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Research Article

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Effect of theophylline, tiotropium bromide and combination of formoterol and budesonide on PEFR in COPD patients

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ABSTRACT

COPD is a chronic, progressive, and not fully reversible disease. It is a leading cause of morbidity and mortality worldwide with estimated 12.36 million Indians aged 30 years and above especially in smokers. Patients with frequent exacerbations experience a faster decline in FEV_1 and peak expiratory flow [PEF] rates than patients with infrequent exacerbations. With various drugs available for this, the present study was undertaken to evaluate the effects of oral theophylline, tiotropium bromide DPI and combination of formoterol and budesonide DPI on PEFR in patients with COPD. Materials and methods: 60 patients were randomised into three treatment groups [Group A receiving active oral Theophylline(400 mgs) one tablet HS, Group B receiving Active Tiotropium bromide(18µgms) DPI, Group C receiving active combination DPI Formoterol (6µgms) + Budesonide (200µgms)], for a period of 12 weeks and their baseline PEFR was compared with their post bronchodilator PEFR. The results achieved were theophylline [26.95 L/m] ($p < 0.05$), Tiotropium [31.87 L/m] ($p < 0.005$), Formoterol and Budesonide combination [28.55 L/m] ($p < 0.05$). Interpretation & conclusion: Tiotropium bromide a novel anticholinergic drug shows a promising effect on PEFR of COPD patients in our study. Regular treatment with bronchodilators like, Theophylline, Tiotropium, and combination of Formoterol and Budesonide leads to bronchodilatation and salbutamol causes additional bronchodilatation despite the presence of other long-acting bronchodilators in COPD patients.

Key words: COPD, PEFR, theophylline, tiotropium bromide, formoterol, budesonide

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INTRODUCTION

Chronic obstructive pulmonary disease [COPD] is a progressive lung disease characterized by the presence of chronic airflow obstruction that is not fully reversible. [1] The disease involves degeneration and destruction of lung tissues, hypertrophy of mucous glands, and airway narrowing and inflammation. Acute exacerbations play an important role in the natural history of COPD and have significant prognostic implications. Patients with frequent exacerbations [defined as two or more every year] experience a faster decline in FEV_1 and peak expiratory flow [PEF] rates than patients with infrequent exacerbations. [2]

Anticholinergic agents are used as first line therapy and tiotropium bromide a novel inhaled anticholinergic with functional relative selectivity for muscarinic receptor subtypes that is given once daily shows spirometric and clinical improvement. [3] In the guidelines for COPD therapy, theophylline is the third line bronchodilator to be used, and its treatment withdrawal leads to significant clinical worsening of the disease. [4] In the ISOLDE study and Paggiaro et al study, there has been renewed interest in the use of inhaled cortico-steroids [ICS] in COPD. The availability of long acting Beta-agonists [LABA], as well their combination with ICS has also increased the range of drugs available for the treatment of COPD. However, there is very little data available about the role of all these drugs in the management of COPD, as well as a paucity of data regarding a comparison of the efficacy of these drugs. [5, 6]

The purpose of this randomised, double blind, double dummy parallel group study was to determine the clinical efficacy of oral theophylline, tiotropium bromide DPI and combination of formoterol and budesonide DPI on PEFR in COPD patients.

EXPERIMENTAL SECTION

After obtaining the approval of institution ethics committee, 60 patients of either sex in the age group of 35-75 years with clinical diagnosis of COPD, [non-reversibility to DPI salbutamol 200mcg <12% increase in FEV_1 or 200mL.] attending medical OPD and in-patients department at Dr B R Ambedkar medical college hospital, Bangalore who gave informed consent were recruited. Patient with h/o Bronchial asthma, allergic rhinitis, atopy, broncheictasis and other chronic respiratory illness, pulmonary tuberculosis, pregnant and lactating women were excluded from the study. After their baseline spirometry they were randomized [simple randomization] into 3 groups for a period of 12 weeks.

Group A: Active oral Theophylline(400 mgs) one tablet HS, placebo DPI resembling Tiotropium bromide(18 µgms) and placebo DPI resembling Formoterol(6µgms)+Budesonide (200 µgms) combination.

Group B: Active Tiotropium bromide(18µgms) DPI, placebo resembling oral Theophylline(400mgs) and placebo resembling DPI Formoterol (6µgms) +Budesonide (200µgms) combination.

Group C: Active combination DPI Formoterol (6µgms)+Budesonide (200µgms), placebo resembling oral Theophylline (400mgs) and placebo resembling DPI Tiotropium bromide(6µgms).

Statistical Analysis: Descriptive data that include Mean, Standard Deviation, and range value were found for each group and used for analysis. Student paired t- test has been used to find the significance using SPSS 11.0 & Systat 8.0 Statistical software.

RESULTS

Out of 60 subjects enrolled, 46 subjects completed the study with 14 dropouts: 5 out of 16 [31.11%], 4 out of 22 [18.18%], 5 out of 22 [22.7 %] from group A, B & C respectively. It was not possible to ascertain the reasons for the dropouts.

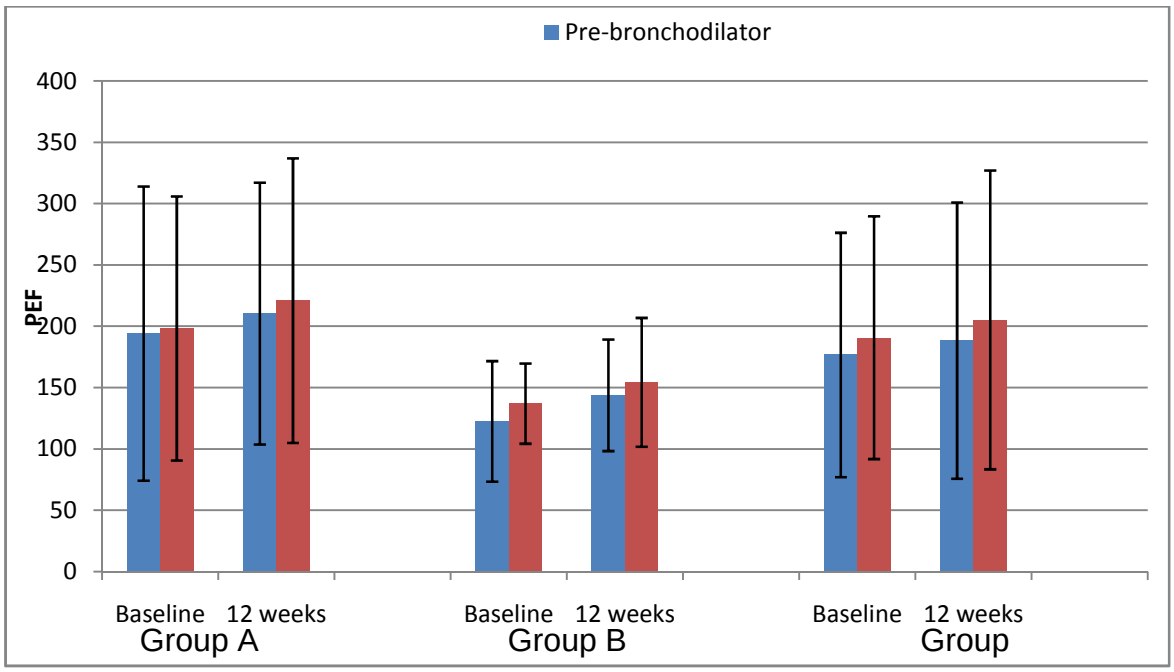
Table 1: Baseline Characteristics

BASELINE DEMOGRAPHICS	MEAN [SD]
Age yrs mean [range]	60.64 [7.67]
Height [cms]	161.42
Weight [kgs]	51.89
Mean PEF	165.41 [105.23]

Table 2: Comparison of PEFR between three groups

PEFR	Theophylline [Mean ± SD]		Tiotropium bromide [Mean ±SD]		Formoterol & Budesonide [Mean ±SD]	
	Baseline	12 weeks	Baseline	12 weeks	Baseline	12 weeks
Predicted	406.69±22.58		399.85±16.74		398.64±25.65	
Pre -bronchodilator	194.07±119.88	210.49±106.70	122.59±49.15	143.83±45.44	176.75±99.55	188.44±112.61
Post-bronchodilator	198.26±107.63	221.02±115.91	137.10±32.69	154.46±52.49	190.78±98.94	205.30±121.75
P value	P=0.044		P=0.004		P=0.028	
Pre values as a % of Predicted	47.71	51.76	30.66	35.97	47.27	46.27
Post values as a % of Predicted	48.75	54.35	34.29	38.63	47.86	51.5

Graph 1: Comparison of PEFR between three groups



The mean pre-bronchodilator PEFR improved little in group A from 194.07 L/m at baseline to 210.49 L/m at end of 12weeks. Post bronchodilator values however improved from 198.26 at baseline to 221.02 L/min at end of 12 weeks. The maximum improvement achieved by theophylline, was computed as the difference between mean baseline pre-bronchodilator PEFR value and mean 12 week post bronchodilator PEFR value as 26.95L/m ($p < 0.05$).

In group B, the mean pre-bronchodilator PEFR improved from 122.59 L/m at baseline to 143.83 L/m at 12weeks. Post bronchodilator values however improved from 137.10 L/m at baseline to 154.46 L/m at 12 weeks. The maximum improvement achieved by Tiotropium, was computed as the difference between mean baseline pre-bronchodilator PEFR value and mean 12 week post bronchodilator PEFR value as 31.87 L/m. (($p < 0.005$)) which was highly significant. In group C, the mean pre-bronchodilator PEFR improved, from 176.75 L/m at baseline to 188.44 L/m at 12 weeks. Post bronchodilator values however improved from 190.78 L/m at baseline to 205.30 L/m at 12 weeks. The maximum improvement achieved by Formoterol and Budesonide, was computed as the difference between mean PEFR baseline pre-bronchodilator value and mean PEFR 12 week post bronchodilator value as 28.55 L/m. (($p < 0.05$) which was significant (Table 2 & Graph 1)

DISCUSSION AND CONCLUSION

In this study, 46 of 60 subjects completed the study with total of 14 dropouts. The reasons for the dropout could not be found out as they failed to turn up for the follow up. But the excess of drop-outs from the theophylline group suggests that the adverse effects due to theophylline may be responsible. High drop-out rates have been noted in ZuWallack et al study [7], 44% of patients withdrew from the study due to adverse events related to theophylline. Kerstjens et al [8] in a meta-analysis, reports that people receiving theophylline were twice as likely to discontinue treatment as those taking placebo. In our study, the theophylline group, even while producing effective bronchodilatation, it produced uncomfortable adverse effects like gastritis, abdominal distension and palpitation which could be the cause for the high drop-out rate. This may translate in the clinical setting to poor compliance. In the theophylline group, mean PEFR improved by 27 L/m at end of 12weeks that is only 7% of predicted where as Motokazu Kato et al showed an increase of >10% [9] and Chrystyn and colleagues[10] observed PEFR changed only slightly [13%]. In the Tiotropium group the mean PEFR increased by 31.87L/m i.e by 8% of predicted. Vincken et al has shown significant increase in the PEFR with tiotropium in their study conducted for a period of 1 year. [11] Tiotropium a novel inhaled anticholinergic with once daily administration has shown spirometric benefits on PEFR in our study. The adverse effects noted in this group were dry mouth and constipation. In the Formoterol and Budesonide combination group the mean PEFR increased by 28.55L/m at end of 12 weeks i.e. 4.23% of predicted. In the studies of Szafranski et al.[12] and Calverley et al.[13] the PEFR was 24L/min. and 18L/min. respectively, whereas in our study it went up to 28.55L/min. The adverse effects in this group was candidiasis, leg cramps and headache.

There was additive bronchodilatation with sabutamol in addition to the bronchodilating effect seen with other bronchodilators used in this study. Since all the 3 drugs induced bronchodilatation by themselves there was scope for further bronchodilatation with SABA ie. Salbutamol 100 mcg DPI. Between the 3 drugs good bronchodilation was seen with tiotropium bromide with a significant P value of 0.004, followed by formoterol & budesonide combination. This could be due to the presence of LABA formoterol. The incidences of acute exacerbations have also been reduced in this group, indicating the use of ICS in COPD. In the theophylline group a small amount of bronchodilatation was seen with salbutamol. As per guidelines, though theophylline is being used as third line drug for COPD, after the use of β2 agonist and anticholinergics, studies on theophylline along with β2 agonist have shown greater improvement. Therefore theophylline can be continued to use because of it long, established history and more so considering it 'in-expensive' compared to other bronchodilators especially in our Indian setup. Some draw backs of the present study was small sample size and smoking status, (current vs. ex-smokers), was not included in the analysis. And for reasons of high cost, pharmcokinetic studies to assess the blood plasma levels of Theophylline to co-relate it to the adverse effects described by the subjects was not done.

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