

A comparative study to evaluate the role of inhaled steroid versus low-dose oral steroid in patients of chronic obstructive pulmonary disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability worldwide. Its prevalence is increasing globally, especially in countries with high frequencies of smoking combined with significant environmental exposures to pollutants and biomass smoke. Currently COPD is the third leading cause of death worldwide, after ischemic heart disease and stroke. Efforts have been made to design a standard protocol for treatment of the disease, and these efforts are still in the process.

Methods: The study was done on 100 subjects to assess whether steroid (inhaled or oral) actually have any role in decreasing the decline in forced expiratory volume in 1 sec and to compare the effect of both to find out which one is superior. Patients were divided into two arms, inhaled steroids group (according to GOLD guidelines), and the other group was oral prednisolone 10 mg in addition to standard treatment except inhaled steroid. The effects were studied with appropriate statistical tests.

Results: Our study data showed that oral steroids are more effective on symptom control as compared to inhaled steroids. Symptoms such as cough (64% vs. 82%) and breathlessness (76% vs. 94%) significantly improved in the oral corticosteroids group. The rate of exacerbation also improved (22% vs. 12%) in the test group.

Conclusion: The use of steroids has ever been a subject of divergence of views ever since its role in the treatment of COPD was first described. Although, overall steroid in any form is beneficial in symptomatic/subjective and objective improvements in COPD, oral steroids stand a better chance as compared to inhaled steroids.

Keywords: Chronic obstructive pulmonary disease, Corticosteroids, Forced expiratory volume in 1 sec, Exacerbation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in the individual patient. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particle or gases.¹ Airflow limitation is best measured

by spirometry, as this is the most widely available and reproducible test of the lung function. Airflow obstruction is defined as forced expiratory volume in 1 sec (FEV₁)/FVC ratio of <70% and if post-bronchodilator increase in FEV₁ is <12% and 200 ml, then it is irreversible airflow obstruction and it points towards the diagnosis of COPD.

Mortality and morbidity from COPD are considerable and increasing, and by the year 2020, COPD is predicted to become the third leading cause of death worldwide.¹

Although the mechanisms are yet to be clearly defined, COPD is thought to be a chronic inflammatory entity accelerates the natural history of some comorbidities, and that these comorbidities merely reflect COPD as a systemic disorder.²

Over the past several years, numerous studies have confirmed the important role of inflammation in the airways and lung parenchyma of COPD many have advocated a central pathogenic role of this inflammatory response.³

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature.⁴ The inflammation in the respiratory tract of COPD patients appears to be an amplification of the normal inflammatory response of the respiratory tract to chronic irritants like cigarette smoke. The mechanisms for this amplification are not yet understood but may be genetically determined. Production of insulin-like growth factor 1, which mediates the growth hormone anabolic action, is counter-regulated by tumour necrosis factor- α , interleukin-1 (IL-1) and IL-6.⁵ In addition, elevated levels of IL-6 correlate negatively with levels of testosterone and dehydroepiandrosterone, which also have anabolic effects.⁶ Oxidative stress may be an important amplifying mechanism in COPD.⁷

Bronchodilators in the form of β_2 agonists and anticholinergic are the baseline treatment which may be complemented by steroids, theophylline, antioxidants, and decreasing occurrence or early efficient management of lower respiratory tract infections.

Inhaled steroids have been known to reduce the frequency and severity of exacerbations, although there is some uncertainty as to whether the anti-inflammatory action of inhaled corticosteroids modifies the decline in FEV₁ associated with COPD progression.⁸

Steroids play a vital role in management of exacerbations of COPD by reducing the inflammation by down-regulating the mediators of inflammation.⁹ Since COPD is a condition of systemic inflammation, use of steroids is very substantial not only for the respiratory system, but also strings have to be kept tight to down-regulate the systemic inflammation. This study is being done in this light to assess the response of systemic versus inhaled steroids in the management of COPD.

METHODS

This study was done to assess whether steroid (inhaled or oral) actually have any role in decreasing the decline in FEV₁, and to compare the effect of both to find out which one is superior. The study was done between January 2009 and June 2010. It was a comparative study. The randomization was done in two arms by a random number. The arm treated

by inhaled steroid the Group A, and the arm treated by low dose oral steroid the Group B. 100 patients with COPD attending the outpatient department were screened based on the inclusion and exclusion criteria.

Inclusion criteria

1. Patient of COPD in Stage 3 and Stage 4 based on history, signs and investigations, irrespective of the etiology, and duration of the disease

Staging of COPD was based on GOLD criteria.

2. Age of the patient between 30 and 60 years.

Exclusion criteria

1. Age <30 years and >60 years
2. Associated diseases like diabetes mellitus, heart diseases, renal disorders
3. Acute exacerbation of COPD
4. Patient in respiratory failure (PaO₂<40 mm Hg, based on ABG report)
5. Pregnant and lactating females.

Patients were divided into two arms, the arm treated with inhaled steroid and the arm treated with low dose oral steroid.

- A. Inhaled steroid treated arm: patient were given standard treatment of COPD. According to GOLD guideline
 1. Tiotropium bromide - 18 μ g by dry powder inhalers or by metered dose inhalers, once daily
 2. Salbutamol inhaler - 200 μ g by dry powder inhalers or by metered dose inhalers SOS
 3. Inhaled steroid as per GOLD guidelines.
- B. Low-dose steroid treated arm: to these patient in addition to the standard treatment (except inhaled steroid) were given low doses oral prednisolone (10 mg/day) was given for a period of 6 months. Patients were assessed clinically at every month. Spirometry was done at 3 months interval (0, 3 and 6).

Statistical methods

Categorical data were expressed in terms of numbers (percentage) and continuous data as mean \pm standard deviation (SD). Two - sample t-test was used to test the significance of the difference in change in the spirometric measurement between the two groups (Group A, the inhaled steroid group and Group B, the low dose oral steroid group) and unequal variance was adjusted, where required. We applied Wilcoxon signed-rank sum test in case of non-normally distributed to test the same.

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RESULTS

Maximum number of patients was in the age group of 51-60 (74 patients, 78% in Group A and 70% in Group B). 69 patients were males (74% in Group A and 64% in Group B) and 31 patients were females (26% in Group A and 36% in Group B). In our study, 59 patients were smoker, 29 patients in Group A (78.38%, all were male) and in Group B, 30 patients were smoker 29 patients were male and only one patient was female in Group B (90.63% of males and 5.56% of females of the Group B were smokers).

In our study, maximum number of patients were from GOLD Stage 3 (62% in Group A and 58% in Group B). Rest were in Stage 4 (38% in Group A and 42% in Group B).

Table 1 shows the subjective improvement of symptoms of COPD at the end of the study in Group A and Group B. At the end of study, 73 patients experienced improvement in cough (64% were in Group A and 82% were in Group B), 57 patients experienced improvement in expectoration (54% were in Group A and 60% Group B), breathlessness was improved in 84 patients (76% were in Group A and 92% were in Group B). None of the patient had weight gain in Group A while in Group B 12% patients experienced improvement in weight loss. Fever subsided in 11 patients 10% in Group A and 12% in Group B). The comparison of improvement between the two groups was statistically significant ($p=0.04$).

Table 2 shows the mean values of post bronchodilator FEV₁ in each group at the entry point in the study and at the end of 3rd month follow-up. The mean change in FEV₁ values at the end of 3 months was 0.01 ± 0.06 in Group A, and that was 0.06 ± 0.08 in Group B. The difference between the two groups is not statistically significant ($p=0.5719$). Thus at the end of first 3 months of follow-up we do not have strong statistical evidence to conclude that the change in FEV₁ is significant in any group.

The mean change in FEV₁ values at the end of 3rd month and end of 6 months was -0.01 ± 0.05 in Group A, and that was 0.08 ± 0.09 in Group B. The difference between the two

Table 1: Overall subjective improvement in symptoms at the end of the study.

Symptoms	N (%) (n=50)	
	Group A	Group B
Cough	32 (64)	41 (82)
Expectoration	27 (54)	30 (60)
Breathlessness	38 (76)	46 (92)
Weight loss	0 (-)	6 (12)
Fever	5 (10)	6 (12)
p - value of change	p=0.04	

Rao Scott Chi-square test

groups is statistically significant ($p=0.0474$). Thus, at the end of last 3 months follow-up, we have strong statistical evidence that the change in FEV₁ is significant in Group B.

The mean change values of post bronchodilator FEV₁ in each group at the entry point in the study and at the end of 6th month follow-up was 0.2 ± 0.10 in Group A, and that was 0.14 ± 0.15 in Group B. The difference between the two group is statistically significant ($p=0.0032$). Thus, at the end of the whole period of follow-up of study, we have strong statistical evidence that the change in FEV₁ is significant in Group B.

Table 3 shows the rate of acute exacerbation in each group at the entry point in the study to the end of 6th month of follow-up. The rate acute exacerbation was 22% in Group A and 12% in Group B. The difference between the two group is statistically not significant ($p=0.183$) though the rate of acute exacerbation is 10% higher in Group A.

DISCUSSION

COPD is a syndrome of chronic and progressive airflow limitation which occurs as a result of chronic inflammation of the airway and lung parenchyma, chronic inflammation leads to a progressive deterioration of airflow which is manifested by an accelerated annual rate of decline in the FEV₁ of approximately 60 ml/year.

Table 2: Comparison of mean post bronchodilator FEV1 (liter) between groups.

Estimation point	Mean±SD (n=50)	
	Group A	Group B
At entry point	0.72±0.20	0.66±0.20
At the end of 3 rd month	0.71±0.20	0.72±0.19
Change	0.01±0.06	-0.06±0.08
p - value of change	p=0.5719	
At the end of 3 rd month	0.71±0.20	0.72±0.19
At the end of 6 th month	0.70±0.20	0.80±0.22
Change	0.01±0.05	-0.08±0.09
p - value of change	p=0.0474	
At entry point	0.72±0.20	0.66±0.20
At the end of 6 th month	0.70±0.20	0.80±0.22
Change	0.02±0.10	-0.14±0.15
p - value of change	p=0.0032	

FEV: Forced expiratory volume in 1 sec, SD: Standard deviation, Wilcoxon rank-sum test

Table 3: Rate of acute exacerbation between groups.

Parameter	N (%) (n=50)	
	Group A	Group B
Acute exacerbation	11 (22)	6 (12)
No exacerbation	39 (78)	44 (88)
p - value	p=0.183	

Chi-square test

Steroids had important effects on the symptoms of COPD mainly on cough, sputum production and breathlessness. The change in mean number of days of cough/month was 4.08 ± 1.40 in Group A, and that was -3.84 ± 2.03 was in Group B difference of which was statistically significant ($p < 0.0001$). These data showed that oral steroids are more effective on symptom control as compared to inhaled steroids. Lam et al.¹⁰ in their study showed a similar response of oral corticosteroids in chronic airflow obstruction comparing prednisolone 40 mg/daily for 2 weeks with placebo. There was a significant improvement in mean FEV₁ by 21.4% and mean FVC by 11.9%, subjective measurements (mean dyspnea score by 16%) and exercise performance in the steroid group.

The mean percentage change in breathlessness was 23.06 ± 4.22 in Group A, and that was -29.52 ± 9.52 in Group B. The difference between the two group is statistically significant ($p < 0.0001$). Patients on oral steroids have much better improvement in breathlessness than on inhaled steroids; this also consistent with the results of the study done by Lam et al.¹⁰

The comparison of mean post bronchodilator FEV₁ (liters) between groups at the end of 3rd month to end of 6th month (end of the study) follow-up was 0.01 ± 0.05 in Group A and that was -0.08 ± 0.09 in Group B. The difference between the two group is statistically significant ($p = 0.0474$). Similarly, the change in EFV1 (% pred) at the end of 3rd month to end of 6th month follow-up was 0.12 ± 2.49 in Group A, and that was -3.82 ± 4.57 in Group B. The difference between the two groups is statistically significant ($p < 0.0001$). Thus, we have strong statistical evidence that at the end of later 3 months of follow-up there was a significant improvement in Group B. The comparison of mean FEV₁ (liter) between groups at the entry point and at the end of the study was 0.02 ± 0.10 in Group A in that was -0.14 ± 0.15 in Group B. The difference between the two groups is statistically significant ($p = 0.0032$). Similarly, the change in FEV₁ (% pred) between the two groups at the entry point and at the end of the study was 0.56 ± 4.96 in Group A, and that was -7.07 ± 7.38 in Group B. The difference between the two groups is statistically significant ($p = 0.0016$). Thus, at the end of the study, we have strong statistical evidence that the change in Group B was significant.

Postma et al.¹¹ on the basis of long-term prognostic study on patients with severe chronic airflow obstruction (FEV₁ < 1000 ml) showed that long-term treatment with oral prednisolone in doses above 7.5 mg/day may slow down the progression of the disease.

In another study, Postma et al.¹² on the basis of long-term study on non-allergic patients with less severe chronic airflow obstruction (FEV₁ \geq 1200 ml) showed that when oral prednisolone was instituted or increased to a dose of at least 10 mg/day continuously, FEV₁ either remain constant, decreased more slowly or even increased over many years

of follow-up. When the oral dose was diminished to below 10 mg/day, FEV₁ decreased. The results of above studies help us to explain the observation of our study that oral steroids might slow down the progression or even may increase FEV₁. On the other hand, different studies have found that inhaled steroids have been most effective in Stage 3 and Stage 4 of COPD and based on these studies, GOLD in their latest guidelines have recommended inhaled steroids as a part of treatment in Stages 3 and 4 of COPD.

Inhaled corticosteroids used alone or in association with long-acting β_2 -agonists have been used in the treatment of patients with asthma with good quality evidences. Nonetheless, despite the difference in the pathogenesis, the same therapeutic concept has been widely used for COPD patients, particularly in patients with moderate to severe disease.¹³

As far as acute exacerbation is concerned, there were 22% patients (11 patients) experienced at least one episode of acute exacerbation in Group A while there were 12% patients (6 patients) in Group B during the whole period of study. The difference between the two groups is statistically not significant ($p = 0.183$) though the rate of acute exacerbation was 10% higher in Group A. Overall the rate of acute exacerbation was higher in Stage 4 patients in comparison to Stage 3 patients. In Stage 4, 36.84% patients have an acute exacerbation in Group A, and that was 19.05% patients in Group B ($p = 0.208$). In Stage 3, 12.90% patients have an acute exacerbation in Group A, and that was 6.90% patients in Group B ($p = 0.438$). Saha et al.¹⁴ raises the possibility that COPD is an inhaled corticosteroids- resistant, oral corticosteroids - responsive condition.

CONCLUSION

Since the identification of the disease in 1950s several efforts have been made to devise a meticulous plan for management of COPD. As the disease has a multidimensional presentation, a single strategy usually is not sufficient for the overall relief from disease symptoms. Although overall steroid in any form is beneficial in symptomatic/subjective and objective improvements in COPD, oral steroid stands a better chance as compared to inhaled steroids. Oral steroids, which have an effect on respiratory airways and systemic inflammation both, they not only reach large- and medium-sized airways but also in small airways and beyond that.

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