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A comparative study on inhaled Corticosteroids versus Placebo in the management of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Role of inhaled corticosteroids (ICS) in COPD is a controversial subject. Studies have reported conflicting results on the effect of ICS therapy in COPD. This study aims to assess the role of Inhaled Corticosteroid (Budesonide-400ug) in the management of COPD. Fifty Patients with newly diagnosed Stage 3 or 4 COPD as per Gold guideline were selected. Baseline FEV1, number of hospitalization and exacerbations were entered. The patients were randomly assigned to receive Long-acting beta2 agonist (LABA) (FORMOTEROL 6ug) + long-acting muscarinic antagonist (LAMA) (TIOTROPIUM 18ug) + placebo or (FORMOTEROL 6ug) + (TIOTROPIUM 18ug) + Inhaled corticosteroid (ICS) (BUDESONIDE400ug). All drugs were given as metered dose inhalers with a spacer. Patients were reviewed after one year and reassessed FEV1, number of exacerbations and hospitalisation. Data were analyzed with SPSS version16. Demographic and baseline parameters were comparable in both groups. Both treatments brought a significant reduction in hospitalisation rate (p-value -.002 and .009 respectively). But there was no difference between two groups with respect to hospitalisation rate (P value-.825). There was a reduction in exacerbation rate in both treatment groups (p-value .001 each). But the difference in exacerbation rate between the two groups was not statistically significant (P value-.192). FEV1 was found to be declining in both treatment groups. Local side effects like oral candidiasis were more common in the steroid group. The inhaled bronchodilators (LABA+LAMA), as well as inhaled bronchodilators with an inhaled steroid (LAMA+LABA+ICS), bring significant reduction in exacerbation and hospitalisation rates of COPD. But the addition of inhaled steroid with bronchodilators does not bring about any additional advantage in bringing down the exacerbation or hospitalisation rates further.

Keywords— *COPD, Inhaled corticosteroids (ICS), Inhaled bronchodilators, FEV1, LABA, LAMA*

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) constitutes a major public health burden worldwide. The World Health Organisation estimates that by the year 2020, COPD will be the fifth leading cause of disability worldwide and the third leading cause of death. Both prevalence and mortality are expected to increase in coming years[1]. Despite the enormous burden of the disease in health economic and personal perspective, there is a lack of satisfactory treatment for the disease. Apart from smoking cessation and oxygen therapy in hypoxemic patients, treatment influencing the progressive nature of the disease is not available so far[2].

Apart from providing symptomatic relief, COPD management is also intended to reduce disease progression, prevent exacerbations, improve the quality of life, and reduce the mortality rate. Based on FEV1, a number of exacerbation/hospitalisation and symptom score COPD patients are classified to groups A, B, C, and D and treated accordingly as per GOLD guidelines. For group C COPD patients, a fixed combination of inhaled corticosteroids /long acting beta agonist or a long acting anticholinergic is recommended[3]. For group D patients' rationale for the first choice, drugs are the same as that for group C patients[4]. As second choice all three classes have been recommended.

One of the most controversial questions in the management of COPD is whether inhaled glucocorticoids are of benefit to patients with COPD[5,17]. Born from the idea that both asthma and COPD result from chronic inflammation and that inhaled corticosteroids are markedly effective in controlling asthma, there is an intense debate as for whether ICS is beneficial in COPD. Inevitably clinicians have prescribed ICS in COPD[6,7]. However, the inflammatory pattern in COPD differs markedly from that in asthma[8,9]. The safety of long term inhaled steroids has not been well established yet. The dose response relationship and long term safety of inhaled steroids are not known[18,19]. Only moderate to high doses of inhaled steroids have been put to trial. Many trials have reported conflicting reports regarding the effectiveness of inhaled corticosteroids in the management of chronic obstructive

pulmonary disease[20]. In this background, this study is undertaken so as to assess the effectiveness of inhaled corticosteroids in COPD patients.

2. OBJECTIVES

- To assess the role of inhaled steroid in the exacerbation rate of COPD
- To assess the role of inhaled steroid in the hospitalisation rate of COPD.
- To assess the effect of inhaled treatment in the lung function of COPD

3. METHODOLOGY

3.1 Study design

This was an experimental study in which stage III, IV COPD patients were randomly assigned to receive either inhaled bronchodilators alone (Non steroid group) or inhaled bronchodilators along with ICS(steroid group). The study was conducted in Dept. of Pulmonary medicine, Kottayam for a period of one year. The study protocol was approved by the institutional review board.

3.2 Study subjects

Patients attending Pulmonary Medicine OPD who are diagnosed to have COPD clinically and by spirometry.

3.3 Inclusion criteria

(i) Patients diagnosed to have stage III, IV COPD by spirometry and clinical evaluation.
(ii) Age> 40 years
(iii) Post bronchodilator FEV1/FVC< 70 and FEV1, < 50% by P.F.T
(iv) COPD patients who were newly diagnosed and not on any inhaler treatment

Patients who were on long term oxygen therapy or on inhaler therapy, who are known cases of bronchiectasis or pulmonary tuberculosis, patients who're PFT showed reversibility were excluded.

The sample size consisted of fifty patients with 25 in each group. After doing pulmonary function tests, the baseline forced expiratory volume and forced expiratory ratio was entered. The baseline exacerbation rate and hospitalisation rate was recorded. On suspicion of bronchial infection, supportive treatment was given to the patient. The patients were enrolled in the trial after controlling the acute infection.

Non steroid group: Received LABA (FORMOTEROL 6 microgram) + LAMA (TIOTROPIUM18 microgram) + Placebo.
Steroid group: Received LABA (FORMOTEROL 6 microgram) + ICS (BUDESONIDE-400ug) + LAMA (TIOTROPIUM 18 microgram).

The drugs were administered through metered dose inhaler with spacer for all patients. Patients were advised to review in OPD after 3months and six months to reassess the technique and also to check compliance. After one year, the severity of disease in each group was reassessed by clinical evaluation, spirometry, and a number of exacerbations/hospital admissions during the follow up period.

4. STATISTICAL ANALYSIS

Data were entered in Microsoft excel and further analysis done using statistical software SPSS 16. Mean, standard deviation, frequency were calculated as summary statistical measures. Appropriate statistical tests like Independent sample T tests, Paired T tests, and Chi Square tests were used for testing the association. The significant level was fixed at a P value of <.05.

5. RESULTS

The study population was randomly assigned to receive LABA-LAMA plus ICS or LABA-LAMA. The baseline demographic characters and disease history were well balanced between two groups (Table 1). The mean age of the study population was 60.60. The mean age in the non-steroid group was 61.24 and that of steroid group was 59.96 (Table1). 94% of the population was males and 6% were females. 88% of the study subjects belonged to stage 3 and 12 % to stage 4.

52.3% of stage 3 was in non-steroid group 47.7% in steroid group (Table 2).33.3% of stage 4 COPD belonged to non-steroid group and 66.7% of stage 4 disease belonged to steroid group(Chi-square=0.758, df=1, p=0.384).
88% of the sample were smokers and 12 % were non- smokers.

83.3 % of the non-smokers were in a non-steroid group and 16.7% were in steroid group.45.5% of the smokers in the non-steroid group and 54.5% were in the steroid group (Table 3). (Chi-square value 3.03, df=1, p=0.082)

Table 1: Baseline characteristics of patients

Characteristic	Non steroid group	Steroid group
Age	61.2± 8	59.9 ± 6.7
Gender(male)	22	25
COPD Stage 3	23	21
Stage 4	2	4

Smoking status Non smoker Smoker	 5 20	 1 24
Baseline FEV1	1.07±.40	.99±.27
Baseline hospitalisation	.84±1.2	1.04±1.36
Baseline exacerbation	4.28	4.4

Table 2: GOLD COPD staging among two groups

		GOLD criteria of staging		Total
		Stage 3	Stage 4	
Non-Steroid Group	Count	23	2	25
	% within Gold Criteria of Staging	52.3%	33.3%	100.0%
Steroid Group	Count	21	4	25
	% within Gold Criteria of Staging	47.7%	66.7%	100.0%

Table 3: Smoking status among two groups

		Smoking Status		Total
		Non-smoker	Smoker	
Non-steroid group	No	5	20	25
	Percentage	83.3%	45.5%	50.0%
Steroid group	Count	1	24	25
	%	16.7%	54.5%	50.0%
Total	Count	6	44	50
	%	100.0%	100.0%	100.0%

The mean baseline exacerbation in the non-steroid group was 4.28 and that of steroid group was 4.40. The mean baseline FEV1 of the non-steroid group was 1.0704 and that of steroid group was .9904. The mean baseline hospitalization rate in the non-steroid group was .84 and that of steroid group was 1.049 (Table 4). No significant difference between two groups when comparing mean baseline values using t –test for equality of means for baseline exacerbation (p value.893), baseline FEV1 (p value-.420) and mean a number of hospitalization (p value-.587) before intervention (Table 5).

Comparison of difference in mean values with smoking status using independent t test showed no significant association between smoking status and mean difference of hospitalization rate (p value -.683), exacerbation rate (p value-.202)and FEV1 (p value-.281) before and after treatment.

Table 4: Baseline comparison in two groups

	Group	N	Mean	Std. Deviation
Baseline exacerbation	Non-steroid	25	4.28	2.865
	Steroid	25	4.40	3.379
Baseline fev1	Non-steroid	25	1.070400	.4048609
	Steroid	25	.990400	.2783206
Hospitalization	Non-steroid	25	.84	1.214
	Steroid	25	1.04	1.369

Table 5: Comparison between baseline variables of two groups

		t-test for Equality of Means		
		T	Df	P value
Baseline exacerbation	Equal variances assumed	-.135	48	.893
Baseline fev1	Equal variances assumed	.814	48	.420
Hospitalization	Equal variances assumed	-.547	48	.587

There was a reduction in the mean hospitalization rate in the non-steroid group from .84 to .00 and the change was found to be statistically significant p with a p-value -.002 (Table 6). In the steroid group also, there was a reduction in the mean hospitalization rate from 1.04 to .28 and the change was statistically significant -p value-.009 (Table 7).

Table 6: Mean hospitalization before and after non-steroid treatment

		Mean	N	Std. Deviation
Non-steroid group	Hospitalization before treatment	.84	25	1.214
	hospitalization after treatment	.00	25	.000

Hospitalization in Non- Steroid group		Mean	P value	Std. Deviation
Non-steroid group	Hospitalization rate	.840	.002	1.214

Table 7: Mean hospitalization before and after steroid treatment group

		Mean	N	Std. Deviation
Steroid group	Hospitalization before treatment	1.04	25	1.369
	Hospitalization after treatment	.28	25	.542

Hospitalization rate steroid group		Paired Differences		t	P-valve
		Mean	Std. Deviation		
Steroid group	Hospitalization rate	.760	1.332	2.854	.009

The difference between the mean hospitalization rate after the follow up period in both groups was not statistically significant -p value-.825 (Table 8).

Table 8: Difference in mean hospitalization rate before and after treatment in both groups

	Group	N	Mean	Std. Deviation
Mean hospitalization rate	Non-steroid	25	.8400	1.21381
	Steroid	25	.7600	1.33167

		t-test for Equality of Means		
		T	df	P value
Hospitalization	Equal variances assumed	.222	48	.825

There was a reduction in the mean exacerbation rate from 4.28 to .68 in the non- steroid group and the change was statistically significant - p value-.001 (Table 9).

The mean exacerbation rate in the steroid group reduced from 4.40 to 1.16 and the change was statistically significant -p value-.001 (Table 10).

The difference between the mean exacerbation rates after the follow up period between two groups was not statistically different - t value -1.325 and p value .192 (Table 11).

Table 9: Change in mean exacerbation after non- steroid treatment

		Mean	N	Std. Deviation
Non-steroid group	Baseline Exacerbation	4.28	25	2.865
	Exacerbation after treatment	.68	25	1.069

Exacerbation rate in non-steroid group		Paired Differences		t	P value Sig. (2-tailed)
		Mean	Std. Deviation		
Non-steroid group	Exacerbation rate	3.600	2.517	7.152	.001

Table 10: Change in mean exacerbation after steroid treatment

		Mean	N	Std. Deviation
Steroid group	Baseline exacerbation	4.40	25	3.379
	Exacerbation after treatment	1.16	25	1.463

Exacerbation rate in the steroid group		Paired Differences		T value	P value
		Mean	Std. Deviation		
Steroid group	Exacerbation rate	3.240	2.587	7.152	.001

Table 11: Difference in mean exacerbation rate after treatment in both groups

	Group	N	Mean	Std. Deviation	T value	P value
Exacerbation after treatment	Non steroid group	25	.68	1.069	-1.325	.192
	Steroid group	25	1.16	1.463		

The mean FEV1 reduced from the baseline during the follow up period in the non-steroid group from 1.0704 to 1.0284 and the change was not statistically significant -p value .457 (Table 12). The mean FEV1 in the steroid group reduced from .9904 to .9488 during the follow up period and the change was not statistically significant p value-.140 (Table 13).

The difference between the mean FEV1 after the follow up period between the non-steroid group and steroid group was not statistically significant (t value-.869 and p value .389 (Table 14).

Table 12: Change in mean FEV1 after non-steroid treatment

		Mean	N	Std. Deviation	Std. Error Mean
Non-steroid group	Baseline FEV1	1.070400	25	.4048609	.0809722
	FEV1 after treatment	1.028440	25	.3509855	.0701971

		Paired Differences		t	P value
		Mean	Std. Deviation		
Non steroid group	FEV1	.0419600	.2775492	.756	.457

Table 13: Change in mean FEV1 after steroid treatment

		Mean	N	Std. Deviation
Steroid group	Baseline fev1	.990400	25	.2783206
	Fev1 after treatment	.948800	25	.2946795

FEV1		Paired Differences		t	P value
		Mean	Std. Deviation		
Steroid group	FEV1	.0416000	.1362803	1.526	.140

Table 14: The difference between the mean FEV1 after follow up period between the non-steroid group and steroid group

		N	Mean	Std. deviation	T value	P value
FEV1 after treatment	Non steroid group	25	1.028440E0	.3509855	.869	.389
	Steroid group	25	.948800	.2946795		

Safety: Adverse effect like oral candidiasis was seen in 2 subjects in the steroid group and none in the Non-steroid group. There was no case of pneumonia in both groups.

6. DISCUSSION

The objectives of the study were to assess the role of ICS in the exacerbation and hospitalisation rate in stage III, IV COPD. The treatment with LAMA (tiotropium) and LABA (formoterol) produced a significant reduction in the exacerbation rate of stage 3 and stage 4 COPD patients. But the addition of inhaled corticosteroid with the above treatment regime did not bring about an added advantage in bringing down the exacerbation rates of COPD patients.

Similarly, the hospitalisation rate was also significantly reduced in COPD patients during the study period who were treated with LABA and LAMA. The inclusion of ICS did not bring about any further reduction in the hospitalisation rate. The mean FEV1 of the study population was found to be on a downhill course during the follow up period, which was not statistically significant.

The study results were tallying with that of TRISTAN[10] trial in which reduction in exacerbation rate with inhaled corticosteroid along with long acting bronchodilators was not significantly different from that of treatment with long acting bronchodilators alone.

The two years INSPIRE[11] trial conducted by Calverley at al, in patients with mean baseline FEV1-39% found no difference in exacerbation rate between long acting bronchodilator group (13%) and long acting bronchodilator with inhaled corticosteroid group (16%) p value (.085).

The Optimal study[12] compared inhaled steroid plus long acting bronchodilators and the effect of long acting bronchodilators alone in COPD patients and reported no significant difference between treatments in the primary outcome –the proportion of patients with exacerbations (63% and 65% respectively) (p value .576)

There is limited evidence that drug treatment can modify the rate of decline in FEV1 in COPD. The TORCH[13] study showed similar rates of decline of FEV1 but without any difference between the long acting bronchodilators alone and their combination with inhaled corticosteroids. The ISOLDE[5] study was conducted by P S Burge et al in the year 2000. No statistically significant difference was noted in the annual rate of decline in FEV1 between the groups treated with inhaled placebo or an inhaled corticosteroid.

In the Copenhagen City Heart Study, subjects with an FEV_1/FVC ratio of ≤ 70% were randomised to treatment with budesonide (400 micrograms) or placebo. No differences were reported between treatment groups for the decline in FEV_1, exacerbation rate or presence of respiratory symptoms during follow-up.

The European Respiratory Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) study was a placebo-controlled trial evaluating the effect of budesonide 400 µg twice daily compared with placebo. The annual decline in FEV_1 was not significantly different between the groups.

In the Lung Health Study II, patients were randomised to treatment with triamcinolone 600 µg twice daily or placebo. In this study, treatment with triamcinolone was not found to slow the rate of decline in FEV_1 compared with placebo.

The local side effects like oral candidiasis were more common in the steroid group. The TORCH study reported rates of candidiasis of .9 with inhaled steroid containing treatment compared with .2 for long acting bronchodilator and placebo group[21]. As shown in TORCH and other trials, therapy with a long-acting bronchodilator alone can be effective in preventing further exacerbations of COPD[22-28]. Similar to the above studies, this study also does not report any additional advantage of adding inhaled corticosteroid along with long acting bronchodilator therapy in bringing down the exacerbation and hospitalisation rate. Neither does it alter the natural declining course of FEV1 in COPD patients.

The reasons for the limited efficacy of ICS in COPD could be:
1. Unlike asthma, the inflammatory pattern in COPD is Neutrophilic predominant[31,32].
2. The decline in the levels of Histone deacetylase 2 with increasing severity in COPD[28,29,30].

Limitations of the study include the short follow up period and a limited sample size. Larger multicentre trials will be able to provide more conclusive evidence.

7. CONCLUSION

Inhaled corticosteroids do not bring about any added advantage in stage 3 or 4 COPD patients in bringing down the exacerbation or hospitalisation rates who are being treated with long acting bronchodilators (LABA + LAMA).

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APPENDIX

COPD	: Chronic Obstructive Pulmonary Disease
PTB	: Pulmonary Tuberculosis
PFT	: Pulmonary Function Test
LABA	: Long Acting Beta2 Agonist
LAMA	: Long Acting Muscarinic Antagonist
ICS	: Inhaled Cortico Steroid
FEV1	: Forced Expiratoery Volume

