

Comparative study to see the incidence of acute exacerbations of COPD by triple drug therapy with single and multiple inhalers in moderate to severe disease

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) refers to a variety of lung conditions that are characterized by persistent, frequently progressive airflow obstruction and chronic respiratory symptoms (dyspnoea, cough, sputum production, exacerbation). COPD patients with persistent dyspnoea are at higher risk of exacerbation in which triple drug inhaled therapy is suggested. Earlier patients who used open triple drug therapy needed at least two inhalers more than once daily. The significance of ICS in the treatment paradigm of patients with severe COPD and recurrent exacerbations has lately been called into question. Our study was conducted to compare acute exacerbation and all-cause mortality among patients who used triple drug regimen via single inhaler and multiple inhalers.

Materials and Methods: The present study was a hospital based prospective cohort study. This study was conducted from February 2021 to March 2022 at the Department of Respiratory Medicine, Mahatma Gandhi medical college & hospital. Eligible patients were aged more than 18 years and FEV1 <50%. Acute exacerbations were observed over the period of 3 months by prescribing single inhaler triple therapy (SITT) or multiple inhaler triple therapy (MITT) according to the symptoms and severity of COPD.

Result: Overall, 60 patients were taken into study cohort. On follow up of 3 months baseline characteristics between the cohorts were comparable. Single inhaler triple therapy was associated with a lower risk of COPD exacerbations compared with multiple inhaler triple therapy. Single inhaler triple therapy led to a more significant improvement in lung symptoms and quality of life compared with multiple inhalers triple therapy.

Conclusion: In this study, triple therapy with single inhaler resulted in fewer moderate or severe COPD exacerbations than patients who used multiple inhalers. In addition, triple therapy single inhaler resulted in a reduced rate of COPD hospitalisation as well as improved lung symptoms and quality of life.

Keywords: Budesonide, glycopyrrolate, formoterol fumarate and triple therapy

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. COPD is currently

one of the top three causes of death worldwide, with low-and middle-income nations accounting for 90% of deaths ^[1]. It is associated with high morbidity and mortality rates, making it a significant public health concern. According to estimates, COPD will overtake heart disease as the leading cause of death globally by 2030 ^[2]. COPD imposes a significant burden in terms of disability and diminished quality of life (QoL), as well as enormous healthcare costs ^[3].

Patients with diagnosis of moderate to severe grade of COPD need triple drug therapy, so they require multiple inhalers to control the symptoms of the disease. These patients often utilized LAMA in one inhaler and a combination of ICS/LABA in another, which may have different sorts and designs. This could result in improper inhaler use and have an impact on the patient's treatment compliance. Recently, several randomized controlled trials (RCTs) have shown that extra fine triple drug (Beclomethasone dipropionate/Formoterol fumarate/Glycopyrronium bromide) therapy could be associated with lower rate of moderate-to-severe COPD exacerbations and mortality as well as improved lung function and health-related QoL compared with other treatment options ^[4].

Exacerbations of the disease are major economic burden factors, and depending on their severity, may necessitate access to Emergency Departments (EDs) and hospitalization. As a result, new therapeutic strategies that allow for a reduction in the frequency of exacerbations are required ^[5]. For COPD patients with continued dyspnoea or at a higher risk of exacerbation, triple inhaled therapy is suggested. Recently, several triple fixed-dose combinations (FDCs) for COPD patients have been developed, in which ICS/LABA/LAMA are delivered simultaneously by a single inhaler device. A single device improved adherence and cost savings ^[6]. Triple treatment, delivered via multiple inhalers, has been found in pooled studies to enhance lung function, health-related quality of life, and exacerbations. There are presently no systematic studies that provide a full and critical assessment of the evidence basis for single-inhaler triple treatment. As a result, due to scarcity of data this study was planned to investigate the impact of single-device triple therapy versus multiple inhaler triple therapy on COPD patient exacerbations ^[7].

Materials and Methods

Study objective: The main objective was to compare incidence of acute exacerbations in triple drug therapy (ICSs, LAMAs, LABAs) between single inhaler and two separate inhalers in COPD patient. Thus, the study aimed to observe number of moderate/severe exacerbations and adherence to the therapy between treatment cohorts. Another objective of the study was to describe and compare the clinical improvement in persistence and demographic characteristics of the two COPD cohorts initiating SITT or MITT using two or single inhalers.

Study design: To identify the clinical studies relevant to the present study, a systemic review of the literature a prospective cohort study was done from February 2021 to March 2022 (13months) at Department of Respiratory Medicine, Mahatma Gandhi Medical College & Hospital.

Study population: Patients of all moderate to severe COPD and FEV1 < 50% according to COPD GOLD guidelines, patients with history of acute exacerbation in previous one year irrespective of FEV1%, aged 18 years or older, starting triple therapy (LAMA, LABA, ICS) between February 2021 to march 22 with either SITT or MITT (using two or single inhalers), were included in the study. A minimum patient history of 12 months before the index date (MITT or SITT initiation) was required. Patients were followed up for 3 months. Exclusion criteria were patients of COPD in morbid condition, respiratory failure, associated with pulmonary tuberculosis, or any other chronic disease. Patients with mild COPD and patients who refused for consent were also excluded from the study.

Study variables: The following data were retrieved from OPD and IPD patients:

demographic data, including age and sex; baseline clinical data, which included the total number of exacerbations and severe exacerbations during the previous year, time since diagnosis, smoking status, lung symptoms (post CAT score) at 1 month and 3 months, the frequency and rate of moderate/severe exacerbations during the observation period and stratified by severity.

Statistical analysis: For statistical analysis data were analysed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Once a *t* value is determined, a *p*-value can be found using a table of values from Student's t-distribution. If the calculated *p*-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis. $P\text{-value} \leq 0.05$ was considered for statistically significant.

Study outcome: The primary outcome was rate of moderate or severe AECOPD during treatment period of 3 months following index date. It showed that triple inhalation therapy with single inhaler resulted in a lower rate of moderate or severe COPD exacerbations than patients who used multiple inhalers. Single inhaler triple therapy offers potential advantages in practicality and adherence to therapy. Secondary outcomes included demographic changes, the change in CAT score and risk of COPD hospitalization and duration of previous history of COPD.

Results

The present study was a hospital based prospective cohort study. In total 60 patients met the eligibility criteria and were included in this study.

Out of 60 individuals in our research, the majority of them were between the ages of 61 and 70 (19) where 8 patients used a double inhaler and 11 patients used a single inhaler triple therapy. The mean age was higher in single inhaler triple therapy compared to double inhaler triple therapy. However, some studies conducted in western nations indicated that patients over the age of 70 made up the majority of the patient population. This might be because people live longer in the west. Van den Berge M *et al.* (2020) ^[8] chronic obstructive pulmonary disease (COPD) also reported mean age 64.9 years, 78.3% males, 43.5% current smokers. According to our research, aging is a risk factor for COPD that may be caused by a steady decrease in lung function over time. Age is an independent risk factor for AECOPD which may be due to a decline in lung function with age gradually as per our study and the risk of exacerbation is increased with increasing age, probably because of risk factors like comorbidities and smoking and increase in duration of disease.

Table 1: Age distribution of study subjects

Age Group	Treatment		Total (n=60)
	Single inhaler Therapy	Double inhaler Therapy	
≤40 years	1	3	4
41-50 years	6	8	14
51-60 years	9	7	16
61-70 years	11	8	19
≥71 years	3	4	7

Total	30	30	60
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Overall (60), there were 45 male patients who received single inhaler treatment than those who received double inhalers which was higher in number than women (15). Male: Female Ratio is 3:1 which was statistically significant. Similar results were reported by Lainscak *et al.* (2011) ^[9], Alexopoulos *et al.* (2015) ^[10] who reported higher male predominance. In India, Mohapatra *et al.* (2010) ^[11], had also reported similar results.

Table 2: Gender distribution of study subjects

Treatment			
Gender	Single inhaler Therapy	Double inhaler Therapy	Total
Female	4	1	15
Male	26	19	45
Total	30	30	60

In total, 24 patients of single-inhaler therapy did smoke compared to multiple inhaler therapy (18) which was not statistically significant ($p=0.0909$). Similar results were seen in Bhatia *et al.* ^[12] who reported 79.6% of smokers and in Koul *et al.* ^[13]. Who reported 68.4% of smokers. Mohapatra *et al.* ^[11] also reported similar results with 88% smokers.

Table 3: Smoking profile in study subjects

Treatment			
Smoking	Single Inhaler Therapy	Double Inhaler Therapy	Total
Absent	6	12	18
Present	24	18	42
Total	30	30	60

In our study the fact that more patients (13) had a history of COPD for more than ten years in Double Inhaler treatment compared to 12 patients in Single Inhaler therapy was not statistically significant. Other western and Indian investigations found that the disease's duration varied. Jiang *et al.* ^[14] reported maximum patients i.e. 41% with a duration of 10-14 years, Gaude *et al.* ^[15] reported maximum patients i.e. 62.5% with a duration of disease 10-19 years and they found that patients with COPD (>10 years duration) were two times more likely to have frequent admissions due to exacerbations.

Table 4: Duration of disease in study subjects

Treatment		
History of COPD	Single inhaler therapy	Double Inhaler therapy
<1 year	3	1
<5 year	6	5
5-10 year	9	11
>10year	12	13
Total	30	30

In our study there were 19 patients who had acute exacerbations of COPD in Single inhaler Therapy whereas 16 patients in Double inhaler Therapy in previous year. More than 2 A/E COPD 12/19 patients in Single inhaler therapy while 6/16 patients in Double Inhaler therapy were present but this was not statistically significant ($p=0.2932$).

Table 5: History of Exacerbation of COPD in previous one year

Treatment			
COPD A/E in previous one year	Single inhaler Therapy	Double inhaler Therapy	Total
Exacerbation Absent	11	14	25
Exacerbation Present	19	16	35
Total	30	30	60

Table 6: Number of exacerbations of COPD patients in preceding year

COPD A/E in preceding year	Single inhaler therapy	Double Inhaler therapy
1	2	2
2	5	8
>2	12	6
Total	19	16

In our study, the number of patients who got A/E during treatment was higher in multiple inhaler therapy (11) than in Single inhaler therapy (9) but this was not statistically significant. In the 52-week phase III ETHOS study, triple therapy with budesonide/glycopyrrolate/formoterol fumarate (BGF) at two inhaled corticosteroid dose levels resulted in significantly lower moderate/severe exacerbation rates compared to glycopyrrolate/formoterol fumarate (GFF) and budesonide/formoterol fumarate (BFF). (BFF). The purpose of this research is to evaluate the impacts of single inhaler triple therapy with dual treatments consisting of LABA/LAMA, ICS/LABA, or distinct ICS/LABA + LAMA triple therapy. The incidence of moderate-to-severe chronic obstructive pulmonary disease (COPD) exacerbations was the main outcome. When compared to LABA/LAMA and ICS/LABA dual therapy, single inhaler triple therapy was linked with a substantially reduced chance of COPD exacerbation. These findings were similar to ours.

Table 7: Incidence of exacerbations during treatment in study subjects

Treatment	Acute exacerbations	
	Present	Absent
Double Inhaler Therapy	11	19
Single inhaler Therapy	9	21
Total	20	40

There was improvement in symptoms of the patients but no significant change in spirometry value were found in both groups. In this research, it was discovered that single inhaler therapy had a statistically substantial advantage over double inhaler therapy in terms of patient adherence to inhalers. Koehorst-ter Huurne *et al.* (2018) ^[16] showed that patients with poor adherence to their prescribed medicine had an increased risk for severe AECOPD because of the effects of inhalation drugs and general behavior influenced by a belief of patient on COPD in relation to treatment modalities. Our study showed that, CAT Score was more initially in Single Inhaler Therapy compared to Double Inhaler Therapy but this is not statistically significant. It was observed that Post treatment CAT Score was less in single Inhaler Therapy compared to double Inhaler Therapy. Other studies didn't take CAT score as a variable, therefore there is lack of evidence in this regard.

Conclusion

For COPD patients, using a single inhaler triple therapy resulted in a lower rate of exacerbations, as well as improved lung symptoms and quality of life. Based on our study, COPD patients who use single inhaler triple drug therapy have a clinically significant improvement resulting in lower all- cause mortality and complications when compared to patients who use multiple inhalers triple drug therapy. Since rate of exacerbations in our

study was not statistically significant, hence it requires a greater number of patients to follow up for more longer duration to get more significant outcome.

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