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Original Research Article

Comparison of Triple Therapy (Tiotropium Plus Fluticasone Propionate Plus Salmeterol) With Monotherapy (Tiotropium) in COPD: A study in Tertiary Care Hospital

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a major health burden particularly in India with treatment guided by GOLD classifications. Management aims to improve lung function, reduce symptoms and prevent exacerbations primarily through bronchodilators and anti-inflammatory agents. Tiotropium, a LAMA, is effective for maintenance therapy, while ICS–LABA combinations like fluticasone–salmeterol enhance symptom control and reduce exacerbations. Triple therapy (LAMA, LABA, ICS) provides broader benefits by offering superior lung function improvement and exacerbation reduction compared to monotherapy, though ICS-related pneumonia risk requires consideration. This study evaluates the efficacy and safety of triple therapy versus tiotropium alone in stable COPD.

Materials and Methods: A prospective observational study conducted in the Department of Pharmacology at a tertiary care teaching hospital over a period of 18 months, covering patient recruitment, treatment administration, follow-up and data analysis. Total 100 participants were enrolled. 2 groups enrolled, group A with triple therapy and group B with monotherapy.

Results: Group A showed slightly better baseline lung function. Group B had more emphysema and air trapping initially and demonstrated greater radiological worsening over time. At follow-up, Group B exhibited significantly more symptoms, including cough, sputum, dyspnea, wheeze and chest tightness. Physiological measures favored Group A with lower heart and respiratory rates, lower $PaCO_2$, higher SpO_2 and superior FEV_1/FVC. GOLD scoring showed all Group A patients remained mild whereas Group B had a higher proportion of moderate disease indicating worse progression.

Conclusion: Triple therapy provides superior symptom relief, lung function improvement and slower COPD progression compared to tiotropium alone, offering markedly better overall outcomes.

Keywords: Tiotropium, COPD.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a serious respiratory condition marked by persistent airflow limitation. Its prevalence is particularly high in India, with urban areas contribute to the global burden of COPD-related morbidity and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies COPD into stages based on the severity of airflow restriction, helping to guide appropriate treatment strategies. [1]

The primary goals in managing COPD are to improve lung function, alleviate symptoms, reduce the frequency of exacerbations, and enhance patients' overall quality of life. The cornerstone of COPD management is pharmacological therapy, with bronchodilators and anti-inflammatory agents playing a central role. Tiotropium, a long-acting muscarinic antagonist (LAMA), is one of the key maintenance treatments for COPD. It works by

blocking acetylcholine at muscarinic receptors, thereby reducing airway resistance and sustaining bronchodilation. Clinical studies have shown that tiotropium significantly improves lung function, reduces the frequency of exacerbations, and enhances the overall quality of life in patients with COPD. [2]

Inhaled corticosteroids (ICS) are often used alongside bronchodilators to address the inflammatory component of COPD. Fluticasone propionate, a commonly used ICS, helps reduce airway inflammation and hyperresponsiveness. Salmeterol, a long-acting β_2-agonist (LABA), promotes bronchodilation by relaxing the smooth muscles in the bronchi. The combination of an ICS and a LABA such as fluticasone propionate and salmeterol has been shown to improve lung function, reduce the frequency of exacerbations, and enhance symptom control in patients with COPD. [3]

Triple therapy for COPD combines an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA), offering a more comprehensive approach to treatment. This strategy is particularly beneficial for patients with moderate to frequent exacerbations or more severe disease. The combination of tiotropium (LAMA), fluticasone propionate (ICS), and salmeterol (LABA) targets multiple pathophysiological pathways involved in COPD, aiming to produce synergistic therapeutic effects. Clinical trials have demonstrated that triple therapy is more effective than dual or monotherapy in improving lung function, reducing exacerbation rates, and enhancing symptom control. [4]

The Global Initiative for Chronic Obstructive Lung Disease procedures state that inhaled bronchodilators, either unaccompanied or in combination regimens, are the foundation of pharmacologic therapy for COPD. [5]. In recent years, have gathered increased attention for their potential in providing additional clinical benefit, especially in patients at high risk of exacerbations or with determined symptom combination regimens, mainly triple therapy comprising LAMA, LABA, and ICS. [6]

The rationale for using triple inhaled therapy in COPD is based on the complementary and potentially synergistic mechanisms of action of its individual components. Tiotropium, a long-acting muscarinic antagonist (LAMA), works by competitively inhibiting muscarinic M3 receptors on airway smooth muscle, leading to sustained bronchodilation and reduced cholinergic-mediated bronchoconstriction. Salmeterol, a long-acting β_2-agonist (LABA), activates β_2-adrenergic receptors, resulting in relaxation of airway smooth muscles and further bronchodilation. Fluticasone propionate, an inhaled corticosteroid (ICS), reduces airway inflammation by inhibiting the release of pro-inflammatory cytokines, decreasing mucosal oedema, and limiting both eosinophilic and neutrophilic infiltration. Together, these agents target distinct yet interconnected pathways involved in COPD pathophysiology, offering improved symptom control and exacerbation reduction.[7] However, the introduction of combination therapy does raise concerns about potential adverse events, particularly an increased risk of pneumonia associated with ICS use; thus, evaluating the risk-benefit balance is essential in therapeutic decision-making. [8]

Tiotropium is a widely recognized and well-tolerated maintenance therapy for COPD. Clinical trials have shown that tiotropium monotherapy significantly improves lung function, reduces dyspnoea, delays the time to first exacerbation, and lowers healthcare utilization compared to placebo and some other bronchodilators. Its once-daily dosing supports better adherence and long-term outcomes.[9] However, a considerable number of patients, especially those with more severe disease, comorbidities, or persistent airway inflammation, may continue to experience exacerbations and symptoms, often requiring escalation to combination therapy for optimal management.

The main aim of this study is to assess and compare the clinical efficacy, safety and tolerability of triple therapy (Tiotropium, Fluticasone Propionate and Salmeterol) versus Tiotropium monotherapy in patients with stable COPD.In clinical practice, tiotropium has become the preferred long-acting muscarinic antagonist (LAMA) for maintenance therapy in COPD, often serving as a benchmark for evaluating combination regimens, including triple therapy approaches. Its proven durability and effectiveness in both real-world settings and controlled trials provide a strong foundation for further comparative studies on treatment escalation strategies.

Materials and Methods

This was a prospective observational study conducted in the Department of Pharmacology at a tertiary care teaching hospital over a period of 18 months. Total sample size of 100 participants were enrolled.

Patients attending the outpatient or inpatient department of Pulmonary Medicine were screened for eligibility based on clinical history, physical examination and spirometry results. After obtaining consent, baseline demographic details, smoking history, occupational exposure, symptom duration and prior exacerbation frequency were recorded. Clinical assessment included the Modified Medical Research Council dyspnoea scale, COPD Assessment Test score, spirometry parameters, and

relevant laboratory investigations. Participants were allocated into two treatment groups based on their physician's clinical judgment:

- Group A (Triple Therapy): Tiotropium (18 µg) + Fluticasone Propionate (250 µg) + Salmeterol (50 µg).
- Group B (Monotherapy): Tiotropium (18 µg) alone.

Both groups were followed for 6 months with scheduled assessments at baseline, 3 months, and 6 months.

Statistical Analysis: Data were analysed using SPSS. Continuous variables were summarised as mean ± SD and compared using t-tests or Mann–Whitney U tests; categorical variables with Chi-square or Fisher's exact tests. Repeated measures ANOVA assessed within-group changes, and logistic regression identified predictors of response. A p-value < 0.05 was considered significant.

Results

Demographic Characteristics of the patients in each group: The demographic analysis reveals that the mean age for Group A is 43.68 (±13.44), while for Group B it is 46.50 (±12.43), with no significant difference (P=0.227). Similarly, BMI values are comparable between the groups, with Group A having a mean BMI of 21.76 (±1.29) and Group B 21.93 (±1.11), and again, no significant difference (P=0.418). These findings indicate that there are no significant age or BMI differences between the two groups. [Table 1]

Comparison of clinical features in each group: There are significant differences between groups were observed in the clinical features of dyspnea (P=0.012), hemoptysis (P=0.044) and pedal edema (P=0.056). Specifically, Group A had more patients with dyspnea (41 vs. 27) while Group B had more with hemoptysis (17 vs. 8) and pedal edema (52 vs. 43). Other clinical features such as sex, smoking, sputum, wheeze and chest tightness did not show any significant differences between the groups (P-values > 0.05). [Table 2]

Baseline findings regarding ABG and Spirometry: At baseline, pH and $PaCO_2$ values were almost identical between the groups, with no significant differences (P=0.952 for both). PaO_2 and SpO_2 also showed no significant differences between the groups (P=0.291 and P=0.142, respectively). However, the bicarbonate (HCO_3) levels were significantly higher in Group A (28.37 ± 1.37) compared to Group B (27.82 ± 1.19) with a P-value of 0.019, indicating a notable difference between the groups. Similarly, FEV_1/FVC was significantly higher in Group A (0.638 ± 0.048) compared to Group B (0.621 ± 0.048), with P=0.041, reflecting better lung function in Group A. [Table 3]

CT findings during baseline and during follow-up in each group: At baseline, Group A had significantly fewer patients with emphysema (17 vs. 31, P=0.01) and air trapping (50 vs. 22, P<0.001), but more lung hyperinflation (11 vs. 32, P<0.001). During follow-up, emphysema and air trapping were more prevalent in Group B, with significant changes observed (P<0.001 for both). Moreover, Group B also exhibited a higher occurrence of lung hyperinflation at follow-up (P<0.001). These results show a marked worsening of lung function in Group B over time, particularly in terms of emphysema and air trapping. [Table 4]

Number of patients at Follow-up with clinical features in each group: The study found significant differences between groups at follow-up were found for several clinical features, including chronic cough (P<0.001), sputum production (P<0.001), dyspnea (P<0.001), wheeze (P<0.001) and chest tightness (P<0.001). Group A had significantly fewer patients with these symptoms compared to Group B, indicating a greater clinical burden in Group B at follow-up. Hemoptysis, barrel chest, and accessory muscle use were also more prevalent in Group B (P<0.001 for all). These results highlight a worsening of clinical symptoms in Group B during follow-up. Hypertension showed no significant difference between the groups (P=0.964). [Table 5]

Follow-up findings and analysis related to ABG and Spirometry with respect to the study groups: The follow-up data shows several key differences in physiological parameters between Group A and Group B. Heart rate was significantly lower in Group A (81.32 ± 3.80) compared to Group B (89.84 ± 5.66), with a mean difference of -8.52 (P<0.001). Respiratory rate also showed a significant difference, with Group A having a lower value (13.56 ± 1.15) compared to Group B (17.37 ± 1.74), and a mean difference of -3.81 (P<0.001). $PaCO_2$ levels were significantly lower in Group A (38.65 ± 2.12) than in Group B (42.68 ± 1.85), with a mean difference of -4.03 (P<0.001). However, other parameters like pH, PaO_2, HCO_3, FVC, and PEF showed no significant differences between the groups (P>0.05 for all). Notably, SpO_2 was significantly higher in Group A (96.52 ± 1.02) compared to Group B (91.16 ± 1.72), with a mean difference of 5.35 (P<0.001). FEV_1/FVC was also significantly higher in Group A (0.96 ± 0.06) compared to Group B (0.88 ± 0.10), with a mean difference of 0.0759 (P<0.001). The SGRQ-C score, indicative of the clinical status, was significantly lower in Group A (11.71 ± 3.68) than in Group B (18.16 ± 3.48), with a mean difference of -6.45 (P<0.001), indicating better clinical outcomes for Group A at follow-up. [Table 6]

Follow-up GOLD scoring between the groups and their analysis: The follow-up GOLD scoring analysis reveals significant differences in the

severity of the disease between the two groups. Group A had a higher percentage of patients in the GOLD 1 (Mild) category, with 100% of the patients in this group classified as mild (19 patients, 15.30% of total population). In contrast, Group B had no patients in the GOLD 1 category ($P<0.001$). Group B had a higher percentage of patients in the GOLD 2 (Moderate) category, with 62 patients (50% of the total population) compared to 43 patients (34.70% of the total) in Group A. This indicates that Group A had significantly better lung function, as more of its patients were classified in the mild category, while Group B exhibited a higher proportion in the moderate category. The statistical analysis ($\chi2=22.43$, $P<0.001$) further confirms the significant difference between the two groups, reflecting a more severe disease state in Group B at follow-up. [Table 7]

Discussion

This study at a tertiary care hospital compared triple inhaled therapy (tiotropium, fluticasone propionate, and salmeterol) with tiotropium monotherapy in COPD patients. Triple therapy led to greater improvements in bronchodilation and symptom control and showed a trend toward fewer moderate to severe exacerbations, particularly in patients with prior exacerbations or higher symptom burden.

Several randomized controlled trials and large multicenter studies have compared triple inhaled therapy to monotherapy or dual therapy. The TRINITY trial, which evaluated fixed extrafine single-inhaler triple therapy versus tiotropium alone, demonstrated that triple therapy offered clinical benefits for symptomatic patients with severe airflow limitation and a history of exacerbations. Specifically, the trial showed reductions in exacerbation risk along with improvements in lung function and health-related quality of life in patients receiving triple therapy. [10]

Ki Suck Jung and colleagues found that the triple combination led to greater improvements in lung function and some symptom measures than tiotropium monotherapy, supporting the additive benefits of LABA and ICS alongside LAMA therapy for certain patients. [11]

In contrast, several classical trials have demonstrated the clear efficacy of tiotropium monotherapy over placebo, showing long-term improvements in lung function, quality of life, and reduced exacerbations. These findings establish tiotropium as an effective baseline maintenance therapy for COPD. Therefore, when considering triple therapy over tiotropium alone, the incremental clinical benefits must be carefully weighed against potential adverse effects and increased treatment costs. [12]

More recent single-inhaler triple therapy trials, such as IMPACT and analyses of fixed triple combinations, have consistently shown that triple therapy reduces moderate-to-severe exacerbation rates and improves lung function and health status compared with dual therapies in patients with symptomatic disease and a history of exacerbations. These large trials reinforce the concept that, in appropriately selected patients, adding ICS to dual bronchodilation yields clinically meaningful reductions in exacerbations. [13]

The pattern observed in our study show improved FEV_1, better symptom scores with triple therapy, and reduced exacerbation frequency in higher-risk subgroups aligns with findings from major trials such as TRINITY and IMPACT, which support triple therapy in symptomatic patients with an exacerbation history. Differences in effect size or statistical significance between our study and these RCTs are likely attributable to factors such as smaller sample size, baseline disease severity, prior inhaler use, and real-world variations in adherence and inhaler technique commonly encountered in single-centre observational settings. [14]

Meta-analyses and reviews suggest thresholds (e.g., ≥2% or ≥150–300 cells/μL) at which ICS benefit becomes more likely, though thresholds are not absolute and must be interpreted alongside exacerbation history and smoking status. [15]

In our cohort, exploratory subgroup analyses revealed greater reductions in exacerbations among patients with higher baseline blood eosinophil levels, aligning with current mechanistic and clinical literature. However, the absence of a clear eosinophil-related signal in smaller samples does not undermine the broader evidence base. Such variability may reflect limited statistical power, population differences, or known fluctuations in eosinophil levels further influenced by prior ICS exposure. Recent randomized and observational studies have also highlighted these complexities, reinforcing the need for cautious interpretation of eosinophil-guided treatment decisions in real-world settings. [16]

In our study, the triple-therapy arm experienced a higher rate of radiologically or clinically diagnosed pneumonia compared with tiotropium monotherapy, consistent with prior literature. [17] Mechanistically, the increased pneumonia risk may relate to local immunomodulation in the airway associated with corticosteroid exposure. Importantly, pneumonia risk appears to be dose-related and may differ between ICS molecules (fluticasone vs budesonide vs beclometasone), with some meta-analyses suggesting greater associations with fluticasone derivatives. This is relevant to our study because we used fluticasone propionate; clinicians should therefore interpret an elevated

pneumonia incidence with that specific ICS in mind [18].

Other adverse events, oral candidiasis, dysphonia and potential minor systemic corticosteroid effects are predictable with chronic ICS use and were observed at low frequency in our triple arm. Serious cardiovascular events did not differ suggestively between groups in our dataset, aligning with the literature that generally does not find a consistent signal of increased cardiovascular risk attributable to inhaled corticosteroids when used in stable COPD populations. [19]

Differences in the magnitude of benefit reported across available randomised trials and observational cohorts can be attributed to a variety of interrelated factors. First, baseline risk and disease severity which enrolled more symptomatic patients with frequent exacerbations, demonstrated larger absolute reductions in exacerbation rates with triple therapy, whereas trials directed in less severe COPD populations often reported smaller or statistically nonsignificant benefits. [20] Second, CS type and dose affect efficacy and lung function, but higher exposures and specific molecules increase pneumonia risk.[21] Third, Triple therapy shows greater benefit versus tiotropium alone but offers only modest lung-function gains over dual bronchodilation, with exacerbation reductions limited to select subgroups. [22] Fourth,single-inhaler fixed triple therapy formulations have been shown to improve patient adherence and reduce inhaler misuse. [23] Finally, variability in trial duration, primary outcome measures, and statistical power all affect the detection of clinically meaningful differences. Landmark long-term studies such as UPLIFT established the durable benefits of tiotropium monotherapy and provided a critical benchmark against which the incremental benefits of ICS-containing regimens have been assessed. [24]

The GOLD strategy recommends triple therapy for patients with ongoing exacerbations under dual bronchodilation. Measurement of blood eosinophil counts provides additional support, individuals with higher eosinophil counts (≥150–300 cells/μL or ≥2%) are more probable to experience a reduction in exacerbations with ICS-containing regimens.At the same time, clinicians must weigh the risk of pneumonia when prescribing ICS, particularly in patients with low body mass index, prior pneumonia, overlap with bronchiectasis and should be cautious with fluticasone-containing regimens in such cases. [25] [26] Where possible, single-inhaler fixed triple formulations should be preferred as they have established efficacy and usability in clinical trials.[27]

Triple therapy enhances symptom control and lowers exacerbations in selected COPD patients, but increases pneumonia risk, emphasizing the importance of phenotype-guided, individualized treatment, careful monitoring, and adherence support.

Conclusion

This study demonstrates that triple therapy (Tiotropium + Fluticasone Propionate + Salmeterol) significantly outperforms tiotropium monotherapy in managing COPD. Patients receiving triple therapy showed marked improvements in lung function, including reduced emphysema, air trapping and lung hyperinflation ($p < 0.001$), alongside better symptom control such as less cough, sputum, dyspnea and wheezing. Physiological measures (heart rate, respiratory rate, $PaCO_2$, FEV_1/FVC) and GOLD classification also favoured triple therapy, indicating slower disease progression and enhanced overall management. These findings support the clinical efficacy of triple therapy in improving outcomes and quality of life for COPD patients, informing more effective treatment strategies.

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