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An Acute Therapeutic Evaluation of Three Regimens of Tiotropium and Formoterol in COPD Patients: A Randomized, Double-blind, Placebo-Controlled Clinical Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author MI wrote the protocol and first draft of the manuscript, enrolled the subjects, collected the data and managed the literature search. Author SKC designed the study, analyses and decoded the data. Author AK performed the decoding along with the statisticians. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate therapeutic rationality of combining long-acting β_2-agonists (formoterol) with duration of action of 12 hours and anticholinergics (tiotropium) with 24 hours as fixed dose inhaled combination (FDC) still widely prescribed in developing countries in COPD patients.
Study Design: A randomized, double-blind, placebo-controlled, parallel design study. The three regimens that were used; tiotropium 18 µg once a day in the morning along with the formoterol matched placebo in the evening, the FDC of tiotropium 18 µg plus formoterol 12 µg once a day in

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the morning and formoterol matched placebo in the evening and the same FDC of the two drugs once a day in the morning and once a day formoterol 12 µg in the evening in patients of COPD without any co-morbidity.

Place and Duration of Study: Tertiary care pulmonary medicine university teaching government hospital of Delhi, India; 1 year.

Methodology: Sixty COPD patients (Male, Avg. age 56±11 years) divided into 3 groups of 20 each without any comorbidity were admitted in the hospital for 24 hours. The spirometry, perception of dyspnea on Borg's scale and vitals such as blood pressure (BP) and pulse rate (PR) were recorded at the following interval 30 minutes, 2 hours, 12 hours after the morning dose and 30 minutes and 12 hours after the evening dose.

Results: Addition of formoterol in the evening along with the FDC in the morning enhanced the peak effects in percentage predicted FEV_1 (*82.55+/-12.639*), FEV_1/FVC (0.592±0.097) that remained till the next dose (24 hours) which was statistically (*P=.05*) superior to the tiotropium alone group (*75.55+/-17.981*) as well as FDC alone group (*74.55+/-12.655*).

Conclusion: There is no advantage of FDC once a day over tiotropium alone. However addition of evening dose of formoterol has shown therapeutic superiority over once a day FDC of the two in COPD.

Keywords: Chronic Obstructive Pulmonary Disease (COPD); Fixed Dose Combinations (FDCs); long acting-muscarinic antagonists (LAMA); long acting β_2 agonists (LABA); tiotropium, formoterol.

ABBREVIATIONS

ANOVA: Analysis of Variance; ATS: American Thoracic Society; BMI: Body Mass Index; BP: Blood Pressure; COPD: Chronic Obstructive Pulmonary Disease; ECG: Electrocardiogram; FDC: Fixed Dose Combination;FEV1: Force Expiratory Volume in 1 second; FVC: Forced Vital Capacity; GOLD: Global Initiative on Obstructive Lung Diseases; LABA: Long acting beta-2 agonist; LAMA: Long acting muscarinic antagonists; PR: Pulse rate.

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by chronic and progressive limitations of airways. As the disease progresses, from mild to moderate and ultimately to severe; obstruction becomes more pronounced leading to the dyspnea even on modest physical activity [1]. It carries huge burden in terms of disability, quality of life, health care cost and caregiver involvement [2-4]. The natural history of the disease can be modified by early recognition at mild to moderate stage and intervention by preventing the remodeling of smooth muscles of the airways [5]. In addition to smoking cessation and avoidance of other occupational health hazards, inhaled bronchodilator medications are central to the management of COPD. Recent guidelines recommend the regular treatment with mono or combination of long acting bronchodilators [1,6].

Many large studies have demonstrated the superiority of combination of short acting β_2-agonists with short acting anticholinergic ipratropium over single agent alone [7-9]. The pharmacological basis of the combinations of short acting agents as FDCs is determined by the comparable duration of action of the two components and additive effects due to action on different receptor mechanisms. Similarly long acting β_2-agonists (LABAs) and long acting anti-cholinergic are recommended for either alone or in combinations for COPD management [10-12]. However, still available FDCs of LABAs such as formoterol and long acting anti-cholinergics such as tiotropium in developing countries appears to be pharmacologically inappropriate [13] in terms of their duration of actions, half-lives and chronobiology of the breathlessness in COPD patients in the night time. LABAs such as formoterol and salmeterol and long acting anti-cholinergics like tiotropium have duration of action of 12 hours [14,15] and 24 hours [16] respectively.

Up to now, there has been lots of confusion on defining appropriate regimen of the combination therapy involving tiotropium and LABAs [17]. As highlighted by Tennat et al. [18] these drugs have complimentary action on the airways. Cazzola et al. [19] also found an additive action of tiotropium and formoterol in COPD using single dose design. Although many FDCs or

Fixed Ratio Combinations are available in the market with formoterol or Indacterol, Yet the prevalent use of combinations with formoterol in developing countries necessitates the examination of its appropriateness. In addition to that not many studies of these have been conducted in plain COPD patients without any comorbidity.

The purpose of present study was to compare the 24 hour effectiveness of three regimens tiotropium 18 µg once a day (Gr1) in the morning along with the formoterol matched placebo in the evening, the FDC of tiotropium 18 µg plus formoterol 12 µg once a day (Gr2) in the morning and formoterol matched placebo in the evening and the FDC of the two drugs once a day in the morning and an once a day formoterol 12 µg in the evening (Gr3) in mild to moderate patients of COPD without any co-morbidity. All the regimens were made similar by providing similar color capsules and formoterol matched placebo in the evening where only tiotropium or FDC was administered. The serial spirometry over 24 hour observation period including 30 minutes reading was done to examine the rationality of formoterol in the once a day morning administration of FDC of tiotropium and formoterol.

2. MATERIALS AND METHODS

2.1 Patients

Patients were all males, aged ≥ 35 years, and current or ex-smoker with a ≥ 10 pack-years smoking history. All patients had a diagnosis of COPD having stable airways obstruction with FEV1 ≥ 50% predicted and a FEV1/FVC < 70% [1]. The patients diagnosed only as mild and moderate COPD were enrolled in this study.

Exclusion criteria were the current or past history of asthma, allergic rhinitis, atopy or an elevated blood eosinophil count (≥ 600 mm^3), significant disease other than COPD, recent history of myocardial infarction, heart failure and cardiac arrhythmia requiring treatment. Also patients with any of the following such as oxygen therapy, known symptomatic prostatic hypertrophy and narrow angle glaucoma were excluded. In addition patients with a respiratory infections or COPD exacerbations in the last 4 weeks were not taken into the study.

2.2 Study Design

This study was approved by the Institutional Ethics Committee (IEC) and written informed consent was obtained from the patients before the administration of medication and scheduled serial spirometry. It was a randomized, double blind, placebo-controlled, clinical study conducted for 24 hours after the patient enrolment. Patients who had history suggestive of COPD were undergone diagnostic spirometry (30 minutes after taking 2 puffs of salbutamol 100 µg puff) and other baseline investigations followed by other tests like chest X-ray, complete hemogram and ECG (Electrocardiogram). Patients were asked to come next day morning at 8 AM for admission and participation in the study for next 24 hours after imparting the training to inhale the dry powder capsules. The study was completed in one year time in April 2008.

2.3 Protocol Change

It was difficult to find COPD patients without comorbidity even in a tertiary care setting such as ours. Therefore the age of the participants having plain COPD was replaced as 35 years and above in place of 35-60 years with the approval of IEC to increase the possibility of enrolling patients without comorbidities.

2.4 Procedure

Patients were admitted in Clinical Research Centre (CRC) now known as Vishwanathan Chest Hospital of Vallabhbhai Patel Chest Institute (VPCI), Delhi, India by the clinical investigator (author). The patients remained in the hospital for one day and a night in order to participate for the 24 hours study period. All patients were categorized into three groups containing 20 patients each (1, 2 and 3) by computer generated simple randomized allocation sequence table. The three separate arms were given three separate regimens with formoterol matched placebo in the evening in tiotropium alone and one of the FDC alone arms. They were given one of the three treatments according to the randomization and order of enrolment in the study. The air sealed containers containing dry powder inhalers capsules were coded as 1, 2 and 3 along with serial numbers for the respective groups by the Biostatician of the institute.

The coded containers were opened and medication was inhaled by the patients in the presence and under the supervision of the clinical investigator each time, keeping all the investigators, pulmonary technician as well as patients blinded for the inhaled medications. The

entire drug intake was made similar by inhaling a capsule in the morning and a capsule in the evening.

The evening dose was administered approximately 12 hours after the morning dose of study medication. All parameters including spirometry, perception of dyspnea on Borg's scale and vitals such as blood pressure (BP) and pulse rate (PR) were recorded at the following interval 30 minutes, 2 hours, 12 hours after the morning dose and 30 minutes and 12 hours after the evening dose.

2.5 Measurements

At the start of study patients underwent a medical examination, ECG recording and other laboratory screening tests. At the screening visit, bronchodilator responsiveness was tested by measuring FEV_1 30 minutes after the inhalation of two puffs of 100 µg of salbutamol.

Patients were then called on a suitable day for 24 hours stay in the ward of the hospital. Initial baseline values of FEV_1 and FVC along with Borg's scale of dyspnea reading were recorded before the morning dose. All these parameters were recorded serially for the next 24 hours on the fixed schedule timings by the expert technician in presence of the clinical investigator. The measurements were performed with a spirometer meeting ATS criteria [20]. The highest values of FEV_1 and FVC from three technically adequate measurements were retained. The primary efficacy endpoints were the improvement or change in FEV_1 and FVC at each assessment scheduled timings till 24 hours and improvement in dyspnea measured at each scheduled timings. Long acting β_2-agonists were not allowed for at least 48 hours before the start of the study and short acting inhaled bronchodilators during the study. Secondary outcome parameters were rescue therapy with salbutamol, adverse events and sleep disturbances monitored by the clinical investigator.

Secondary end points were trough and peak FEV_1 and FVC as well as FEV_1 and FVC values at individual time points. Trough value was defined as the value measured at the end of the 24 hours observation period i.e. 24 hours and 12 hours after the morning and evening dose respectively.

2.6 Analysis

The planned sample size was 60 completed patients, assuming a difference of 140 ml in FEV_1 for paired differences. This sample size provides a power of 90% (Confidence interval of $61.814 \leq x \leq 68.185$) to detect a true difference in average FEV_1 over 24 hours (type I error rate .05). The intragroup and intergroup analysis with respect to each group baseline was done for each time points. For all end-points, adjusted means for the three treatments were calculated using a Hierarchical Repeated measures Analysis of Variance (ANOVA) followed by post-hoc Tuckey test and line graph was drawn with the help of Microsoft Excel 2010.

3. RESULTS AND DISCUSSION

3.1 Results

All patients who were diagnosed with COPD during the study period were screened according to the study protocol in the outpatient department of the CRC of the VPCI. After screening of 1435 patients, a total of 60 patients were enrolled in the study by the clinical investigator. The demographic and baseline characteristics of enrolled patients are presented in Table 1. Patients were classified according to the GOLD guidelines [1] and they were randomized to get any of the three regimens.

All enrolled60 patients completed the study. The effects of three regimens were studied for 24 hours on lung functions (spirometry) at 30 minutes, 2 hours, 12 hours, 12 hours and 30 minutes and 24 hours intervals. Dyspnea was measured on Borg's scale each scheduled timing. The BP and PR were measured at above-mentioned interval till 24 hours. Decoding was done by statisticians and results were analysed.

3.1.1 The effects of three regimens on lung functions: Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC)

Effects of Gr1 showed significant improvement in FEV_1 and FVC at 30 minutes and it remained almost same at all observation time intervals till 24 hours after its inhalation. In addition the effects in Gr2 showed added improvement with time at 2 hours and 12 hours. The 24 hours value of FEV_1 and FVC came back almost to the same as that of observed at 12 hours in this group. However the Gr3 had extra response when added with the formoterol (12µg) after 12 hours and there was improvement in FEV_1 at 12:30 hours and 24 hours. FEV_1 value at 24 hours in this group was highest among the three groups and statistically more than the value observed at

12:30 hours. FEV_1/FVC in percentage predicted (Fig. 1) as well as FEV_1/FVC in Litres (Table 2) showed similar results in all the three groups as that of individual FEV_1 and FVC value changes. Thus administration of formoterol in the evening led not only the improvement at 30 minutes after its administration but also increased values at 12 hours (i.e., 24 hours value).

Magnitude of change in FEV_1 (percentage predicted) at each observation from the baseline clearly showed the superiority of adding formoterol in the morning in Gr2 over the tiotropium alone but the values are returned back to the 12 hours value levels however in case of Gr3 they do not returned back to the 12 hours values (Table 3).

3.1.2 Dyspnea

Dyspnea was measured on Borg's scale [21] which is a perception dyspnea score in which patients marked the answers according to their own perception of breathlessness. Borg's scale values showed improvement in all the three regimens. At each observation time point there was statistically significant improvement in dyspnea in all the three regimens over 24 hours of the study period.

Table 1. Demographics and baseline characteristics of the study population

Variables	Values	
Subjects	60	
Male	60	
Age (yrs)	56±11	
Smoking history (pack years)	30±27	
BMI (Kg/m^2)	21.5±3.7	
FEV_1 Reversibility¶	% baseline	65±15
	FVC predicted (litre)	3±0.6
	FEV_1/FVC percentage predicted	81±1.7
Dyspnoea (on Borg's scale)	2.2±0.6	
Systolic blood pressure (mmHg)	120±10	
Diastolic blood pressure (mmHg)	74±7	
Pulse rate (Beats per minute)	79±7	
Baseline FEV_1(L) of each group:		
Tiotropium (morning) & Formoterol matched Placebo (Evening)	1.814±0.561	
Tiotropium + Formoterol (morning) & Formoterol matched Placebo (Evening)	1.730±0.512	
Tiotropium + Formoterol (morning) & Formoterol (Evening)	1.657±0.500	

The values are presented as Mean±SD, FEV1: forced expiratory volume in 1 second. FVC: forced vital capacity, BMI: body mass index (Kg/m^2), ¶:30 minutes following two puffs of salbutamol (100 µg/puff)

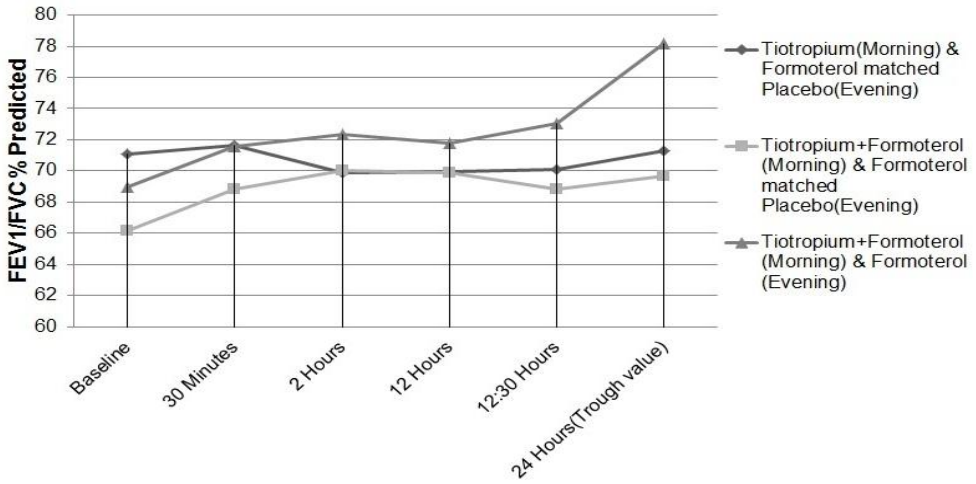

Fig. 1. Effects of three regimens on FEV_1/FVC percentage predicted

Table 2. Effects of three regimens on FEV_1 in percentage predicted and FEV_1 (L)/FVC (L) over 24 hours

Treatments	Baseline	30 min	2 hrs	12 hrs	12:30 hrs	24 hrs
FEV_1 (Forced Expiratory Volume in 1 second over 24 hours)						
T(M) &P(E)	68.60±19.110	73.05±18.016*	73.50±18.297*	75.20±17.127*	75.90±16.924$^{*\dagger\$}$	75.55±17.981*†
T+F(M) &P(E)	63.75±12.611	68.85±15.856*	71.85±16.554*†	74.75±14.186$^{*\dagger\$}$	74.20±11.808$^{*\dagger\$}$	74.55±12.655$^{*\dagger\$}$
T+F(M) & F(E)	64.00±12.674	69.15±12.688*	72.40±12.517*†	74.75±11.557*†	76.70±14.186*†	82.55±12.639$^{*\dagger\$\P}$
FEV_1(Litre)/FVC(Litre)(over 24 hours)						
T(M) &P(E)	0.576±0.094	0.585±0.097	0.571±0.010	0.572±0.100	0.574±0.093	0.580±0.091$^{*\$}$
T+F(M) &P(E)	0.545±0.090	0.565±0.104	0.575±0.111	0.573±0.100	0.583±0.093†	0.572±0.090†
T+F(M) & F(E)	0.566±0.085	0.589±0.096	0.597±0.090*†	0.578±0.097*†	0.586±0.101*†	0.592±0.097*†

$^{*\dagger\$\P}$(p=.05); *-significant difference from baseline, †-significant difference from 30 minutes, $^{\$}$-significant difference from 2 hour value, ¶-significant difference from 12 hour value; T(M) & P(E)=Tiotropium in Morning and Formoterol matched Placebo in the evening,T+F(M) & P(E)=Tiotropium plus Formoterol in the morning and Formoterol matched Placebo in the evening, T+F(M) & F(E)=Tiotropium plus Formoterol in the morning and Formoterol in the evening

Table 3. Effects of three regimens on magnitude of difference in FEV_1 in litres over 24 hours

Treatments	30 min	2 hrs	12 hrs	12:30 hrs	24 hrs
FEV_1 (Forced Expiratory Volume in 1 second over 24 hours)					
T(M) &P(E)	0.127±0.140	0.139±0.138	0.187±0.132*	0.208±0.120*†	0.195±0.232*
T + F(M) &P(E)	0.144±0.181	0.224±0.196*	0.292±0.121*†	0.311±0.148*	0.285±0.117*†¶
T + F(M) & F(E)	0.126±0.129	0.198±0.168*	0.213±0.112*	0.344±0.135*†	0.380±0.151$^{*\dagger\$}$

*$^{*\dagger\$\P}$(p=.05); *-significant difference from baseline, †-significant difference from 30 minutes, $- significant difference from 2 hours; T(M) & P(E)=Tiotropium in Morning and Formoterol matched Placebo in the evening, T+F(M) & P(E)=Tiotropium plus Formoterol in the morning and Formoterol matched Placebo in the evening, T+F(M) & F(E)=Tiotropium plus Formoterol in the morning and Formoterol in the evening*

3.1.3 Rescue therapy, adverse events, blood pressure and pulse rate

None of the patients on any of the three treatments required rescue therapy with salbutamol. All patients were well controlled on every regimen**.** No adverse events were noticed or reported by the patients. There was no sleep disturbance or tremors reported during the study period. The BP and PR were recorded at each observation point i.e., 30 minutes, 2 hours, 12 hours, 12:30 hours and 24 hours for all patients during the study. No change was observed in BP and PR in any of the patients at any observation time during the study.

3.2 Discussion

The 2014 update of the global initiative for chronic obstructive lung disease (GOLD) management protocol states that long acting bronchodilators are more effective and convenient than short acting bronchodilators [1]. Moreover, combining two bronchodilators from different classes improve efficacy and reduce additional side effects as compared to increasing the dose of a single bronchodilator. Long acting β_2-agonist formoterol and salmeterol are still commonly used two long acting bronchodilators that are prescribed clinically and are inhaled twice daily [14,15].

Tiotropium is the long acting anticholinergic drug available and is inhaled once daily. It has greater than 24 hrs duration of action [16,17]. Recently, few studies have shown that combining tiotropium and LABA produce additive effects on FEV_1 throughout the 24 hours dosing intervals [13,18,19,22]. Duration of actions of components of this FDC of tiotropium and formoterol is different. The present study was conducted as an academic clinical trial to find out the best regimen for combining long acting anticholinergic (tiotropium) with formoterol (long acting β_2-agonist) for the symptomatic relief in mild to moderate COPD. There was no use of rescue salbutamol therapy in this study as consistent with other studies showing reduction in rescue medication need with short acting β_2-agonists in patients receiving long acting bronchodilators [16,17,23-26]. The present study has shown that addition of formoterol to tiotropium has significantly improved the lung function as compared to the patients who were given tiotropium alone. Addition of formoterol enhanced the peak effect in FEV_1, FVC and this enhanced effect remains till the next dose (24 hours). These results are in agreement with other studies that have shown superiority of combination after 6 weeks of treatment [13,22]. The combination of tiotropium once daily with formoterol twice daily produce almost similar effect in first 12 hours but significant improvement in next 12 hours of the night time including the magnitude of difference in FVC percentage predicted (Table 3). We observed that second dose of formoterol improve the lung functions (FEV_1 and FVC) in the night and the values were highest in the next day morning (24 hours).

The COPD patients have increased parasympathetic activity during the night and increased sympathetic activity during the day [27]. However combining tiotropium with formoterol improves the lung functions as formoterol decreases the sympathetic over activity. Addition of second dose of formoterol in the evening significantly improves all the lung functions. It clearly indicates that during the night also sympathetic activity is playing an important role and thus formoterol producing bronchodilation.

Published studies investigating the spirometric effects of formoterol are mainly limited to day time dosing interval of 12 hours and not much reported on nocturnal effect of LABA on lung functions [22]. Another study has reported that the additive effects of the evening doses of formoterol have disappeared by the next morning [28]. Postma et al have pointed out that the circadian changes in FEV_1 can be explained by increased sympathetic activity during the day and an increase in parasympathetic activity during the night [27]. As the disease progresses parasympathetic tone may be increased further. It seems this study is first of its kind revealing the effect of formoterol in the night time suggesting the role of adrenergic system in exacerbations in the COPD patients. We could not find any study suggesting the role of sympathetic over activity rather than parasympathetic during the night.

4. CONCLUSION

In conclusion, addition of formoterol to tiotropium as fixed dose combination once a day in the morning has shown improvement in lung functions in COPD. However, our study shows tiotropium alone is as good as the FDC once a day obviating the need for such prescription. It may be because of the predominance of the parasympathetic system in COPD patients.

Addition of second dose of formoterol in the evening in addition to the FDCs of tiotropium and formoterol once in the morning have shown the superior effects than the tiotropium/FDC alone implying the role of sympathetic component in the night time.

LIMITATION OF THE STUDY

Although it was a randomized controlled academic trial (RCT) with three parallel arms but our study had many limitations. First of all it was an acute study and we believe that chronic dose regimen could have provided more clinically applicable results. Therefore the future chronic long term treatment experiments with these medicines may reveal the exact clinical picture. Second, numbers of subjects were fewer in this study and large sample size in a multi-centric clinical study can be instituted for better statistical powers. Third, an open label study may help in appropriate matching of the potential confounding factors such as baseline FEV_1, FVC, age and pack years in each study arm. Fourth aspect in which our study had the limitation was lesser serial time points which can be increased to accommodate the night time variability in pharmacodynamics effects and spontaneous respiratory changes. Fifth, this study further necessitates the future evaluation of widely used combination regimens in COPD for their fixed dose rationality, addition of long acting β_2-agonists (LABA) along with the long acting muscarinic antagonists (LAMA) and ensuing burden of therapy due to addition of the other components.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki after obtaining written informed consent.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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