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Role of Low-Dose Theophylline on Functional Improvement in Patients of Moderately Severe Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: To determine the frequency of functional improvement in patients of COPD receiving low-dose Theophylline.
Study Design: Case series.
Place and Duration of Study: Tertiary Care Hospital Mansehra, Shinkiari, Mansehra Pakistan, from Feb to Jul 2021.
Methodology: Patients with a previous chronic obstructive pulmonary disease diagnosis with Global Initiative for Chronic Obstructive Lung Disease stage 2/3, taking long-acting muscarinic antagonists were included in the study. In addition, patients were prescribed sustained released Theophylline 150mg daily and other previously prescribed medications. The assessment was done before the start of the study with the COPD assessment tool (CAT) questionnaire and followed up with monthly CAT scores.
Results: There were 78(81.25%) males and 18 females (18.75%). An increase in the CAT score of more than 2 was a significant improvement. The most common baseline CAT score was 34.26±2.67 (range 0-40 with a higher score denoting a more severe impact of COPD) with a frequency of 16(16.7%). The least commonly occurring CAT score at baseline was 39 and 40(2.1%). The improvement in the CAT score was observed in 42 patients.
Conclusion: Early and prompt treatment for COPD will reduce the outcomes by decreasing hospital admissions and better quality of life. This study reaffirms low-dose Theophylline as an add-on therapy in patients with moderately severe COPD.

Keywords: Chronic obstructive lung disease, Global initiative for COPD, Methylxanthines.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an ever-growing cause of morbidity and mortality worldwide. Pakistan is no exception, with low socioeconomic status and poor follow-up of patients adding more and more burden on the ever-saturated health care system. An accurate estimate of the prevalence of this disease is needed to anticipate the future burden of COPD, target key risk factors, and plan for providing COPD-related health services.[1,2] This disease state is characterized by airflow limitation that is not fully reversible and contributes significantly to the outpatient and inpatient burden in medicine departments nationwide. Multiple risk factors pertinent to COPD and Asthma, dyspnea, and chronic cough are the most prevalent, all being well studied for a correlation.[3,4]

The morbidity and mortality are multifold in chronic cases of chronic obstructive lung diseases, and the most important contributors are cardiovascular diseases.[5,6] Muscle atrophy and weakness carry important consequences, such as difficulties engaging in physical activity, exercise intolerance, poor quality of life, and premature mortality.[7] Corticosteroids are commonly and frequently used in the chronic and acute management of COPD. However, it is found that there is an inadequate response to their anti-inflammatory properties which underlies the definition of this disease.[8] Approximately 62% of patients with moderate to severe COPD report variability in symptoms (e.g., dyspnea, cough, sputum, wheezing, or chest tightness) over the day or week-to-week; morning is typically the worst time of day.[9,10]

Adequate COPD management is the cornerstone of improving functional status. Work in this regard has favoured the use of 'low dose' Theophylline in improving the anti-inflammatory properties of corticosteroids and hence the disease activity overall.[8] Our study on the use of Methylxanthines in our setup will provide insight into the impact of its use in resource-poor setup and help to optimize the treatment of patients with COPD.

METHODOLOGY

The case series was conducted at the Outpatient Department of Tertiary Care Hospital from February 2021 to July 2021. Approval from the Ethical Committee was taken (MED-OPD-001-21). The sample size was estimated via the WHO sample size calculator while keeping the anticipated population proportion of 45%.[9]

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Inclusion Criteria: Patients aged 40 to 80 years diagnosed with COPD for the last three years or more, with a GOLD score of 3/4 and a baseline CAT score of 30 or more were included in the study.

Exclusion Criteria: Patients in renal failure of any stage, patients taking already Theophylline and bedridden patients were excluded from the study.

The patients were assessed before the start of the study with the COPD assessment tool (CAT) questionnaire. The patients were informed about the study, and informed consent was taken before enrollment in the program.

The patients presenting in the outpatient department fulfilling the inclusion criteria were accessed with a baseline CAT questionnaire. They were regularly followed with the help of electronic data saved on every visit. Regular records were kept for the number of exacerbations, and the COPD assessment tool (CAT) questionnaire was on monthly follow-up visits for six months.

Data were analyzed using Statistical Package for the social sciences (SPSS) version 23.00. The mean and standard deviation were calculated for the age, and the initial COPD assessment questionnaire (CAT) was calculated at the start of the study and every month. The monthly frequency of improvement in the CAT scores measured the improvement. For association chi-square test was applied. The *p*-value of ≤0.05 was considered significant.

RESULTS

The total 96 patients were included, out of which there were 78 males (81.25%) with a mean age of 63.38±10.45 years and 18 females (18.75%) with a mean age of 59.55±8.17 years. The CAT scores were measured on presentation as baseline (Table-I) and then every month till the completion of the study result. The CAT was divided into two categories Improvement and not improvement. The most common baseline CAT score at the start among the males was 34, with a total of 15 males representing 19.2% of the male population whereas in females it was 31, with a total of 4 females representing 22.2% of the female population. There was no significant association between CAT score and gender (*p*-value=0.791), shown in Table-II.

The frequency and percentage of improvement age-wise showed that the age group of 61 years to 70 years showed the most improvement of 14% in the CAT score, and the age group which showed the least improvement in the CAT score was 41 years to 50 years with 4% improvement in their CAT score (Table-III).

Table-I: Mean Baseline COPD Assessment Tool (CAT) Score and Subsequent Scores Every Month (Range 0-40 with higher Score Denote More Severe Impact of COPD) (n=96)

	Baseline CAT Score	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months
Gender							
Males	33.3±2.5	34.2±2.6	33.9±2.7	33.8±3.0	33.6±3.2	33.2±3.5	33.0±3.9
Females	34.5±3.1	34.3±3.0	34.3±2.9	34.0±2.9	33.6±2.6	33.4±2.4	33.3±2.5
Age (years)							
41-50	34.3±3.2)	34.1±3.2	34.1±3.0	34.4±3.0	34.2±2.9	34.3±2.8	34.1+3.1
51-60	34.2±2.4	34.0±2.5	33.7±2.9	33.5±2.4	33.3±3.4	32.9±3.6	32.5+4.1
61-70	34.3±2.4	34.3±2.3	34.1±2.1	33.6±2.5	33.3±2.8	33.0±3.2	32.7+3.5
71-80	34.5±2.9	34.4±3.0	34.2±3.0	34.0±3.2	33.9±3.3	33.4±3.3	33.4+3.6

Table-II: Association of COPD Assessment Tool (CAT) Score with Gender (n=96)

Gender	CAT score		Total (%)	*p*-value
	Group A (Improvement) (n=40)	Group B (No improvement) (n=55)		
Male	32(41.0%)	46(59.0%)	78(100)	0.791
Female	8(44.4%)	10(55.6%)	18(100)	
Total	40(41.7%)	56(58.3%)	96(100)	

Table-III: Age Wise Improvement (n=96)

Age Group (years)	Improvement (%)	No Improvement(%)	Total(%)
41-50	4(4.1%)	11(11.4%)	15(15.5%)
51-60	12(12.5%)	15(15.7%)	27(28.2%)
61-70	14(14.5%)	15(15.7%)	29(30.2%)
71-80	10(10.4%)	15(15.7%)	25(26.1%)
Total	40(41.5%)	56(58.5%)	96(100.0%)

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a cluster of the complex interplay between clinical and molecular (i.e., genetic) risk factors.[11] This different interplay of clinical and pathophysiological pathways has led to the clinical picture of two groups of people with identical risk factors and comorbidities, with one developing COPD and the other not. In a similar study

on chronic bronchitis and obstructive airway disease, Tager *et al*. estimated smoking as the significant contributing factor, with 82% of the prevalence of chronic bronchitis attributed to cigarette smoking.[12] The genetic factors in this regard may enhance the predisposed individuals to the development of overt disease. Celedon *et al.* in a study observed a genetic correlation in which the bronchodilator responsiveness is used as an indirect measure of progressive decline in lung functions, which proved to be more prevalent in current or past smokers having a first-degree relative with COPD compared to those who did not.[13] Among the other important risk factors include airway responsiveness to different allergens, environmental exposure to different particulate matter, dust, different noxious gases, organic antigens, predisposition to atopy, sex of the patient in which women appear to have more chances of developing COPD as compared to men with equivalent risk factor profile, antioxidants deficiency and tuberculosis.[14] In this regard, a clinically significant disorder known as bronchopulmonary dysplasia must also be considered. It is also known as neonatal chronic lung disease.[15] It is defined by preterm birth, accompanied by oxygen dependency for 28 days or more postpartum. Radiographic emphysema and evidence of airflow limitation on pulmonary function testing have been noted in young adult survivors of moderate and severe bronchopulmonary dysplasia.[16] This disease has contributed to significant morbidity & mortality in the form of acute exacerbations and chronic debilitating conditions, which reduces the functional status and exercise tolerance over some time.[17] Its successful management is the cornerstone of preventing progressive decline over the period and reducing the incidence of acute exacerbations over the period.[18] Over the past several decades, the use of drug therapy in COPD has expanded and provides an optimistic picture.[10] The use of Methylxanthines in patients with COPD as bronchodilators has been in practice for the last several decades. Theophylline has been in clinical practice for several decades, whereas the newer in this group is Acebrophylline. According to their availability and cost-effectiveness, these are an add-on to the backbone of LAMA (long-acting muscarinic antagonists like Tiotropium) in respiratory clinics worldwide.[10] A randomized comparative study conducted on moderate-degree COPD patients, including 40 patients, was conducted over one year. The comparison was made between the drugs with two different parameters using symptom scores and spirometric parameters showing significant improvement (p-value> 0.05). Other parameters that showed improvement were the frequency of reliever medication, sputum production, and dyspnea.[9] This study has further helped validate the use of Methylxanthines as an add-on therapy to the backbone of LAMA in managing COPD in our setup.[10]

COPD is an interplay of multiple pathophysiological pathways with specific predispositions leading to clinical signs and symptoms of airway obstruction and chronic lung function changes. Its management includes treating chronic debility, improving clinical status, managing comorbidities, & successfully preventing acute exacerbations. A multidisciplinary team approach involving a pulmonary physician, pulmonary rehabilitation, general practitioners, and thoracic surgery is paramount to its successful management. The cornerstone of this management is early treatment with medical intervention, which will reduce the outcomes in the form of decreased hospital admissions and better quality of life.

LIMITATIONS OF STUDY

Our study lacked comparative data on the effects of weather on COPD. We could not include people with exacerbations of COPD.

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CONCLUSION

We conclude that adding Methyl-xanthines to the backbone treatment of long-acting beta-agonists and long-acting anti-muscarinic significantly improves the patients' functional status.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MUF & IS: Study design, drafting the manuscript, data interpre-tation, approval of the final version to be published.

SUH & SZ: Data acquisition, data analysis, critical review, approval of the final version to be published.

MS & SH: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of

any part of the work are appropriately investigated and resolved.

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