (90)
FEV1:FVC ratio of >0.7	84 (70)	12 (10)
	Mean – ($\bar{x}$) 60 SD – 24 95% CI; **p<0.001; df=1; t=9.487 Significant (Chi-square test)	Mean – ($\bar{x}$) 60 SD – 48

Data were expressed in Mean±SD; values in the groups were in n (%).
FEV1: Forced expiratory volume, FVC: Forced vital capacity

Table 7: Distribution of patients based on their FEV1:FVC ratio pre- and post-treatment with triple therapy

Indices	Number of patients – Pre-medication, n (%)	Number of patients – Post medication (After 3 months), n (%)
FEV1:FVC ratio of <0.7	20 (16.67)	112 (93.33)
FEV1:FVC ratio of >0.7	100 (83.33)	8 (6.67)
	Mean – ($\bar{x}$) 60 SD – 24 95% CI; **p<0.001; df=1; t=9.487 Significant (Chi-square test)	Mean – ($\bar{x}$) 60 SD – 48

Data were expressed in Mean±SD; values in the groups were in n (%)

study observed no significant differences in the baseline characteristics of the two groups regarding age, gender, smoking status, and comorbidities, ensuring a balanced comparison. The statistical analysis confirmed that demographic factors did not influence the outcomes, attributing the observed benefits directly to the treatment regimens. In the current study, males accounted for the prevalence of COPD, which was consistent with the previous studies. This dominance of males was positioned and contributed to the smokers recorded. In both groups, smoking was identified in 60–70% of the patients, whereas female smokers were not documented.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines listed female sex and advancing age as risk factors for COPD [16]. Smoking cigarettes became trendy during the last few decades in women in industrialized nations, which led to the deterioration of lung function and more decline annually in FEV1. While males remain predominant in prevalence, a significant rise in disease incidence among young females aged 50–59 years and older was remarkable. Furthermore, further studies have suggested a potential connection between autoimmune and COPD. As women are more likely to have autoimmune illnesses, they would like to have COPD and reported [17].

The symptoms were evaluated in the present study and revealed that among all the symptoms noticed, more than 90 patients experienced with cough, whereas >100 suffered from shortness of breath, and >50 patients had fever in both groups A and B. The latter symptoms are caused by constriction of the airways and excessive mucus secretion. Comorbidities and COPD have a complicated relationship. The

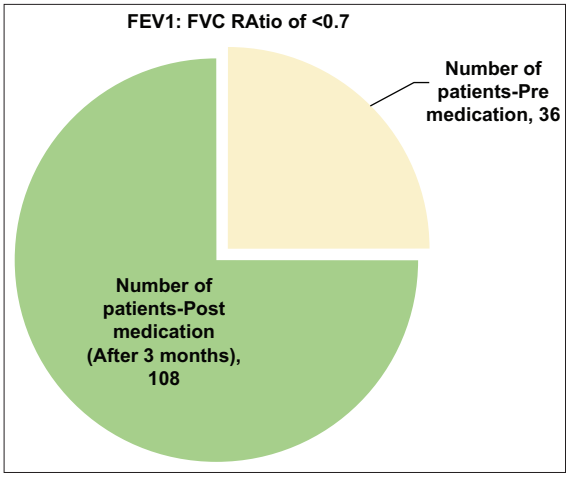

Fig. 3: Distribution of patients based on their forced expiratory volume: Forced vital capacity ratio pre- and post-treatment with dual therapy, n=36 (pre-medication); n=108 (post-medication)

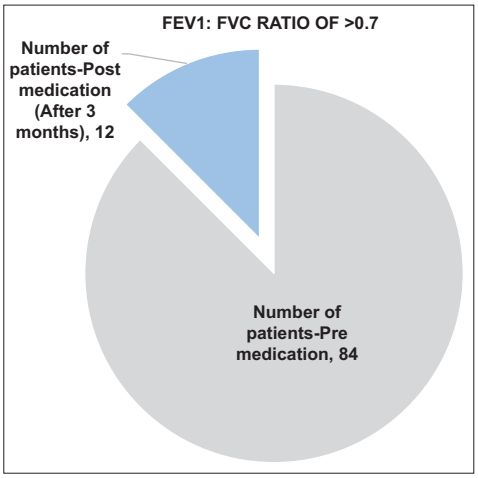

Fig. 4: Distribution of patients based on their forced expiratory volume:forced vital capacity ratio in pre- and post-treatment with triple therapy, data were expressed in Mean±SD; values in the groups were in n (%)

present analysis revealed that 70 and >70% of the patients consisted of hypertensive individuals in Groups A and B. As for comorbidities, diabetes mellitus was the second most common. About 72 and 68 patients suffered from diabetes, followed by other heart diseases, pneumonia, and GIT-related disorders.

Our findings revealed that both the dual and triple therapies substantially improved lung function, as evidenced by a significant increase in the FEV1/FVC ratio in the post-treatment. However, triple therapy demonstrated a more pronounced enhancement in lung function as compared to dual therapy. Before the treatment, only 16.67% of patients in the triple-therapy group had an FEV1/FVC ratio of <0.7, which dramatically increased to 93.33% post-treatment. In contrary, the dual therapy group experienced an increase from 30 to 90% in the FEV1/FVC ratio. These results underscore the enhanced effectiveness of triple therapy in restoration of lung function and reduction of airflow limitation.

Patients with COPD bear a heavy burden when their condition worsens [18]. Regular exacerbations are linked to a faster rate of lung function decline, a major reduction in the quality of life of patients,

and a higher death rate. Therefore, a major therapeutic objective for COPD care is reducing the frequency of exacerbations. A reduction in exacerbation rates is another crucial finding, emphasizing the superiority of triple therapy [19]. Exacerbations are critical events in COPD progression, leading to a decline in lung function, increased hospital admissions, and heightened mortality risk. A marked decline in exacerbation rates with triple therapy indicated better disease control and potentially improved long-term prognosis for patients [20,21].

The results were consistent with findings from other studies. For instance, Vestbo *et al*. demonstrated that a fixed triple therapy, with a combination of two long-acting bronchodilators and an ICS, significantly reduced moderate-to-severe COPD exacerbations as compared to tiotropium alone and open triple therapy (BDP/FF plus tiotropium) [19]. Similarly, Ferguson *et al*. reported that triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered-dose inhaler significantly improved the lung function over dual therapies in a 24-week multi-centered phase 3 trial, even in patients without a history of exacerbations [20].

However, it is crucial to consider the appropriate use of triple therapy, as highlighted by Cazzola *et al*., who addressed the overuse of triple therapy in COPD treatment compared to guideline recommendations. They emphasized that while triple therapy is beneficial in certain COPD patients, its effectiveness in other cases remains uncertain and requires further research to determine its clinical and cost-related implications [21].

Overall, the study supported a preferential use of triple therapy in the management of COPD, particularly in patients with severe disease or frequent exacerbations. Combined use of ICS, LABAs, and LAMAs offered a comprehensive approach targeting multiple pathophysiological aspects of COPD that resulted in superior clinical outcomes compared to dual therapy [22].

In contrary with the GOLD guidelines of enlisting with the triple drug regimen for severe cases with frequent exacerbations, the current research entailed administering triple therapy to patients regardless of the severity of their condition. The present study was evident that the triple therapy consisted of formoterol, tiotropium, and budesonide, whereas the dual therapy was loaded with etofylline and theophylline combination and also formoterol along with budesonide. The use of corticosteroids encompasses side effects and also implies that the therapeutic response to triple therapy is elicited gradually over a 2-week period and that the treatment is unsuccessful when administered in a single dose. Anticholinergics work by preventing bronchoconstriction that is brought on by the parasympathetic nervous system. They also help to improve FEV1, reduce lung inflation, and reduce exacerbations. Hence triple might be considered to be effective upon dual therapy [23,24].

These results are consistent with the framework of research and clinical recommendations that support and intensify treatment plans depending on the severity of the illness and the history of exacerbations [25]. Future studies should examine the long-term advantages and economic viability of triple therapy keeping in view of the significant financial burden associated with COPD. In addition, by looking into the possible biomarkers for improved patient stratification, therapeutic approaches could be optimized, thereby enhancing the quality of life for individuals with COPD.

CONCLUSION

The study demonstrated that triple-drug therapy significantly outperformed over dual-drug therapy in the management of COPD by the marked improvement in lung function and thereby reduction in exacerbation rates. With a balanced baseline characteristic ensuring the validity of the comparison, the findings strongly supported the preferential use of triple therapy, especially for patients with severe disease or frequent exacerbations. The number of individuals with severe COPD is also decreased by the use of triple therapy. It showed an improvement in lung function and symptom relief, thus causing an amelioration in the quality of life for patients. This evidence aligns with current clinical guidelines and underscores the importance of personalized, escalated treatment approaches to enhance patient outcomes and manage COPD progression effectively.

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CONFLICTS OF INTEREST

There are no conflicts of interest as declared by the authors.

DECLARATION BY AUTHORS

By signing this document, the writers attest to the originality of the material provided in this article and to their own assumption of liability for any claims pertaining to its content.

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