Original Article

Evaluation of Efficacy of Budesonide in Prevention of Cardiovascular Risks in Chronic Obstructive Pulmonary Disease Patients

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ABSTRACT

Background: Cardiovascular disease is a major cause of mortality and morbidity in COPD patients. Systemic inflammation plays a major role in the pathogenesis of cardiovascular disease in COPD. It has, therefore, been suggested that anti-inflammatory agents may prevent cardiovascular disease. it would be plausible that inhaled steroids, such as Budesonide, reduce the local inflammation and subsequent cardiovascular morbidity, thus a local effect on the lung resulting in diminished spill-over of inflammation systemically to the cardiovascular system is an attractive hypothesis.

Objective: To assess the impact of Budesonide in reducing the cardiovascular risk in COPD patients**.**

Study Design: Experimental Randomized Study.

Place and Duration of Study: This study was conducted in the Department of Pharmacology and Therapeutic, Basic Medical Sciences Institute, JPMC Karachi in collaboration with Department of chest medicine, JPMC, Karachi from Dec. 2010 to March, 2011.

Materials and Methods: Thirty five patients with moderate stable COPD, with hsCRP level >3mg/lit, were evaluated in an open label, intention to treat clinical trial. The patients were assigned to give Budesonide (Pulmicort) inhaler 200mcg BD for 12 consecutive weeks. The primary study outcome was to evaluate the reduction in cardiovascular risk by evaluating the improvement in FEV1 and reduction in hsCRP levels, was evaluated at day 30, 60 and day 90.

Results: Thirty four (96%) patients were completed the study. At baseline hsCRP levels was 6.68±0.26 which decrease to 5.82±0.20 (P<0.010) at day 90. FEV1(L) at baseline was 2.12±0.05 and at day 90 FEV1 increased upto 2.40±0.04 (P<0.001). This shows that, the Budesonide can statistically significant decrease the hsCRP levels and increase the FEV1.

Conclusion: In conclusion, Budesonide effectively decrease the cardiovascular risk by decreasing the systemic inflammation which were indicated by decreasing the hsCRP levels and also improve pulmonary functional capacity in COPD patients.

Key Words: COPD, Budesonide, Pulmicort, hsCRP, FEV1, CVD,ICS.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a syndrome of chronic progressive airflow limitation which occurs as a result of chronic inflammation of the airways and lung parenchyma, and is at most partially reversible[1]. The abnormal inflammatory response found in COPD appears to be an amplification of the normal inflammatory response to inhaled noxious agents (cigarette smoke or other irritants) in the susceptible patient. It is characterized by influx of neutrophil into the airway lumen and by increased macrophage and T lymphocyte numbers in the airway wall[2].

COPD is leading cause of death and disability worldwide. The rise in morbidity and mortality from COPD will be most dramatic in Asian and African countries over the next two decades, mostly due to progressive increase in the prevalence of smoking[3].The WHO estimates that 80 million peoples worldwide have moderate to severe COPD with 5% of all death being attributed to the disease[4] WHO estimated that COPD is currently the 12th most common cause of morbidity and the 6th leading cause of death in the world. By 2020 it is estimated to become the 5th most common cause of disability and 3rd most frequent cause of death just behind coronary and cerebrovascular disease[5,6].

Although these figures are alarming, they are likely to be gross underestimates of the true health and economic burden of COPD because COPD is an important risk factor for other causes of morbidity and mortality, including cardiovascular disease[7]. In Pakistan, the estimated COPD mortality rate is 71 deaths per 100,000 and the fourth highest rate among 25 most population in the world[8].

COPD is not longer being considered a disease only of the lungs. It is associated with a wide variety of systemic consequences, most notably increased risk of cardiovascular diseases, depression, osteoporosis and vascular weakness[9].

Systemic inflammation in COPD reflected by elevated CRP levels and impaired pulmonary functions may have additive effects in increasing the risk of cardiac disease[10]. Impaired lung function is a strong predictor of cardiovascular death, both independent of and additive with the risk conferred by smoking. It has also been proposed that coronary artery disease in patients with COPD results in part from spillover of pulmonary derived inflammatory cytokines (e.g. IL-6, TNF-α)[11].

High sensitive C-reactive protein analyses have already been recommended for clinical application in the detection and prevention of cardiovascular disease[12,13]. It has, therefore, been suggested that anti-inflammatory agents may prevent cardiovascular disease[14].

Corticosteroids are effective in reducing airway and systemic inflammation. Budesonide is a new generation glucocorticosteroids with high anti-inflammatory activity and reduced systemic side effects and it is widely used to treat COPD in clinical practice[15].

Thus, it would be plausible that inhaled steroids, such as Budesonide, reduce the local inflammation and subsequent cardiovascular morbidity[16]. In this case, a local effect on the lung resulting in diminished spill-over of inflammation systemically to the cardiovascular system is an attractive hypothesis, since systemic steroids may have a dose–dependent harmful effect on the risk for ischemic heart disease[17].

MATERIALS AND METHODS

Patients: A total of 35 patients having diagnosis of stable moderate COPD met the inclusion criteria were enrolled after taking written and informed consent. Patients of both sexes with moderate COPD as indicated by spirometry assay FEV1 < 80% and FEV1/FVC < 70%, with age ranges between 35-65 years and with hsCRP levels >3mg/lit were included in this study. Patients with unstable COPD, history of exacerbations previous 3 months, patients already on Steroid therapy, or history of oral steroid usage during previous 3months, pregnant or lactating mothers, patients with connective tissue disorders, patients with active or chronic peptic disease and with documented history of active coronary artery disease are excluded from the study.

Study procedure: The study was extended over 12 week's period. During this treatment period patients were assigned to tablet Budesonide (200 µg) 2puffs daily for 12 weeks followed by monthly follow up visits. The rescue medications were allowed SOS during the study.

At baseline pulmonary function test (FEV1, FVC, FEV1/FVC ratio) were performed. Impact of therapy on health related quality of life were assessed by BODE index and SGRQ score and impact of therapy on cardiovascular risk were assessed by changes of FEV1 and hsCRP levels from the baseline which were the primary outcomes of this study. The safety and tolerability of drug was assessed by maintaining adverse events at each follow up visits and performed LFT and creatinine kinase levels at baseline and at end of study.

Statistical Analysis: Statistical software SPSS (statistical Package for Social Sciences) ver 11.5 was used for data feeding and analysis. Clinical characteristics will be summarized in terms of frequencies and percentages for qualitative variables (gender, smoking history, sputum production, family history, etc.) mean ± S.D. for quantitative variables (age, PEFR, FEV1, FVC, FEV1/FVC ratio, Liver function test (LFT), lipid profile, etc). Student t-test (paired) was used for comparison of quantitative data from baseline (day-0) to day-30, day-60 and day-90. In all statistical analysis only p-value <0.05 was considered significant.

RESULTS

35 patients were selected for treatment. One patient withdrew during treatment period and therefore failed to complete the study. Reason for withdrawal was non compliance. Demographic and baseline clinical characteristics are shown in table 1.

Table No.1: Demographic characteristics of enrolled patients

Characteristics	**Group B** (n=34)
Gender	
Male	25 (73.5)
Female	9 (26.5)
Smoking history	26 (75.8)
Cough	25 (73.5)
Sputum production	14 (41.6)
Age (years)	56.8 ± 0.68
Smoking, Pack/year	28.1 ± 1.43
MMRC Dyspnoea score	2.88 ± 0.11
History of exacerbation in last 6 months	1.8 ± 0.11
Peak expiratory flow rate	165 ± 2.01
BMI (Body Mass Index)	19.9 ± 0.35
FEV1	2.12 ± 0.05
FVC	3.1 ± 0.08
FEV1/FVC ratio %	0.60 ± 0.01
History of any comorbodities	
Hypertension	9 (26.5)
Diabetes mellitus	4 (11.)
Stable ischemic heart disease	2 (5.9)
Family history of COPD	15 (44.1)
Family history of ischemic heart disease or hypertension	23 (67.6)

At baseline the mean±SEM of CRP was 6.68±0.26 and FEV1 was 2.12±0.05.

At day 30 the mean±SEM of CRP was 6.50±0.22 and percent change from baseline was 2.7% and p-value from the baseline was statistically non significant (0.599). The mean FEV1 was 2.24±0.05 and p- value from the baseline at day 30 was statistically non significant (0.094).

Table No.2: Assessing the reduction of cardiovascular risks by assessing the C-Reactive protein and forced expiratory level in one second levels (FEV1) with treatment Inhaled Budenoside

Variables	Mean ± SEM (n=34) (% change)	P-value
Reduction in C-reactive protein levels		
Day – 0	6.68 ± 0.26	-
Day – 30	6.50 ± 0.22(2.6%)	0.599
Day – 60	5.97 ± 0.18(10.7%)	0.028 *
Day – 90	5.82 ± 0.20(12.9%)	0.010 **
Improvement in FEV1 levels		
Day – 0	2.12 ± 0.05	-
Day – 30	2.24 ± 0.05(5.7%)	0.094
Day – 60	2.31 ± 0.04(9%)	0.004 **
Day – 90	2.40 ±0.04(14.2%)	0.001 **

- ** p<0.01, * p<0.05 statistically significant from base line (Day-0)
- Percentage change in parenthesis

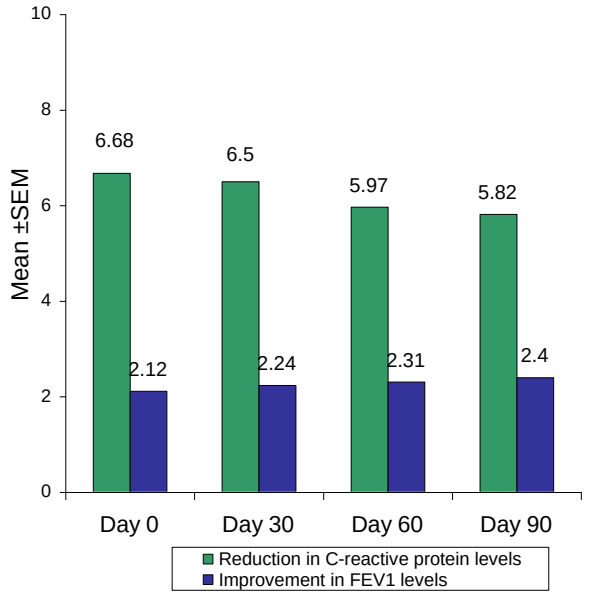

Figure No.1: Assessing the reduction of cardiovascular risks by assessing the C-Reactive protein and forced expiratory level in one second levels (FEV1) with Budesonide treated patients

At day 60 the mean±SEM of CRP was 5.97±0.18 and percent change from baseline was 10.7% and p-value from the baseline was considered statistically significant (0.028). The mean FEV1 was 2.31±0.04 and percent change was 9% and p- value from baseline was statistically highly significant (0.004).

At day 90 the mean±SEM of CRP was 5.82±0.20, percent change from baseline was 12.9% and p-value from the baseline was considered highly significant (0.010). The mean FEV1 was 2.40±0.04 and p-value was considered statistically highly significant (0.001).

DISCUSSION

Coronary artery disease is the most common cause of death in COPD patients, estimated to affect between 20-50%. Reduced FEV1 is a powerful marker for CAD and mortality from CVD. It is striking that reduced FEV1 ranks second only to smoking, just above blood pressure, social class and cholesterol as predictor for CVD related mortality in COOPD patient in both males and female[18].

Melbye et al. shows a strong link between bronchial airflow limitation and the circulating CRP levels in an elderly population. Measuring CRP may be useful part of the diagnostic work up in COPD patients[19].

Glucocorticoids have potent anti-inflammatory effects and therefore are of theoretic benefit in patients with COPD[20]. Furthermore, the anti-atherogenic properties of corticosteroids have been demonstrated in several animal studies[21,22,23].

The beneficial effects of ICS on the risk of acute myocardial infarction may be explained by the anti-inflammatory effects of ICS. Anti-inflammatory actions of corticosteroids involve the modification of the expression of a wide number of genes, in turn, inhibiting the synthesis of cytokines (interleukin (IL)-2, IL-6, tumor necrosis factor -a, interferon-c), adhesion molecules (intercellular adhesion molecule 1, endothelial leukocyte adhesion molecule 1), enzymes (inducible nitric oxide synthase, cyclooxygenase, collagenase) and other proteins (granulocyte-macrophage colony-stimulating factor) involved in inflammation[24], and implicated in the pathogenesis of acute coronary syndromes[25].

In 2004, Sin and colleagues reported that ICS therapy may provide a similar CRP benefit for those patients with respiratory disease. The authors performed a randomized, double-blind, placebo-controlled trial involving 41 patients with mild-to-moderate COPD to examine the effects of ICS therapy on systemic inflammation. The withdrawal of ICS therapy increased baseline CRP levels by 71%, while a return to ICS therapy for 2weeks reduced CRP levels by 50%. No significant changes were observed with placebo. An additional 8 weeks of ICS therapy was associated with CRP levels that were lower than those at baseline (29% reduction).Interestingly, 2 weeks of prednisone therapy reduced CRP levels by a comparable amount (63%) to that of ICS therapy, even though the ICS dosage (fluticasone,500 µg bid) was thought to be too low to

mimic the effects of therapy with systemic corticosteroids[26].

These findings are consistent with a recently published observational study by Pinto-Plata and colleagues, who found that users of inhaled corticosteroids had serum CRP levels that were on average ~40% lower than those among corticosteroid non-users[27].

Huiart L et al, conducted the population based cohort study in mild to moderate COPD patients and found a protective effect of ICS on the risk of AMI for daily medication doses ranging 50–200 mg of beclomethasone or the equivalent. For higher doses of ICS the risk returned to baseline[28].

Analysis of the European Respiratory Society's study on Chronic Obstructive Pulmonary Disease (EUROSCOP); which is a 3-yr, placebo-controlled study of an inhaled corticosteroid Budesonide 800 *µg/day in mild COPD patients.* The results of this study support the hypothesis that treatment with inhaled Budesonide reduces ischaemic cardiac events in patients with mild chronic obstructive pulmonary disease[29].

Inhaled corticosteroids may reduce CRP production indirectly by downregulating the expression of IL-6[30]. Previous studies indicate that IL-6 is a major signaling cytokine for CRP expression by hepatocytes[31]. Importantly persistent therapy with inhaled corticosteroids attenuates IL-6 expression in patients with COPD[32].

Thompson and associates by comparing treatment with inhaled beclomethasone to placebo in a group of subjects with mild chronic bronchitis concluded that inhaled steroid treatment led to significant improvement in spirometry, BAL cellularity, and protein content as compared to placebo, in 50% of the patients[33].

Riancho and colleagues performed a meta-analysis of 12 placebo- controlled trials of ICS in COPD. Short-term studies showed that ICS induced a small increase in FEV1 (mean 96 ml after 1 to 6 months). Longer-term studies indicated that after 1 to 3 years of continued therapy, FEV1 was higher in steroid treated subjects than in control subjects, but only by 51 ml[34]

In conclusion this study demonstrated that the Budesonide (Pulmicort inhaler) effectively decreases the cardiovascular risk by decreasing the systemic inflammation which was indicated by statistically significant decrease in hsCRP levels and decrease in pulmonary component of inflammation was indicated by improvements of pulmonary functional capacity in COPD patients.

CONCLUSION

In conclusion, Budesonide effectively decrease the cardiovascular risk by decreasing the systemic inflammation which were indicated by decreasing the hsCRP levels and also improve pulmonary functional capacity in COPD patients.

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