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Evaluation of the effectiveness and safety of treatments used in patients suffering from chronic obstructive pulmonary disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is now one of the top three causes of death worldwide. Despite the availability of various kinds of treatments, there is a paucity of data regarding potential treatment for COPD. **Aims and Objectives:** This study has been carried out to evaluate the effectiveness and safety of treatments used for COPD. **Materials and Methods:** A prospective, longitudinal, observational study was carried out at a tertiary care teaching hospital. A total of 105 patients were included and divided into two treatment groups: Group budesonide + formoterol (BF) and group fluticasone + salmeterol (FS) based on the treatment they received. Patients' details were recorded in a pre-defined case record form. Effectiveness was evaluated and compared between the two treatment groups in terms of the number of exacerbations experienced, the mean reduction in COPD assessment test (CAT) score, and the mean change in forced expiratory volume 1 s (FEV1%) at the end of the study period. Safety was assessed by recording adverse drug reactions. **Results:** Out of a total of 105 patients with COPD, 67 (63.80%) patients belonged to group BF and 38 (36.19%) patients belonged to group FS. Twenty-seven (40.30%) patients from Group BF (n = 67) and 18 (47.37%) patients from group FS (n = 38) developed exacerbations. No statistically significant difference between group BF and group FS was observed in terms of mean reduction in CAT score (P = 0.17) as well as mean change in FEV1% (P = 0.38) from baseline to the end of 6 months of treatment. **Conclusion:** Our study concludes that inhalational corticosteroids/long-acting beta-agonist combinations such as BF and FS are equally effective in terms of reduction in frequency and severity of exacerbation, reduction in CAT score, and improvement in lung functions (FEV1%).

Key words: Budesonide + formoterol; Chronic obstructive pulmonary disease assessment test, Chronic obstructive pulmonary disease; Effectiveness; Fluticasone + salmeterol

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, treatable, and preventable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or other alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Chronic COPD is now one of the top three causes of death worldwide.[1] The prevalence ranged between 2% and 22% among men and 1.2–19% among women in different population-based studies across India. Some studies have estimated prevalence between 6.5% and 7.7%.[2] The diagnosis of COPD is based on the clinical symptoms which include dyspnea, cough, and sputum production. The confirmatory test for COPD is the pulmonary function test (PFT) or spirometry. The presence of post-bronchodilator forced expiratory volume (FEV1)/forced vital capacity <0.70 confirms the presence of persistent airflow limitation and thus of COPD in patients with appropriate symptoms and significant exposure to noxious stimuli.

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The global initiative for chronic obstructive lung disease (GOLD) criteria classifies COPD into four stages based on PFT as follow:[1]

GOLD 1	Mild	FEV1 ≥80% predicted
GOLD 2	Moderate	50% ≤FEV1 <80% predicted
GOLD 3	Severe	30% ≤FEV1 <50% predicted
GOLD 4	Very severe	FEV1 <30% predicted

The mainstays of management of COPD include lifestyle changes such as smoking cessation and pharmacological management.[3] Pharmacotherapy for stable COPD includes different types of bronchodilator drugs such as short-acting bronchodilators (short-acting beta agonist [SABA] and short-acting muscarinic antagonist) and long-acting bronchodilators (long-acting beta-agonist [LABA] and long-acting muscarinic antagonist). These drugs can be used alone or in combination with each other or in combination with inhaled corticosteroids.[1] Combining drugs with different mechanisms and duration of action may increase the degree of bronchodilation with equivalent or less adverse effects. A combination of a SABA and anticholinergic drug in stable COPD produces greater and more sustained improvement in FEV1 than either alone.[4] Accordingly, there is evidence that inhalational corticosteroids (ICS) combined with a LABA are more effective than the individual components in reducing exacerbations and improving lung function and health status. The addition of theophylline to beta 2 agonists or anticholinergic drugs may produce additional improvements in lung function and health status.[5] Because of the availability of drugs with different mechanisms, efficacy, and safety, it is important to select the appropriate treatment regimen that is more effective and has less side effects for COPD as it is a chronic condition. Despite the importance of COPD as a major disease burden, there is a paucity of high-quality efficacy and safety data concerning potential treatments. Frequent exacerbations which are potentially life-threatening are also a major concern to patients with chronic COPD. Therefore, this study was conducted to evaluate the effectiveness and safety of different treatments used in COPD patients.

Aims and objectives

To evaluate effectiveness and safety of treatments used in patients suffering from Chronic Obstructive Pulmonary Disease attending out patient department of pulmonary medicine at tertiary care teaching hospital.

MATERIALS AND METHODS

Study patients

Patients between the ages of 18 and 70 years and of either gender who attended the outpatient department (OPD) of pulmonary medicine at a tertiary care teaching hospital, and were diagnosed to have moderate-to-severe COPD (30% ≤FEV1<80%) as per GOLD[1] criteria by a clinician were included in the study after taking written informed consent-ICF.

Patients who were suffering from very severe COPD (FEV1 <30% predicted) or terminally ill patients and patients having concomitant medical disorders such as cardiac disease, bronchial asthma, and active tuberculosis were excluded from the study.

Patients having incomplete or inadequately filled COPD assessment test (CAT) questionnaires were also excluded from the study.

Study design

The present study was a prospective, longitudinal, observational, and single-center study conducted at OPD of pulmonary medicine at a tertiary care teaching hospital, situated in the western region of India. The total duration of the study was 24 months. Enrolment of new patients was done for 18 months. Each patient was followed up for the next 6 months.

Statistical analysis

Data were recorded in a Microsoft Excel worksheet and analyzed using descriptive statistics and compared using the Chi-square test and z-test. $P<0.05$ was considered statistically significant.

RESULTS

A total of 117 patients of COPD were enrolled as per inclusion and exclusion criteria and followed up for the next 6 months, out of which 12 patients were lost to follow-up (FU), nine after the baseline visit, two after the first FU visit, and one after the second FU visit and excluded from analysis. Based on the treatment given for COPD, out of 105 patients who were included in the analysis, 67 (63.80%) patients belonged to group BF, and 38 (36.19%) patients belonged to group FS. Group BF patients were treated with metered dose inhaler (MDI) containing a fixed dose combination of budesonide 200 mcg and formoterol 6 mcg twice a day. Group FS patients were treated with MDI containing fluticasone 250 mcg and salmeterol 25 mcg twice a day.

Baseline demographic characteristics for both the treatment groups were found comparable when analyzed using z-test and Chi-square test (Table 1).

In the present study, dyspnea (105 patients, 100%), cough (98 patients, 93.33%), and chest pain (19 patients, 18.09%) were observed. Other clinical symptoms were fever (18 patients, 16.66%), generalized weakness (17 patients, 16.19%), and sore throat (12 patients, 11.42%).

Table 1: Baseline demographic details

Characteristic	BF* (%)	FS** (%)	P-value
Age (years)	56.83±7.80	59.21±7.74	0.06
Gender			
Male	47 (70.15)	24 (63.15)	0.294
Female	20 (29.85)	14 (36.84)	
BMI#	20.08±2.10	19.57±1.40	0.067
H/O smoking			
Current smoker	39 (58.21)	21 (55.26)	
Non-smoker	28 (41.79)	17 (44.74)	0.183
Past history			
Tuberculosis	36 (53.73)	19 (50)	0.57
Occupational lung disease	5 (7.46)	3 (7.89)	0.78

*BF: Budesonide and Formoterol, **FS: Fluticasone and Salmeterol, #BMI: Body mass index

Effectiveness analysis

The effectiveness of both treatment regimens was measured and compared by the parameters such as a number of exacerbations the patient has experienced during 6 months of the FU period, mean reduction of CAT score, and mean change in FEV1%.

Exacerbation

Out of a total of 105 patients, who completed the study period, 27 (40.30%) patients from group BF (n=67) and 18 (47.37%) patients from group FS (n=38) developed exacerbations. No statistically significant difference was observed between treatment group BF and treatment group FS regarding the rate of exacerbation (P=0.31) (Table 2).

No statistically significant difference was observed in the severity of exacerbation experienced by patients between treatment group BF and treatment group FS (Figure 1).

CAT score

Out of a total of 67 patients who belonged to group BF, the CAT scores ranged from 12 to 20 at the time of enrolment with mean±standard deviation (SD) of 16.32±2.23, whereas, out of a total of 38 patients who belonged to group FS, the CAT scores ranged from 12 to 22 with mean±SD of 16.63±2.80, which was found comparable as there was no statistically significant difference in CAT scores between group BF and group FS (Z-test) (Table 3).

The reduction in CAT score at each FU visit as compared to the previous visit was found statistically significant in both the treatment groups (BF and F) as shown in Table 3. However, no statistically significant difference between group BF and group FS was observed in the mean reduction in CAT score from baseline CAT score at the end of 6 months of treatment (P<0.05, z-test) (Figure 2).

A statistically significant difference was observed in the mean reduction in CAT score in group BF and group FS at the end of 6 months of treatment from baseline CAT score (Figure 2).

Table 2: Number of patients with exacerbations in each treatment group during study period

Treatment groups	No. of patients with exacerbations (%)	No. of patients without exacerbations (%)	P-value
Group BF (n=67)	27 (40.30)	40 (59.70)	
Group FS (n=38)	18 (47.37)	20 (52.63)	0.31

BF: Budesonide and Formoterol, FS: Fluticasone and Salmeterol

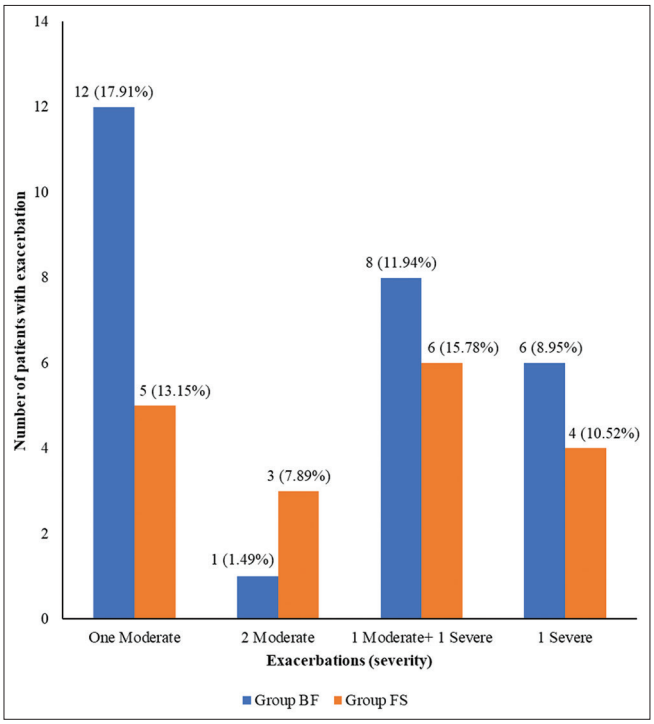

Figure 1: Comparison of the number of exacerbations experienced by patients in different treatment groups

PFT

In group BF, FEV1% ranged from 35 to 53 at the time of enrolment with a mean FEV1% of 43.28±4.63, whereas, in group FS patients, the FEV1% ranged from 35 to 52 at the time of enrolment with the mean FEV1% of 43.10±4.85. Both the treatment groups were comparable in terms of baseline mean FEV1% as there was no statistically significant difference observed.

No statistically significant difference was observed between the two groups in terms of mean change in FEV1% at the end of 6 months of treatment (Figure 3).

A statistically significant difference was observed in the mean change in FEV1% in group BF and group FS at the end of 6 months of treatment from baseline FEV1% (Figure 3).

Table 3: Difference in CAT score at each FU from baseline

Mean CAT score 1st visit (Baseline)	Group BF (Mean±SD) 16.32±2.23	P-value	Group FS (Mean±SD) 16.63±2.80	P-value
1st FU	15.43±2.13*	0.008	15.50±2.50*	0.031
2nd FU	15.37±2.33*	0.007	15.60±2.44*	0.045
3rd FU	15.28±2.58*	0.006	14.97±2.67*	0.004
4th FU	15.02±2.47*	0.0007	15.05±2.42*	0.004
5th FU	14.86±2.42*	0.0001	14.68±2.10*	0.0003
6th FU	14.20±2.30*	0.0000000338	14.73±2.32*	0.0006

*Statistically significant difference in mean reduction in CAT score from baseline visit (Z-test, *P*<0.05), FU: Follow-up

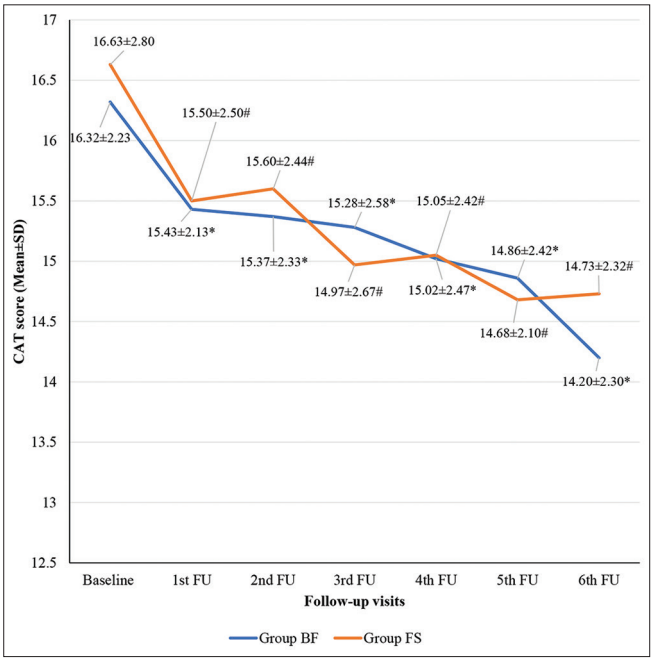

Figure 2: Comparison of chronic obstructive pulmonary disease assessment test scores between different treatment groups (mean±standard deviation). *The mean chronic obstructive pulmonary disease assessment test (CAT) score was significantly reduced at each follow up from baseline visit from the visit in group BF (Z test, P<0.05), #The mean CAT score was significantly reduced at each follow up visit from baseline visit in groups FS (Z test, P<0.05)

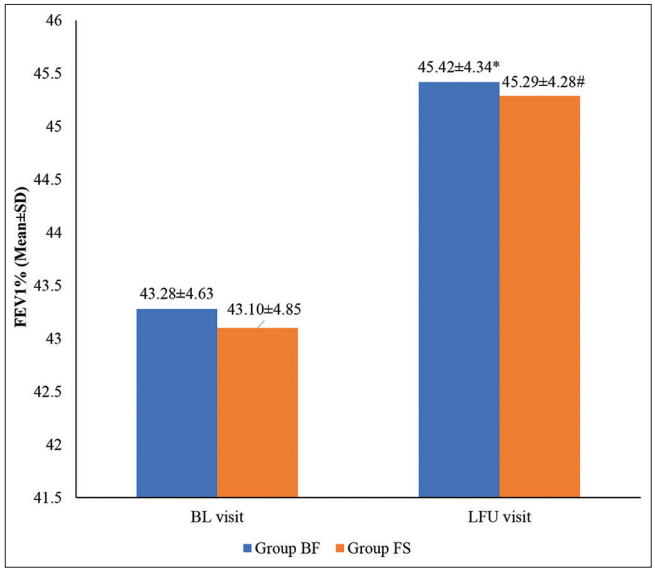

Figure 3: Change in forced expiratory volume 1% at 6 months of treatment from baseline visit (mean±standard deviation). *Statistically significant difference observed in the mean forced expiratory volume 1 s (FEV1%) at last follow up visit from the baseline visit in group BF (Z test, P<0.05), #Statistically significant difference observed in th mean FEV1% at last follow up visit from the baseline visit in group FS (Z test, P<0.05) (BL- Base line, LFU- Last follow up)

Safety analysis

Out of 105 patients, 61 patients developed a total of 74 adverse drug reactions (ADRs) during the study period. Out of the reported 74 ADRs, 46 (62.16%) ADRs were observed in treatment group BF, whereas 28 (37.83%) ADRs were observed in treatment group FS.

The most common suspected drug for reported ADR was amoxicillin (27.02%), followed by dyphyllin (25.67%). Other suspected drugs were ambroxol (24.32%) and iron and folic acid (24.32%). However, in seven patients, the suspected drug was budesonide+formoterol (BF) and in only one patient, the suspected drug was fluticasone+salmeterol (FS).

As per the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale, all reported ADRs showed a possible causal relation with suspected drugs. However, as per the Naranjo scale, 48 (64.86%) ADRs had a possible causal relation and 26 (35.14%) ADRs had a probable causal relation with suspected drugs.

Reported ADRs were analyzed for severity by the modified Hartwig and Siegel Scale and preventability by modified Schumock and Thornton criteria. All the ADRs reported were found to be mild and non-serious. No additional treatment was required for the management of ADRs in both treatment groups. Out of a total of 74 ADRs, 55 (74.32%) were not preventable, whereas 19 (25.68%) were probably preventable.

DISCUSSION

COPD is now in the top three leading causes of death in the world and its burden is projected to increase in the

coming days due to increasing exposure of populations to the various risk factors of COPD such as pollution and smoking.[1] A study done in 2012 has shown that the prevalence of the COPD in male population ranged from 2% to 22% whereas in the female population, it ranged from 1.2% to 19%.[2] The diagnosis of COPD is mainly based upon symptoms such as dyspnea and cough and it is confirmed by PFT. As per GOLD reports, management of COPD includes pharmacological therapy, smoking cessation, influenza and pneumococcal vaccines, etc. Pharmacological therapy includes short-acting or long-acting bronchodilators and ICS. Combining drugs with different mechanisms and duration of action may increase the degree of bronchodilation with equivalent or less adverse effects. Our study was intended to analyze commonly used ICS and LABA combinations, that is, BF and FS in COPD patients.[1]

A total of 105 patients completed the study. Out of the 105 patients, 67 patients were prescribed BF combination (Group BF), and 38 patients were prescribed FS combination (Group FS). In group BF, patients were prescribed budesonide 200 mcg and formoterol 6 mcg combination inhaler 2 puffs twice a day. In group FS, patients were prescribed fluticasone 250 mcg and salmeterol 25 mcg combination inhaler 2 puffs twice a day.

In this study, out of a total of 105 patients, 45 (42.85%) patients developed exacerbations, of which 27 patients (60% of 45 patients) belonged to group BF, and 18 patients (40% of 45 patients) belonged to group FS. There was no significant difference in the number of patients with exacerbations between the two treatment groups at the end of the study. The number of exacerbations in our study was found slightly lower than the other study done in 2011 in which 63.4% of patients from BF group (n=3385) developed exacerbations, whereas, 62.5% of patients from FS group (n=3385) developed exacerbations. However, there was no significant difference between the two treatment groups in the number of patients with exacerbations an observation similar to this study. In our study, the number of patients with exacerbations in both treatment groups was lower compared to the study done in 2011.[6] The higher number of exacerbations experienced by patients in later studies might be due to the inclusion of patients with comorbidities such as asthma, diabetes mellitus, which were excluded from our study. In our study, out of 67 patients of group BF, 12 patients (17.91%) experienced one moderate exacerbation, 1 patient (1.49%) developed two moderate exacerbations, 8 patients (11.94%) developed one moderate and one severe exacerbation and 6 patients (8.95%) developed one severe exacerbation, whereas out of 38 patients of group FS, 5 (13.15%) experienced one moderate exacerbation, 3 patients (7.89%) developed two moderate exacerbations, 6 patients (15.78%) developed one moderate and severe exacerbation and 4 patients (10.52%) developed one severe exacerbation. In another similar study (n=90), there were 171 episodes of exacerbations observed during the period of study, out of which 72.5% were moderate, whereas 27.5% were severe exacerbations, which is similar to our study. The majority of exacerbations experienced by patients of both treatment groups were found moderate in severity. This was suggestive of the effectiveness of both these treatment groups to prevent the occurrence of exacerbations and also to reduce the severity of acute exacerbations. There was no significant difference between the two treatment groups in the mean number of moderate and severe exacerbations in another study, an observation similar to this study.[7] In our study, the mean number of total exacerbations observed in treatment group BF and group FS were 0.53±0.70 and 0.71±0.83, respectively. In another study, the rate of exacerbations per patient per year in BF group (n=1131) and FS (n=1131) were 0.63 and 0.71, respectively.[8] Another study showed an annual exacerbation rate of 0.8 in BF group whereas 1.09 in patients treated with FS group.[9] Hence, observations from the above-mentioned studies further approved that both the treatment groups are equally effective in terms of reduction in occurrence and severity of acute exacerbations in COPD patients.

There was no significant difference between the two treatment groups in mean improvement in FEV1% in our study. Similar observations were found in a study in which the average FEV1% in BF group (n=30) and FS group (n=30) at the initial visit were 33.73% and 33.47% respectively, which improved to 36.8% in BF group and 36.60% in FS group at the end of 6 months study. This improvement in both the treatment groups was significant which is similar to our study.[7]

A study carried out in 2016 by Calverley et al., reported that improvement from baseline in FEV1 at the end of 3 months of treatment with BF was 0.16 L in moderate COPD, 0.10 L in severe COPD, and 0.09 L in very severe COPD. This improvement in FEV1 from baseline was significant compared to placebo.[10] Very high improvement of around 10% in FEV1% was observed in one study in China, over a period of 1 year, in which FS was used in higher doses as compared to other studies, as well as patients, were followed up for longer duration of treatment which might be the reason for better improvement in FEV1%.[11]

In our study, a reduction in CAT score from baseline CAT score in both the treatment groups was significant but the difference between the two groups was not significant. In a study carried out by Tamási et al., the mean CAT score

reduction was found to be around 6 after 12 weeks of treatment with BF (n=778). The later study was conducted to evaluate inhaler effectiveness in patients treated by pulmonologists in Hungary, in which patients were well compliant with a newer drug delivery device – Easyhaler that might be the reason for better effectiveness for CAT score reduction.[12]

A total of 74 ADRs were observed in a total of 61 patients in our study, out of which 46 (62.16%) ADRs were observed in treatment group BF, whereas 28 (37.83%) ADRs were observed in treatment group FS. Commonly observed ADRs in treatment group BF patients were abdominal discomfort (30.43%), followed by nausea (23.91%), and diarrhea (17.39%). In group FS patients, commonly observed ADRs were abdominal discomfort (28.57%) and nausea (28.63%) followed by sedation (21.42%). The majority of the observed adverse reactions were due to concomitant medication use. The most common suspected drug for reported ADR was amoxicillin (27.02%), followed by dyphyllin (25.67%). Other suspected drugs were ambroxol (24.32%), iron, and folic acid (24.32%). However, in seven patients, the suspected drug was BF and in only one patient, the suspected drug was FS. In another study done in 2012 over a period of 6 months, the most commonly observed ADRs were nasopharyngitis, sinusitis, diarrhea, and candidiasis which is different from our study as it was a randomized controlled trial where no other concomitant medications were used and also medication where given by MDI as well as dry powder inhaler.[13] In our study majority of ADRs were due to concomitant medications. In our study, study drugs were given by inhalation route by MDI so caused less ADRs compared to other concomitant medications which were given by oral route.

All the suspected ADRs reported by patients were possible as per the WHO-UMC scale, whereas 48 (64.86%) were possible and 26 (35.14%) were probable as per the Naranjo scale. All the reported ADRs were mild in nature and non-serious. Out of a total of 74 ADRs, 55 (74.32%) ADRs were not preventable, whereas 19 (25.68%) ADRs were probably preventable.

The strength of our study was the stringent inclusion criteria and exclusion criteria. We have used the number of parameters/tools such as exacerbation rate, PFT components, and CAT questionnaire to assess the efficacy which makes our study different from other previous studies.

Limitations of the study

There were certain limitations in our study, first, the sample size of the study was small. Furthermore, patients were followed up for 6 months of the treatment and findings can not be generalized based on such a short duration considering the fact that COPD is a chronic disease.

CONCLUSION

Our study concludes that ICS/LABA combinations such as BF and FS are equally effective in terms of reduction in frequency and severity of exacerbation, reduction in CAT score, and improvement in lung functions (FEV1%). Both treatment strategies are found safe as the number of ADRs observed is less in number, mild, non-serious, and preventable in nature. We further recommend a large-scale study with a longer duration for evaluation of the efficacy and safety of BF and FS with due consideration of economic aspects in COPD patients.

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JC- Concept, design, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation and submission of article; **MS-** Concept, design, manuscript editing, manuscript revision and supervision; **CD-** Design, revision, supervision and validation.

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