Original Article

Combinations of long acting β_2 agonists to tiotropium: A randomized, double-blind, placebo-controlled, active-drug controlled, parallel design academic clinical trial in moderate COPD male patients

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ABSTRACT

Introduction: The fixed dose combinations used in chronic obstructive pulmonary disease (COPD) patients need their rationale evaluation. If there is no added benefit; then it amounts economic burden on the society, reduced compliance, and unsuccessful therapy. This study evaluated the effectiveness of three regimens of dry powder inhaled preparations including tiotropium 18 μg once a day; tiotropium 18 μg plus formoterol 12 μg once a day, and tiotropium 18 μg once a day plus formoterol 12 μg twice a day in moderate COPD patients. **Materials and Methods:** A randomized, double-blind, placebo-controlled, active drug controlled parallel design study was conducted in 42 moderate COPD patients without any other comorbidity. Three (R1, R2, and R3) regimens were evaluated in patients to assess the appropriate evidence-based pharmacotherapy regimen. The forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), Borg's scale of dyspnea, and vital signs (blood pressure and pulse rate) were measured on serial time points for 24 h. **Results:** The trough FEV_1 values of R1, R2, and R3 in liters were 1.836 $\pm$ 0.51, 1.886 $\pm$ 0.47, and 1.805 $\pm$ 0.37, respectively and did not show any statistical difference. No statistical significance was observed in FVC (liters), FEV_1% predicted, ΔFEV_1 (liters), ΔFEV_1% predicted, ΔFVC % predicted, and Δ FVC (liters) except in 24 h FVC percentage predicted values where *P* - value for R3 is in the range between 0.05 and 0.1 over R1. **Conclusions:** Study shows that tiotropium alone once a day is the evidence based and rationale pharmacotherapy in moderate COPD. There is no advantage or statistical significance of adding long acting β_2 agonists (LABA) such as formoterol to tiotropium either for 12 h (once daily) or 24 h (twice daily).

INTRODUCTION

The chronic obstructive pulmonary disease (COPD) is categorized as progressive obstructive limitation of airways leading to breathlessness. It has shown growing trends all over the world including developing countries such as India.[1,2] It is the fourth leading cause of the death[3] and major morbidity factor for increased cost and healthcare burden in the society.[4,5] The data for its early diagnosis are lacking which pose a major obstacle for its prevention, treatment decision making and further management outcomes.[6] It has been categorized into different severities by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and American Thoracic

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Society (ATS)/European Respiratory Society (ERS) guidelines.[1,7] The long acting bronchodilators are preferred over the short acting bronchodilators.[1]

There is increased use of fixed dose combinations of long acting muscarinic antagonists (LAMA) and long acting β_2 agonists (LABA) for its treatment.[8] They have been excitingly used in COPD patients within all the severities and thought to impact the treatment process.[9] Although there are conflicting data regarding the efficacy of combination of tiotropium and salmeterol[10-12] but the addition of formoterol with tiotropium also have not shown consistent outcomes.[12,13] The developing countries such as India vehemently prescribe such fixed dose combinations and has become the first country to approve the marketing authorization to the triple inhaler.[8,14] One such combination uses formoterol having 12 hours duration of action[15] and tiotropium having 24 hours.[16] Certainly such combinations increase the cost of therapy and financial burden on the healthcare system and may lead to poor patients' compliance in developing countries.[1]

The present study was done to evaluate the effectiveness of three different regimens consisting of tiotropium and formoterol combinations in moderate COPD patients so that to observe the 12 hour as well as 24 hour protection by the LABA along with 24 hour acting LAMA.

MATERIAL AND METHODS

Participants

A total of 42 patients were enrolled in the study after Institutional Ethical Committee (IEC) approval from Vallabhbhai Patel Chest Institute, Delhi. All the patients were diagnosed with the help of spirometry and clinical symptomatology. Those having forced expiratory volume in 1 s (FEV_1)/ forced vital capacity (FVC) ratio less than 0.7 and FEV_1 percentage predicted in the range of ≥50 to <80 were categorized as moderate COPD patients as per the GOLD guidelines criteria.[1] All the enrolled patients were ≥35 years of age who were current or exsmoker having smoking history of ≥10 pack years. The patients were excluded from the study if there was history of significant disease of cardiovascular system apart from the COPD such as recent history of myocardial infarction, heart failure, and cardiac arrhythmias. The patients were also not taken in the study if there was current or past history of asthma, allergic conditions, taking oxygen therapy, known to have a diagnosis of benign hyperplasia of prostate, narrow angle glaucoma, other respiratory infections, and COPD exacerbations in last 4 weeks.

Allocation

Once the diagnosis of COPD was made clinically and with the help of diagnostic spirometry 30 min after the two puffs of 100 μg salbutamol, the other baseline investigations such as complete hemogram, chest X-ray, and electrocardiogram (ECG) were done. The patients were allocated to one of the three computer-generated randomized groups and training of dry powder inhalation intake was given. They were asked to come next day in the morning at 8 AM for 24 h hospital admission under the supervision of principal investigator. Those patient who had taken short-acting bronchodilators just before the enrolment or long-acting bronchodilators at least 48 h before were not allowed to take part in the study. The study was made double blind by keeping the principal investigator (doctor), patients, and spirometry technicians blind. All the three treatment arms had active drugs in the morning and two of them had formoterol-matched placebo in the evening. The study was planned for 1 year and all the moderate COPD patients who came in that year were enrolled, thus exceeding 12 patients in each arm. It was completed in 1 year in 2008.

Protocol changes

The comorbidities are usually associated with higher age group COPD patients and they impact the net mortality and hospitalization.[17] It was difficult to find COPD patients without comorbidity, thus age criteria was relaxed with the proper approval of the IEC from 35 to 60 years to 35 years and above.

Data collection

The medication was administered and serial spirometry was done after written informed consent from the patients. The three groups were categorized as R1 (morning tiotropium + evening placebo-matched for formoterol), R2 (morning tiotropium and formoterol + evening placebo-matched for formoterol), and R3 (morning tiotropium and formoterol + evening formoterol). The patients were stayed in the ward of Clinical Research Centre (CRC) of University teaching tertiary care pulmonary medicine hospital, Delhi, India for 1 day and one night under the supervision of principal investigator. Each patient was assigned to the subsequent group as per their order of diagnosis. The

biostatistician of the institute maintained the blinding by providing air-sealed container containing the dry powder capsules for each patient. The containers were opened and inhaled in the supervision of the principal investigator. The measurement of FEV_1, FVC, Borg's perceptional dyspnea score,[18] blood pressure, and pulse rate was done at the baseline followed by the scheduled time points on 30 min, 2 h, 12 h after morning dose and 30 min and trough values 12 h after the evening dose. The highest values from three technically adequate readings based on ATS criteria were retained. The primary efficacy end points were defined as the improvement or change in FEV_1, FVC, and dyspnea. And secondary end points were FEV_1, FVC peak and trough values, and other spirometry values at individual time points. Apart from this second outcome parameters such as rescue therapy with salbutamol, sleep disturbances and adverse events were measured during the 24 h of the stay of the patients in the hospital.

Statistical analysis

The intra- and intergroup statistical analysis was done with the help of Statistical Package for Social Sciences (SPSS) 20 software. The hierarchical repeated measures analysis of variance (ANOVA) used adjusted means values for calculation followed by Tukey's test. The total sample size was 36 patients; 12 in each group. But patient enrolment continued to get the large number of patients within the stipulated time period of 1 year. There were 42 completed participants; 13 in R1, 15 in R2; and 14 in R3.

RESULTS

The moderate COPD patients without comorbidity underwent spirometry as per the protocol. Around 1,435 patients screened and classified as per the GOLD guidelines;[1] out of which 42 patients turned out to moderate COPD without any comorbidity. All patients who completed the study were male with average age of 47.45 ± 11.12. Table 1 shows the demographic and other baseline characteristics of the participants including average numbers of 'pack years' (calculated by multiplying the number of packs of cigarette smoked by a person per day to the number of years). The therapeutic effects of three different regimens were measured on 30 min, 2 h, 12 h, 12 h 30 min, and 24 h based on the pharmacological effects.[15,16] The FEV_1, FVC, Borg's Scale values, and vitals data were obtained. The data was decoded and analyzed by the statistician.

The 24 h mean values of FEV_1 (liters) in R1, R2, and R3 are 1.836 ± 0.51, 1.886 ± 0.47, and 1.805 ± 0.37, respectively. R1 showed significant improvement in FEV_1 at 30 min (1.717 ± 0.40) and trough values (24 h value) also showed an incremental increase upto 1.836±0.51 [Table 2]. The effects of R2 regimens did not sustain till 24 h and the trough values fell below the 12 h values in that regimen. Same effects were observed in R3 except that the 24 h values were numerically superior to other regimen, although there was no statistical significance (1.805 ± 0.37).

Table 1: Baseline characteristics and demographics of the moderate COPD patients

Variables	Value
Subjects	42
Males	42
Age (years)	47.45±11.12
Smoking history (pack years)	33.90±30.64
BMI (kg/m^2)	21.53±3.73
FEV_1 (reversibility¶)	
% baseline	57.00±7.00
FVC predicted (L)	3.23±0.60
FEV_1/FVC percentage predicted	81.00±2.00
Dyspnea (on Borg's scale)	2.33±0.61
Systolic blood pressure (mmHg)	119.95±10.41
Diastolic blood pressure (mmHg)	73.85±7.38
Pulse rate (beats/min)	79.57±6.09
Baseline FEV_1 (L) of each group	
R1	1.53±0.40 (13)
R2	1.69±0.41 (15)
R3	1.46±0.31 (14)

Values are presented mean±SD (number). COPD=Chronic obstructive pulmonary disease, FEV_1=Forced expiratory volume in 1 s, FVC=Forced vital capacity, BMI=Body mass index, R1=Tiotropium (morning) and formoterol-matched placebo (evening), R2=Tiotropium+formoterol (morning) and formoterol-matched placebo (evening), R3=Tiotropium+formoterol (morning) and formoterol (evening), SD=Standard deviation. ¶30 min following two puffs of Salbutamol (100 µg/puff)

When magnitude of difference (Δ) with the baseline was assessed statistically, there was no statistical significance in ΔFEV_1 (liters), ΔFVC (liters), ΔFEV_1% predicted, and ΔFVC % predicted values. Figures 1 and 2 shows the magnitude of difference (Δ) in FVC in liters (FVC (L)) and FVC in % predicted versus the magnitude of difference time points 1,2,3,4, and 5; which corresponds to difference between the baseline and 30 min, 2 h, 12 h, 12:30 h, and 24 h values. There is no significant difference in all the time points except the 24 h mean FVC% predicted value which corresponds to *P* - value between 0.05 and 0.1. The Borg's Scale of perceptional dyspnea score showed a persistent significant improvement at each time point throughout the 24 h time period. The vitals did not show any significant changes during the observation period. All the participants were well-tolerated on

Table 2: Effects of three regimens on FEV_1 (L) over 24 h in moderate COPD patients

Treatments	No. of patient	Baseline	30 min	2h	12 h	12:30 h	24 h
Forced expiratory volume in 1 s over 24 h (FEV_1)							
R1	13	1.583±0.42	1.717±0.40*	1.733±0.42*	1.800±0.45*	1.838±0.45*	1.836±0.51
R2	15	1.601±0.42	1.702±0.48*	1.786±0.51*	1.878±0.49*	1.954±0.51*	1.886. ± 0.47*
R3	14	1.541±0.38	1.652±0.38*	1.726±0.34*	1.752±0.37*	1.775±0.36*†¶	1.805±0.37*†§¶

*†§¶(P<0.05), *Significant difference from baseline, †Significant difference from 30 min, §Significant difference from 2 h, ¶Significant difference from 12 h. COPD=Chronic obstructive pulmonary disease, R1=Tiotropium (morning) and formoterol-matched placebo (evening), R2=Tiotropium+formoterol (morning) and formoterol-matched placebo (evening), R3=Tiotropium+formoterol (morning) and formoterol (evening)

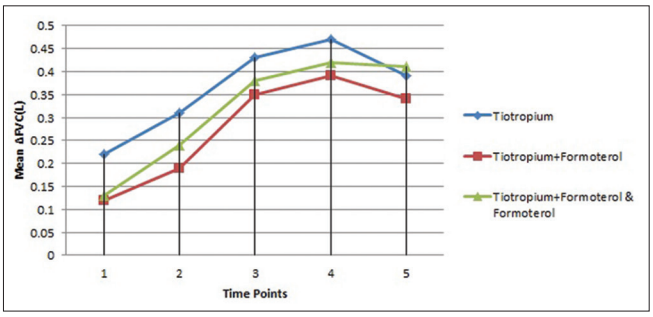

Figure 1: Effect of three regimens on magnitude of difference (Δ) FVC (liters): Moderate COPD patients. COPD=Chronic obstructive pulmonary disease, FVC=Forced vital capacity

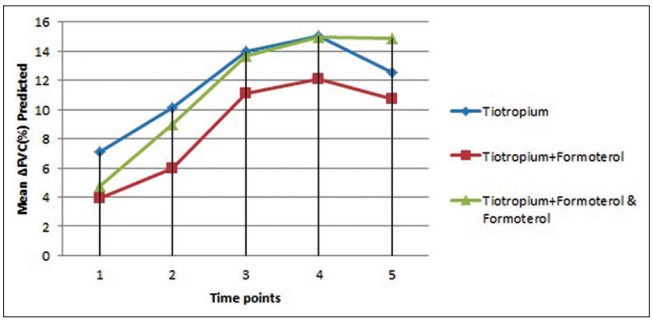

Figure 2: Effect of three regimens on magnitude of difference (Δ) FVC % predicted: Moderate COPD patients

each treatment regimens. There was no use of rescue therapy with salbutamol and no incidents of any adverse events such as tremors and sleep disturbances were seen.

DISCUSSION

The findings of present study revealed that there is no advantage of adding formoterol once a day as well as twice a day along with the tiotropium in moderate COPD patients. It simply reflects that titrated tiotropium alone is an appropriate and rationale therapy in moderate category of COPD patients. This may be because of the predominance of parasympathetic system as a part of etiopathogenesis.[19] The addition of LABA drugs either for 12 h period such as formoterol and salmeterol or for 24 h such as indacaterol along with LAMA may not prove to have an additional favorable statistical outcome.[20,21] As per our findings, the trough values in R3 are found to be numerical superior in comparison to R1 and R2, but there was not much statistical significance.

Although GOLD guidelines 2014 recommends the use of long-acting bronchodilators over the short-acting bronchodilators; but it admits the lack of screening data for making management decisions in early COPD categories.[1] Many studies have provided the conflicting data for the usage of LABA along with LAMA.[10-15,20,21] However, appropriate intervention and evidence-based medicine may provide favorable clinical or economic outcomes.[1] We conducted our study as randomized double-blind controlled clinical academic trial (RCT) with three parallel arms to eliminate the unrecognized biases in patient enrolment as this design has an advantage in drug intervention trials.

Limitation of the study

Despite being it a RCT, there were many limitations in our study. It was an acute study with less numbers of subjects in a single center, and therefore more number of subjects in multicentric sites along with long-term study design may provide exact clinical applicable results. Our study was double blind, hence many of the potential confounding factors such as baseline FEV_1, FVC, age, and pack years could not be matched before the start of the investigations. In addition to the open label design, more number of serial datapoints can be incorporated so that wide variability can be captured in the study. Further studies obviating the limitation of present study may lead to understanding about the rationale treatment for different categories of COPD patients, compliance to the therapy and reducing the cost and burden of therapy on the society.

CONCLUSION

It can be concluded that each category of patients can be considered as separate subset of population and they need individualization of therapy as per the severity. In moderate COPD patients, tiotropium alone is efficacious and appropriate evidence-based therapy. Therefore, the

combinations of other components may add to the cost of the therapy and economic burden and also may even reduce the compliance in poorer countries.

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