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ORIGINAL ARTICLE

Blood eosinophils and inhaled corticosteroid/long acting β_2 agonist efficacy on Quality of life and COPD exacerbation rate in Stable Chronic Obstructive Pulmonary Diseases

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Abstract:

Background: *COPD patients with increased airway eosinophilic inflammation show a favorable response to inhaled corticosteroids (ICS) in combination with a long-acting bronchodilator(LABA). Thus, this study investigated the effect of 3-months treatment with Inhaled Corticosteroid/long-acting beta2-agonist (LABA) in stable COPD patients with high blood eosinophils with an improvement in quality of life and reduction of COPD exacerbation rate.*

Methods: *It was a interventional study conducted at the outpatient department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka from which 80 stable COPD patients were selected. Baseline blood eosinophils level was measured of all patients and randomly assigned to 12-weeks treatment withSalmeterol/fluticasone proprionate inhaler (ICS/LABA) 25/250 mgin group A and Salmeterol 25mg in group B. Subjects began 3-month ICS/LABA treatment after washout period. Subjective measurement of symptoms by COPD assessment test (CAT) score were done in initial visit and during follow up at 4^{th} ,8^{th} and 12^{th} week. Among all , 29 patients in group A and 28 patients in group B came up to final follow-up.*

Results: *In this study, Mean COPD Assessment Test (CAT) score change between two group in first visit was 1.53 ($p<0.01$), at second visit 1.45 ($p<0.05$) and at final visit was 2.06 ($p<0.05$). Differences were statistically significant.CAT score decreases in consecutive 3 follow up than baseline record in both group.CAT score with baseline records between group A and group B showed statistically significant differences ($p=<0.05$).Thus, patients with eosinophilia, ICS-based therapy was associated with significant improvements in CAT scores and lower incidence of acute exacerbation (3.45% vs 7.14%) compared with bronchodilator (BD) therapy alone.*

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Conclusions: *High blood eosinophils are associated with improved lung function after 3-months ICS/LABA treatment in COPD patients. So, in combination with age and baseline lung function parameters, blood eosinophils may be a possible biomarker for identification of COPD patients with favorable response to ICS/ LABA treatment.*

Key words: *COPD, Eosinophil, Inhaled corticosteroid, COPD Assessment Test (CAT) score.*

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Introduction:

COPD is a progressive inflammatory disorder that is characterized by persistent airflow limitation[1]. It affects approximately 10% of adults over 40 years of age and is the fourth leading cause of death worldwide[2]. Although most COPD guidelines advocate the use of inhaled corticosteroids (ICS) for only those with frequent exacerbations, in real clinical practice, they are widely used especially in combination with a long-acting beta2- agonist (LABA)[3]. Because only a small fraction of COPD patients are responsive to ICS-based therapy[4], identifying characteristics associated with ICS-responsiveness is crucial for clinicians to make therapeutic decisions. Although neutrophils are thought to play a prominent role in the pathogenesis of COPD[5], Christenson et al[6] recently reported that eosinophilia and T helper type 2 (Th2) inflammation might also play a significant role in a subset of patients with COPD and that approximately 20% of smokers with COPD have a Th2-high signature. This result is consistent with previous findings that airway eosinophilic inflammation is not uncommon, but is present in approximately 20%–40% of COPD patients[5]. Inhaled corticosteroids (ICS) are an important treatment for COPD[1]. Exacerbations, defined as acute worsening of symptoms necessitating treatment with antibiotics and/or systemic corticosteroids or hospitalization, are a key determinant of COPD morbidity, mortality and healthcare costs[7]. Compared with placebo, ICS such as fluticasone propionate (FP) and budesonide reduce exacerbations by up to 20% as monotherapy, and up to 30% in combination with a long-acting β_2-agonist (LABA)[8]. National and international guidelines on the management of COPD[1] recommend that patients with COPD at risk of exacerbations receive ICS/LABA maintenance therapy. A predictive marker for ICS/LABAeffectiveness in preventing COPD exacerbations could aid clinical decision-making by identifying patients likely to gain the most beneût from ICS-based treatment. Blood eosinophil count may provide such a marker. Studies have demonstrated associations between airway eosinophilia and exacerbations of chronic bronchitisand COPD[9]. Exacerbations are heterogeneous, presenting as one of four distinct phenotypes, and airway eosinophilia in the stable state was found to be predictive of subsequent exacerbation phenotype[10]. The use of systemic corticosteroids in patients experiencing acute exacerbations of COPD has shown greater beneût in patients with a blood eosinophil level of ≥2% versus those with <2%[11]. There is also evidence for an association between airway eosinophilia with response to systemic corticosteroids for quality of life[11]. A recent retrospective analysis of data from two parallel 1-year studies of once-daily ICS/LABA, ûuticasone furoate (FF)/vilanterol (VI) in patients with moderate-to-very severe COPD showed a greater reduction of moderate and severe exacerbations in patients with a blood eosinophil level ≥2% vs <2% when treated with ICS/LABA compared with LABA alone[12].Thus this study is designedto investigate the potential of blood eosinophil level as a marker for the efûcacy of ICS/LABA on quality of life and prevention of exacerbations in stable COPD patients. The relationship between dyspnea and quality of life in COPD has previously been indicated in a few studies[13]. Perceived dyspnea was shown to have a greater impact on health-related quality of life than spirometric or functional measurements in these patients[14]. In an international study, the most frequently reported symptom was dyspnea (78%)and the most frequent complaint reported by patients with COPD was daily activity limitation[15]. Hajiro, et al.[13] showed that dyspnea is one of the main determinations of disease specific health related quality of life, and has moderate to strong correlations with impairments in the health related quality of life in patients with COPD. On the other hand, quality of life measurements did not correlate well with the severity of airflow limitation[16].

Furthermore, factors such as dyspnea, depression, anxiety and exercise tolerance were found to be more correlated with health status than the widely used spirometric values[16]. The CAT was developed as a short validated COPD-specific questionnaire for assessing the impact of COPD on health status. It provides a reliable measure of overall COPD severity from the patient's perspective, independent of language[17]. It is not a diagnostic tool; its role is to supplement information obtained from lung function measurement and assessment of exacerbation risk[17]. The relative frequency of severe exacerbations within these patients was shown to be higher in patients with higher CAT scores. We observed that the increase of exacerbation frequency was parallel to the increase of CAT scores. Additionally, CAT scores were the same in males and females, and were not influenced by age[18].

Methods:

This was an interventional study. COPD Patients attending outpatients department(OPD), National Institute of disease of the chest and Hospital during the study period from November, 2016 to October, 2017 for the treatment and follow up, were the study population and those fulfilling the inclusion and exclusion criteria were enrolled as study sample by purposive sampling. Patients of more than 40 years of age with history of smoking, post bronchodilator FEV1/forced vital capacity (FVC)<70%, pre-treatment blood eosinophil count >5% and absence of feature of acute exacerbation for last one month were included whereas patients having any cardiac diseases or long term oxygen therapy were excluded. 80 stable COPD patients were selected and randomly assigned to 12-weeks treatment with Salmeterol/fluticasone proprionate inhaler (ICS/LABA) 25/250 mg in group A(n=40) and Salmeterol 25 mg in group B(n=40). They were evaluated by taking history, examined thoroughly and Spirometry was done to confirm the diagnosis, in addition to the other necessary baseline investigation (including Chest X-ray PA view, CBC with ESR, Serum bilirubin, Serum creatinine, sputum for AFB, Electrocardiography etc.). Baseline peripheral blood eosinophil count, Spirometry along with other clinical data were obtained after cessation of the fol-lowing respiratory medications: an ICS for 2 weeks, an inhaled LABA, or long-acting muscarinic antagonist for 2 days, an inhaled short-acting β_2-agonist or inhaled short-acting antich-olinergic for 12 hours. After 2 weeks of washout period, all patients with baseline eosinophil count >5% were allocated to 'Group-A' and 'Group-B' by simple randomization. Each subject were treated with fixed-dose combination of ICS and LABA (25¼g salmeterol/ 250¼g fluticasone) along with conventional therapy for COPD twice daily for the following 3 months in group A and only with conventional therapy for COPD for the following 3 months in group B.All patients were assessed at monthly for 3 months by CAT score and compared with the baseline values to see the outcomes. De-worming was done by albendazole for every patient.Total 23 patients had lost to follow up. All the information were properly documented in the prescribed forms. Data were processed manually and analyzed with the help of SPSS (Statistical package for social sciences) Version 21.0.

Eosinophilia : Eosinophils constitutes up to 5% total leukocyte count in blood. So, differential count of blood eosinophil more than 5% regarded as higher eosinophil count or eosinophilia[18].

Results:

Table-I

Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score at the end of the first visit(4th week). (N=57; n1=29, n2=28)

CAT score	Group AMean(±SD)	Group BMean(±SD)	P-value
Initial	16.26(±1.32)	16.08 (±1.14)	$>0.05^{NS}$
First visit	14.42(±1.08)	15.77(±1.03)	$<0.05^{S}$
P-value	$<0.001^{S}$	$>0.05^{NS}$	

P-value reached from unpaired and paired t test.
Group A = Salmeterol/fluticasone proprionate 25/250µg; Group B = Salmeterol 25¼g
S: Significant NS: Not significant
*CAT Score Decrease means improvement of symptoms.
The mean difference of CAT score of initial and 1st follow up record in Group A shows statistically significant difference (p <0.01).

Table-II

Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score at the end of the second visit (8th week). (N=57; n1=29, n2=28)

CAT score	Group AMean(±SD)	Group BMean(±SD)	p-value
Initial	16.26(±1.32)	16.08(±1.14)	>0.05^{NS}
Second visit	13.99(±1.07)	15.26(±1.01)	<0.01^{S}
P-value	<0.001^{S}	>0.05^{NS}	

P-value reached from unpaired and paired t test.
The mean difference of CAT score of initial and 2nd follow up record of both Group A and B shows statistically significant difference (p <0.001).

Table-III

Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score at the end of the third visit (12th week). (N=57; n1=29, n2=28)

CAT score	Group AMean(±SD)	Group BMean(±SD)	P-value
Initial	16.26(±1.32)	16.08 (±1.24)	>0.05^{NS}
Third visit	13.28(±1.36)	15.16(±1.06)	<0.001^{S}
p-value	<0.001^{S}	>0.05^{NS}	

P-value reached from unpaired and paired t test.
The mean difference of CAT score of initial and 3rd follow up record of both Group A and B shows statistically significant difference (p = <0.001^{S})

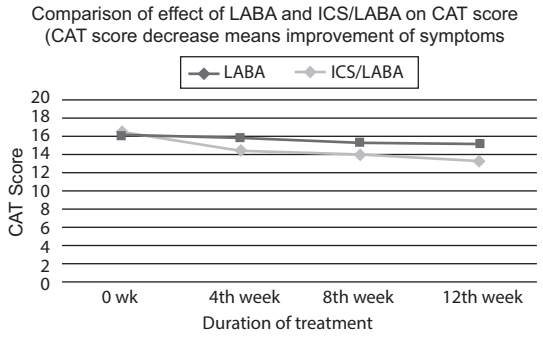

Fig.-I: *Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score.*

Table-IV: *Effect of drugs on risk measurement among groups during study period (N=57; n1=29, n2=28).*

Group	Exacerbation occured	Exacerbation not occurred	EER	CER	RR	NNT
Group A	1(a)	28 (b)	0.03	0.07	0.42	25
Group B	2 (c)	26 (d)				

EER : Experimental event rate; a/a+b
CER: Control event rate; c/c+d
RR: Relative Risk ; EER/CER
NNT: Number of patients needed to be treat ; 1/CER-EER

Discussion

In this study, all patients of COPD were selected with blood eosinophilia (>5%). Pre-treatment blood eosinophil count in group A was 5.93±2.16 and group B was 5.84±1.86 which correlates with the study of in which they aimed to investigate the potential of blood eosinophil level as a marker for the preventive efûcacy of ICS/LABA in COPD patients[19].In this study the mean age of the group A patients was 58.70 ±8.56 years and group B patients was 57.25±10.03 years. The mean age difference was not statistically significant.A similar study[20] showed mean age of patients in both groups were 64.3±18.1 years. The mean age of the present study was lower can be explained, as the average life expectancy is comparatively low in our set up as compared to the Western world[21].Among group A patients, highest percentage were male (93.1%) and 6.9% female. Similarly in group B patients, highest percentage were male (96.4%) and only 3.6% were female. No statistically significant sex difference was found between the two groups of patients which correlated with the study[22], in which overall male were 97% and only 3% were female.In the present study, COPD Assessment Test (CAT) score change in 1st visit decreased 1.84(±0.67) in group A and decreased 0.31(±0.02) in group B that was statistically significant ($p<0.01$). Mean CAT score change in 2nd visit decreased 2.27 (±0.53) in group A and decreased 0.82 (±0.07) in group B that was statistically significant ($p<0.05$). Mean CAT change in 3rd visit decreased 2.98 (±0.38) in group A and decreased 0.92 (±0.13) in group B that was statistically significant($p<0.05$) . Findings of this study consistent with the result of the study[22], in which their data extend these findings by demonstrating that high blood eosinophils were associated with treatment response (defined as an increase in FEV1 and decrease in CAT score from baseline) following ICS and LABA treatment in COPD for 3 months.Few previous studies have evaluated the use of eosinophil cell counts as a biomarker of ICS responses in patients with COPD. Leigh et al.2006[23]observed an association of sputumeosinophilia(>3% in induced samples) with significant improvements indyspnea following treatment with inhaled corticosteroid. Similar findings were reported for prednisone[24].A post hoc analysis of data from the Foster 48-week trial to reduce exacerbations in COPD to examine the role of blood eosinophil levels on treatment responses and observed that in the highest eosinophil count group, treatment with fluticasone plus LABA resulted in significantly better improvements of quality of life, measured by decremental CAT score(P-values <0.001)[25]. Cheng et al. 2017 used data from a previous prospective randomized study and classified patients into higher and lower eosinophil count groups[26]. The authors observed that patients with high plasma eosinophilia have a significantly greater pulmonary response, a reduced risk of acute exacerbations and improved CAT scores when treated with a combination of ICS- and bronchodilator-based therapy, compared with bronchodilator therapy alone. ($P<0.05$).Lee et al.2016 also evaluated the effectiveness and safety of high- or medium-dose ICS when combined with salmeterol for patients with different blood eosinophil counts in COPD and found similar results as this study reveals[26]. DiSantostefano et al.2013 also found that blood eosinophil level was the primary driver of treatment response, with a greater treatment effect observed in patients with blood eosinophil levels >2.4% when treated with ICS/LABA versus LABA alone[27].

Conclusions:

This study concludes that ICS with conventional therapy significantly improves lung functions as revealed by FEV1 and quality of life as revealed by CAT score in patients with COPD with higher blood eosinophils. ICS with conventional therapy significantly reduce frequency of exacerbation with improvement of clinical outcomes as compared to conventional therapy.

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Author Contributions: Dr. Md. Shahjada Tabrez had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Dr. Md. Shahjada Tabrez contributed to study conception and design, data collection, analysis and interpretation of data, drafting of the manuscript and critical revisions of the article.

Professor Md. Ali Hossain, Dr. Md. Mahabubur Rahman, Dr. Mahboba Akther, Dr. KaziSaifuddinBennoorcontributed to concept and design of the study and critical revisions of the manuscript.

Conflict of Interest: The authors of this paper have declared that there is no conflict of interest to any of the authors.

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