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THE EFFECT OF FORMOTEROL (LONG ACTING BETA AGONIST/LABA) VS TIOTROPIUM (LONG ACTING MUSCARINIC ANTAGONIST / LAMA) IN MANAGEMENT OF COPD: A COMPARATIVE STUDY.

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ABSTRACT

BACKGROUND AND OBJECTIVES: COPD is a major public health problem worldwide. Over the past few decades, spectrum of pharmacological therapy in COPD has expanded and more objective and optimistic picture is evolving. Now this is the time to explore the effectivity of available COPD medications for more cost effective management.

METHODS: Thirty moderate degree COPD patients who volunteered and completed washout period of two weeks showing clinical stability, were allocated in two groups through randomization. Group-1 received inhaled Formoterol (LABA/ Long acting beta agonist) while Group-2 had Tiotropium (LAMA/ Long acting muscarinic antagonist). Inhaled Budesonide (ICS/ inhaled corticosteroid) was given to all patients beside LABA or LAMA. Patients were assessed for six weeks with testing sequence of Pulmonary Function Test and CAT (COPD Assessment Test) score at visit-1 (day '0' i.e, the day of start of the therapy), visit-2 (day '21') and visit-3 (day '42').

RESULTS: 77% patients were male and 23% female, while 70% was smokers and 30% non smokers. In Group-1 (LABA) patients, significant improvement of FEV1, FVC, FEF25-75%, CAT score was noted (p-value<0.05) in visit 2, 3 and PEFR in visit-3 (p-value=0.05), but no significant improvement of FEV1/FVC. In Group-2 (LAMA) patients, there was gradual improvement of FEV1, FEF25-75% and CAT score in visit 2, 3 (p-value<0.05), significant betterment of FVC, FEV1/FVC and PEFR in visit-3.

CONCLUSION: We conclude that in management of moderate COPD, both Formoterol (LABA) and Tiotropium (LAMA) are almost equally effective in improvement of spirometric parameters and symptom score beside Budesonide (ICS). However, Formoterol+ ICS may be more user-friendly as available in a single canister compared to Tiotropium+ICS.

KEYWORDS

COPD, Formoterol (LABA), Tiotropium (LAMA).

INTRODUCTION:

COPD is defined by The Global Initiative for Chronic Obstructive Lung Disease [1] (GOLD) as a disease state characterized by airflow limitation that is not fully reversible. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person [2].

COPD is a leading cause of morbidity and mortality worldwide and a major public health problem. It is a social and economic burden in our country regarding cost of treatment, loss of man-days. GOLD estimates suggest that COPD will rise from the sixth to the third most common cause of death worldwide by 2020. Presently, COPD is the fourth leading cause of death and affects >16 million people in the United States [3].

Over the past several decades, the use of drug therapy in COPD has expanded, and provides an objective and generally optimistic picture that such treatment is effective. Bronchodilators and anti-inflammatory agents are used in COPD to reverse broncho-constriction and improve airflow limitation. The goals of drug therapy are not only to improve lung function, but also to improve quality of life, exercise capacity, and prevent exacerbations [4].

Tiotropium is an anticholinergic (long acting M3 receptor antagonist/LAMA) bronchodilator that has the benefit of once-daily dosing, and is effective to improve exercise capacity, quality of life, and reducing exacerbations. Long-acting inhaled beta agonist/LABA such as Formoterol is also useful because of the long duration of action and documented benefit on quality of life and exercise tolerance [4]. Both these agents are used in management of moderate COPD.

The present study was designed to compare the efficacy of the two drugs in terms of lung function improvement, symptomatic benefit and cost effectiveness to help the patients to lead a socially and economically productive life.

MATERIALS & METHODS:

The present study was conducted in the Department of Physiology and Department of Pulmonary Medicine of a tertiary care hospital at Kolkata for 1 year. It was an open randomized longitudinal study of 6 weeks duration. The inclusion criteria were 1) Adult patients of both sexes above 40 years attending Pulmonary medicine OPD, 2) Patients having symptoms like dyspnoea, cough, sputum etc, 3) Spirometric assessment showing both of the following – a) post bronchodilator $FEV_1/FVC < 70\%$, b) $FEV_1 < 80\%$ but $> 50\%$ of predicted, thus defining moderate COPD according to GOLD guidelines 2010 (1), 4) Patient clinically stable for 6 weeks. Exclusion criteria were 1) Patients unwilling to give consent, 2) Other cardio-respiratory disorders such as bronchial asthma, atopy, pulmonary TB, pulmonary fibrosis, lung malignancy, myocardial infarction, heart failure, uncontrolled hypertension, 3) frequent acute exacerbation, 4) Severe or very severe COPD {GOLD grade 3 and 4}and 5) Pregnant and lactating female patients.

Informed consent was collected prior to inclusion in the study and the study protocol was approved by the institutional ethics committee.

Initially, 50 patients were enrolled; out of which 8 did not give consent, 7 did not satisfy inclusion and exclusion criteria and 5 failed to report on subsequent visits.

Following the screening visit, eligible patients entered a 2-week wash-out period to ensure clinical stability (i.e. no exacerbations). Inhaled rescue salbutamol was permitted at any time but ≥6 h before pulmonary function tests (PFT). All the long acting β2 agonist, oral steroids and methylxanthines were withheld during this wash-out period. Patients who successfully completed this phase have entered into the study phase of 6-week period. Patients were then randomized at a ratio of 1:1, according to the table generated by random allocation software into two groups. Group-1 patients received Formoterol (two puffs twice daily delivering 12 µg/ dose) and Group-2 patients received Tiotropium (two puffs once daily delivering 18 µg/dose). During the study period all the patients of either group received inhaled

corticosteroid (ICS) Budesonide two puffs twice daily delivering 400 µg/ dose through metered dose inhaler with spacer.

Efficacy assessment

a) Spirometry - All the patients were investigated with electronic spirometer (model: Recorders and Medicare system's RMS Helios 702) in the department of Physiology. Pulmonary function test parameters included were forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV^1/FVC ratio, peak expiratory flow rate (PEFR), forced expiratory flow from 25 to 75 % ($FEF_{25-75\%}$). The results were recorded in percent of predicted values. Spirometry was performed at visit-1 (day '0'), visit-2 (day '21') and visit-3 (day '42'). The same equipment was used throughout study and the test was performed according to a Standard operative Protocol (SOP).

b) Clinical improvement was assessed by CAT score

Finally, all the data were analyzed by using SPSS version-17 for Mean±SD, student independent t-test and paired t-test.

RESULT:

Total 30 patients were studied and randomly placed into two groups. The demographic parameters like age, BMI and relevant PFT parameters (FEV^1, FVC, FEV^1/FVC, $FEF_{25-75\%}$ and PEFR) of group-1(Formoterol/LABA) and group- 2 (Tiotropium/LAMA) are presented in Table-1.

Table-1: Shows the base line demographics and PFT parameters in group-1 and group-2 (Mean±SD). P-values <0.05 is considered as significant.

PARAMETERS (MEAN±SD)	GROUP-1	GROUP-2	P-VALUE
Age (Years)	58.93±10.98	59.53±9.44	0.874
Height (cm)	157.6±7.68	154.13±9.91	0.293
Weight (kg)	52.6±10.91	49.67±10.12	0.451
BMI(kg/m^2)	21.13±3.93	20.72±3.71	0.773
FEV_1	59.93±7.93	56±10.93	0.269
FVC	80.13±10.69	74.73±12.34	0.211
FEV_1/FVC	76.13±10.54	75.4±13.52	0.869
PEFR	51±19.23	42.87±16.81	0.228
FEF_{25-75}	25.33±7.06	20.67±7.38	0.088
CAT SCORE	23.47±3.91	22.2±3.84	0.378

Among the 30 patients, 77% were male and 23% were female; 70% were smokers and 30% were non-smokers.

Table-2 shows comparison of the baseline PFT parameters (percent of predicted value) between smokers and non- smokers.

Table-2 shows comparison of the baseline PFT parameters (percent of predicted value) between smokers and nonsmokers (Mean±SD). P-values <0.05 is considered as significant.

PFT PARAMETERS (MEAN ±SD)	SMOKERS	NON-SMOKERS	P-VALUE
FEV_1	57.73±7.50	58.63±14.56	0.825
FVC	77.55±11.68	77.13±12.46	0.932
FEV_1/FVC	75.45±10.99	76.63±14.98	0.817
PEFR	48.5±19.72	42.63±13.39	0.444
FEF_{25-75}	23.27±6.14	22.25±10.87	0.747

Table-3 shows intra group comparison of the PFT parameters in visit-1, visit-2 and visit-3. In group-1(LABA), there was significant improvement of FEV1, FVC, FEF25-75% and CAT Score in all the visits (p-value<0.05), whereas there was significant betterment of PEFR in visit-3 compared to visit-2 (p-value = 0.015). Regarding FEV1/FVC, no significant change was observed.

Table-3 shows intragroup comparision of PFT parameters and CAT Score in group-1 and group-2 patients (Mean±SD). P-values <0.05 is considered as significant.

Parameters	Group-1 (Formoterol)									Group-2 (Tiotropium)								
FEV_1	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value
	59.93±7.93	66.4±10.59	**0.003**	66.4±10.59	73.27±12.34	**0.000**	59.93±7.93	73.27±12.34	**0.000**	56±10.93	60.47±8.79	**0.004**	60.47±8.79	68.73±16.43	**0.004**	56±10.93	68.73±16.43	**0.0001**
FVC	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value
	80.13±10.69	90.27±15.45	**0.002**	90.27±15.45	96.07±19.93	**0.034**	80.13±10.69	96.07±19.93	**0.0007**	74.73±12.34	77.13±11.46	**0.254**	77.13±11.46	84.07±12.48	**0.005**	74.73±12.34	84.07±12.48	**0.0002**
FEV_1/FVC	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	Visit-1	visit-3	p-value
	76.13±10.54	74.93±11.31	**0.528**	74.93±11.31	77.87±11.89	**0.133**	76.13±10.54	77.87±11.89	**0.406**	75.4±13.52	79.53±13.94	**0.05**	79.53±13.94	81.87±12.55	**0.289**	75.4±13.52	81.87±12.55	**0.006**
PEFR	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	Visit-1	visit-3	p-value
	51±19.23	51±18.07	**0.951**	51±18.07	59.27±14.56	**0.015**	51±19.23	59.27±14.56	**0.137**	42.87±16.81	47.93±19.14	**0.105**	47.93±19.14	55±21.77	**0.105**	42.87±16.81	55±21.77	**0.017**
$FEF_{25-75\%}$	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	Visit-1	visit-3	p-value
	25.33±7.06	29.67±9.48	**0.010**	29.67±9.48	34.13±10.58	**0.002**	25.33±7.06	34.13±10.58	**0.000**	20.67±7.38	24.53±7.89	**0.0007**	24.53±7.89	30.13±15.61	**0.129**	20.67±7.38	30.13±15.61	**0.009**
CAT SCORE	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	visit-1	visit-3	p-value	Visit-1	Visit-2	p-value	visit-2	visit-3	p-value	Visit-1	visit-3	p-value
	23.37±3.91	15.6±4.404	**0.000**	15.6±4.40	9±1.20	**0.000**	23.37±3.91	9±1.20	**0.000**	22.2±3.84	13.8±3.10	**0.000**	13.8±3.10	8.6±1.24	**0.000**	22.2±3.84	8.6±1.24	**0.000**

In patients of group-2(LAMA), there was significant gradual improvement of FEV_1 and CAT Score in all the three visits (p-value<0.05), whereas the most significant change of FVC was observed in visit-3 in comparison to both visit-1 and visit-2. Significant change of $FEF_{25-75\%}$ was observed in visit-2 and visit-3 compared to visit-1. Regarding FEV_1/FVC and PEFR, significant change was observed only in the final visit (visit-3) compared to visit-1.

Table-4 shows intergroup comparision of PFT parameters and CAT Score in group-1 and group-2 patients (Mean±SD). P-values <0.05 is considered as significant.

PARAMETERS	VISIT-2			VISIT-3		
FEV_1	Group-1	Group-2	p-value	Group-1	Group-2	p-value
	66.4±10.59	60.47±8.79	0.106	73.27±12.34	68.73±16.43	0.400
FVC	Group-1	Group-2	p-value	Group-1	Group-2	p-value
	90.27±15.45	77.13±11.46	0.013	96.07±19.93	84.07±12.48	0.058
FEV_1/FVC	Group-1	Group-2	p-value	Group-1	Group-2	p-value
	74.93±11.31	79.53±13.94	0.329	77.87±11.89	81.87±12.55	0.378
PEFR	Group-1	Group-2	p-value	Group-1	Group-2	p-value
	51±18.07	47.93±19.14	0.691	59.27±14.56	55±21.77	0.533
$FEF_{25-75\%}$	Group-1	Group-2	p-value	Group-1	Group-2	p-value
	29.67±9.48	24.53±7.89	0.118	34.13±10.58	30.13±15.61	0.418
CAT SCORE	Group-1	Group-2	p-value	Group-1	Group-2	p-value
	15.6±4.404	13.8±3.098	0.206	9±1.195	8.6±1.242	0.376

DISCUSSION:

The patients of group-1 and group-2 were comparable in respect of demographic parameters (age, height, weight, BMI) [p-value >0.05]. So far the base-line PFT parameters and symptom score (CAT score)

are concerned, the patients of two groups were matched in terms of all the baseline PFT parameters (FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25-75\%}$) and CAT score [p-value >0.05].

In our study, out of thirty patients, 70% were smokers and 30% were non smokers. All the PFT parameters were comparable in both smokers and non-smokers and smoking had not confounded the results.

There was consistent improvement of spirometric parameters like FEV_1, FVC, $FEF_{25-75\%}$ and CAT score in all the three visits of the patients of group-1(LABA + ICS), which was statistically significant (p-value<0.05). These findings are in agreement with P.M. Calverley [5], W. Szafranski [6]. There was significant increase of PEFR in visit-3 compared to visit-2 (p-value = 0.015). But, no significant change was observed in FEV^1/FVC ratio.

On the other hand, patients of group-2 (LAMA+ ICS) showed significant improvement of FEV_1 and CAT Score in all the three visits (p-value<0.05), Significant change of FVC was observed in visit-3 compared to both visit-1 and visit-2 ,whereas significant improvement of $FEF_{25-75\%}$ was observed in visit-2 and visit-3 as compared to visit-1. . These are in agreement with Daryl Freeman [7], F.P.V. Maesen [8], Richard Casaburi [9], Michael R. Littner [10]. Significant change of FEV_1/FVC and PEFR was observed in visit-3 compared to visit-1.

Gradual deterioration in FEV_1 and FEV_1/FVC is commonly observed in COPD due to persistent narrowing of airways. The progression of COPD is associated with impairment of small airways which is likely related to infiltration of airway walls by inflammatory cells, accumulation of exudate and narrowing of the lumen [11]. With successful management of COPD, this pathophysiology may be arrested or may be improved to some extent. Thus spirometric parameters like FEV_1, FVC, FEV_1/FVC ratio, $FEF_{25-75\%}$ and by that way the CAT score showed improvement with treatment.

Treatment of COPD includes the use of inhaled ICS, LABA and long-acting muscarinic antagonists (LAMA). These therapies have been shown to reduce symptoms, prevent exacerbations and improve health-related quality of life [12,13]. Fixed combinations of ICS+LABA have anti inflammatory effects proven by reduction of CD8+ T lymphocytes in large airways of COPD patients [14, 15]. On the other hand, Tiotropium is a bronchodilator, not an anti inflammatory agent, like ICS, which is also known to reduce frequency of exacerbations [16]. However, a recent study evaluates the effect of tiotropium on inflammatory markers in sputum and in serum. Apart from this, a 52% reduction in exacerbation frequency was observed [17].

Bronchial tone depends upon a delicate balance between adrenergic and cholinergic system. Adrenergic system is responsible for bronchodilatation whereas cholinergic system is responsible for broncho-constriction. Impaired lung function in COPD is caused by structural narrowing of the airways, combined with the effects of cholinergic vagal bronchoconstrictive tone and decreased lung elastic recoil [18,19]. Bronchodilators improve the airflow limitation observed in patients with COPD by producing airway smooth-muscle relaxation, although β2-agonists and anticholinergics achieve this effect through different mechanisms. Anticholinergic bronchodilators (in particular, tiotropium) produce relaxation of airway smooth muscle through antagonism of acetylcholine at M_3-muscarinic receptors on airway smooth muscle[20], whereas β_2-agonists induce bronchodilation through stimulation of β_2-receptors, leading to an increase in cyclic adenosine monophosphate (as also occurs with phosphodiesterase inhibitors, such as oral methylxanthines)[21].

In COPD, adrenergic activity is highest in order to maintain bronchodilation. So, by administering LABA, it is not possible to further increase the level of bronchodilatation and thereby PEFR. But, as tiotropium is an anti cholinergic agent, it can achieve further bronchodilation and thus could increasePEFR. Moreover, LABA shows beta adrenoreceptor tolerance on prolonged use whereas Tiotropium does not show such tolerance effect. That is likely the possible explanation of maintenance of the improvement in PEFR and FEV_1/FVC ratio over 6 – weeks period by Tiotropium.

On intergroup comparison ofspirometric parameters, there was no significant difference between the two groups and thus were comparable in terms of spirometric improvement. These observations are quite similar with the findings of J.A.Van Noored et al[16] and Fabiano D Marco et al [30].

CONCLUSION:

There was no statistically significant difference in improvement of dynamic lung function or symptom score between Formoterol (LABA) and Tiotropium (LAMA) treated participants of moderate degree COPD. However, Formoterol+ ICS is likely to be more user-friendly as available in a single canister compared to Tiotropium and ICS, where patients have to use two inhalers seperately. Here the study population was small and further studies with large sample size and involving multicentric design is desirable.

LIMITATION:

1. The issue of observer's bias could not be eliminated as 'blinding' was not done.
2. The benefit of treatment is also attributable to inhaled corticosteroid.

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