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Inhaled corticosteroids in COPD patients with type II DM: Incidence, Prevention and Management of oropharyngeal candidiasis

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Abstract

COPD, a commonly treated disease in pulmonology OPD has different treatment aspects. One among them is use of ICS. ICS commonly used in severe and very severe patients along with bronchodilators. It effectively reduces the frequency of future exacerbations, to be most effective way of having clinical results. It's also understood that it has certain complications on chronic usage and specially in patients with other comorbidities like type II DM. Otherwise immune compromised patients are further detoriated by use of ICS resulting in high risk of oral candidiasis. Hence this study was designed to imply the importance of regular examination, treatment when required in oral cavity to reduce the incidence of such side effects. Material and Methods: 226 COPD patients with type 2 DM divided in two group based on the willingness to participate in the study. Willing patients are kept under regular follow up dental treatment and required oral prophylaxis. Results: Group which received oral prophylaxis showed less incidents of oral candidiasis statistically. Conclusion: Regular follow up and oral prophylaxis reduces the risk of oral candidiasis in COPD patients with type2 DM.

Keywords: COPD, Inhaled corticosteroids, Oral candidiasis, Type 2 Diabetes Mellitus, Oral prophylaxis

INTRODUCTION

Pulmonology OPD regularly encounters COPD patients on day today basis and it is the one of commonest chronic respiratory disease handled by pulmonologist. Tobacco smoking is considered to be the most important risk factor associated with development of COPD. Other risk factors may include environmental exposure such as biomass fuel exposure, air pollutions and genetic abnormalities like Alpha 1 antitrypsin deficiency, congenital anomalies and accelerated aging. Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by a decline in lung function over time and accompanied by respiratory symptoms, primarily dyspnea, cough, and sputum production[1]. COPD is considered one of the leading causes of death worldwide. Enhanced chronic inflammatory response which is responsible for airway abnormality and architectural distortion of lung paranchyma is the character associated with COPD. This leading to airflow limitation that is progressive and not fully reversible. Hence affected individual's lung function deteriorates progressively over several years, with increasing symptoms like cough, cough with sputum and dyspnoea. COPD is diagnosed using clinical history, physical examination and investigations like chest x ray and spirometry. Currently spirometry is considered gold standard for diagnosing and confirming the disease. Spiromery can be performed

as a OPD procedure in stable patients for diagnosing this respiratory illness. Current guidelines emphasize on use of inhaled medications as first line treatment. Inhaled medications include bronchodilators like anti muscarinic agents, beta 2 agonists and inhaled corticosteroids. Second line treatment includes theophylines, oral β_2-agonist, posphodiesterase inhaibitors like roflimulast and oral steroids. Inhaled corticosteroids (ICS) is indicated as it reduced the execerbations, prevents rapid decrease in lung function in COPD patients. But ICS use is associated with increased risk of pneumonia and local side effects like oropharyngeal candidiasis. On the other hand, according to studies prevalence of DM in COPD patients is 25.63 % when actively screened in tertiary care hospitals[2]. On the other hand, COPD is a common comorbidity as in contributes 10% of patients with diabetes[3]. Even though type II DM is a common comorbidity of COPD, the relation between two is not an established fact. In a study conducted in 2014 it was noted that the association between two diseases was present only in obese subjects with moderate to severe COPD, but not in mild COPD [4]. Same study also indicates that slight association of ICS use with DM II in COPD patients, and this association was insignificant when ICS was used with β_2-agonist 4. Type II DM is also a common medical disorder and leading cause of mortality and morbidity. As ageing population of the world is rising, incidence and prevalence of both type II DM and COPD is bound to rise. Hence it is important to study the common comorbities and complications common due to both conditions. Oropharyngeal candidiasis is one of the most common conditions found in type 2 DM and in COPD patients using ICS. Overgrowth of candida species especially Candida Albicans is responsible for common opportunistic infections like oropharygeal candidiasis. This opportunistic infection may cause painful or painless white or red lesions all over the oral cavity and oropharynx. Candida is present as a normal commensal in healthy individuals in oral cavity but overt infection is associated with immunocompromised state. This infectious state can cause altered taste, speech and painful swallowing. Its incidence is commonly noted in COPD patients using ICS. Further its incidence is increasing in Type 2 DM patients in COPD using ICS. Hence this study was conducted to evaluate the prevelance , its prevention and management of oropharyngeal candidiasis in patients suffering from COPD with type II DM.

Aims:

Aims of this study was to,

- To evaluate the risk of oral candidiasis in usage of ICS in COPD patients with type II DM
- To draw possible guidelines for preventing oral candidiasis in COPD patients taking ICS having type II DM
- To outline the treatment options for oral thrush in COPD patients with ICS and type II DM.

Methodology:

A prospective study conducted in DM WIMS, Wayanad over the period 23 months between January 2018 and November 2020. Total of 226 patients diagnosed with COPD using spirometry, with the history of type II DM were included in this study irrespective of gender. These patients with type II DM diagnosed with COPD between Jan 2018 and May 2018 with follow up done till November 2020.

Inclusion criteria:

- Patients between age group of 45 to 70 years irrespective of the gender
- Patients who are willing to participate in the study
- Patients with the history of Type II DM and under medication
    - Newly diagnosed COPD patients by spirometry, willing to start ICS as part of treatment modality.

Exclusion criteria:

- Patients bellow 45 and above 70 years of age
- Type I diabetic patients, Type II DM patients not under medication for the same
- Known COPD patients reporting to OPD Dept of pulmonology for follow up or continued treatment
- Patients with underlying immunocompromised conditions other than DM
- Patients with existing oraopharyngeal candidiasis

Once diagnosed with COPD , these Type II DM patients were sent to department of dentistry for

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evaluation. Detailed history of type II DM recorded, including present control of diabetic status, medication history and duration of the disease. After obtaining informed and written consent oral examination is done. Hard tissue and soft tissue examination is carried out to record dental findings and state of presence of candida. These patients are then categorised in two categories.

Group I : Patients willing to undergo regular follow up in the department of dentistry and department of gastroenterology , including all required time to time treatments (required dental treatments and oral prophylaxis) and oral medications (Chlorhexidine mouthwash, Betadine gargle etc) along with continued treatment from dept of pulmonology.

Group II : Patients are not willing for any kind of regular follow up in departments other than dept of pulmonology but willing to participate in the study.

Between Jan 2018 and May 2018 total of 96 patients chose to be in group I , for regular oral examination and willingness to undergo required treatments. 130 patients who were not willing for any kind of regular oral examination or treatment, requested to report dept of pulmonology in case of change in taste, painfull swallowing or any kind of changes in oral tissues. Patients in Group I underwent oral prophylaxis, all required dental treatments (including extractions, fillings, root canal treatments etc) on the first appointment. All these patients were kept under regular follow up, interventions done, mouthwash prescribed when required and gastroenterology consultations were obtained when there was difficulty and pain in swallowing noted. All patients in this study were advised to gargle their mouth with warm saline after the use of ICS. All the patients were examined for the presence of oral candidiasis at the end of the study period.

Results:

The study had two groups based on patient's willingness to participate in the dental examination and required treatment. Mean age of patients in the group who underwent dental treatment was 59.93 and who didn't show interest in dental follow up had mean age of 60.02

Without oral treatment	86(66.7)	43(33.3)		

Table 1: Comparison of age between 2 groups

Groups	Mean	SD	P value
With oral treatment	59.93	7.11	0.92
Without oral treatment	60.02	6.67	

Total 226 patients were in two groups. Total of 95 patients participated in the study had their dental treatments done as scheduled, which contributes to 42.9% of the study population. And remaining 129 patients didn't show interest in the dental treatments contributed to 57%.

Table 2: Distribution of two groups

Groups	n	%
With oral treatment	95	42.4
Without oral treatment	129	57.6

11 patients out of 95 patients participated in dental treatment and followed up ended up showing clinical signs of oral candidiasis at the end of the study. And 43 patients who didn't undergo dental follow up showed presence of candidiasis at the end of study duration on clinical examination. On statistical analysis following conclusions were drawn. Chi square was used for association between variables. Probability value ($p < 0.05$) was considered statistically significant.

Table 3: Distribution based on incidence of oral candidiasis

Groups	Absent n(%)	Present n(%)	Chi square value	P value
With oral treatment	84(88.4)	11(11.6)	14.15	0.001**

Discussion:

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COPD is an important cause of mortality and morbidity around the world. This disease is a growing problem as use of tobacco products increases worldwide**.** Mostly middle aged or elderly are seen effected by COPD. Principal risk factor for this disease is tobacco smoking Lung irritants like occupational and environmental exposures to chemical fumes,dusts accounts for 10-20% of copd cases [5]. We have considered age group above 45 years in this study, but should be suspected that Alpha -1 antitrypsin deficiency can cause COPD in whom emphysema develops before the age of 40 .[6] Long asymptomatic phase is common in COPD due to slow progressive nature of the disease, during which lung function continues to decline. Progressive dyspnea, persistent cough, cough with mucus production, wheezing and chest tightness are the common symptoms. Most patients report to OPD/Healthcare only with first acute exacerbation of COPD at an advanced stage. Exposure to irritants may induce an inflammatory process in the bronchial tree that leading to parenchymal and small airway disease[7]. Emphysema is characterized by loss of elasticity of alveolar attachments or destruction. Dyspnea on exertion is due to inability of lungs to empty resulting in air trapping and hyperinflation. Rib cage enlargement and diaphragm flattening can be noted over the time. Hypoxemia develops in the late stages of COPD. Increased resistance to airflow and decreased expiratory flow rate is the outcome of pathophysiologic processes of COPD. As disease progresses exacerbation becomes more frequent and life-threatening complications may develop. Diagnosis of COPD is based on clinical history, physical examination and investigations. Clinical diagnosis is based on history of chronic sputum production, chronic progressive exhertional breathlessness and exposure to noxious particles like tobacco smoking, firewood smoke and air pollution. Treatment of stable COPD includes both pharmacological and non-pharmacological approach. Pharmacological therapies include bronchodilators and anti-inflammatory agents. Bronchodilators include beta 2 agonists, anti-muscarinic agents and theophylines. Inhaled corticosteroids is given for COPD patients with FEV1 less than 50%.

The development of COPD may act directly on airway and alveolar tissue, promoting airway narrowing and airflow limitation due to the presence of increased numbers of inflammatory cells in airway biopsies and bronchoalveolar lavage, including, alveolar macrophages, T lymphocyte and neutrophils in smokers' lungs [8,9]. The results from this study justified the use of inhaled corticosteroids in copd patients. There has be demonstration of two-way synergistic activity between ICSs and LABAs [10,11]. The action of ICSs is to translocate glucocorticoid receptors from the cytoplasm to the nucleus in airways[11] . Without the need to increase in the ICS dosage,this action is enhanced in the presence of β-agonists and causes an anti-inflammatory effect greater than either drug alone, [10] Along with this , ICSs activate β-receptor genes to produce more β-receptors, thereby increasing the bronchodilator effect of LABAs[12].There was a significant 13% reduction in the rate of exacerbations was noted (RR 0.87, 95% CI 0.80–0.94) and the odds of death were significantly lower with combination therapy (OR 0.78, 95% CI 0.64–0.94)- in all the six studies that compared ICS-LABA vs ICS monotherapy[13]. In a study done in COPD patients SUN using budesonide–formoterol over a period of 1 year showed adverse effects like oral candidiasis, ocular effects, skin effects, and bone effects, in the ICS-LABA group than the LABA-alone or placebo groups[14]

Common comorbities associated with COPD include cardiovascular diseases, pulmonary malignancies, metabolic syndrome, skeletomuscular disorders and many others, which affects significantly on patients' quality of life, exacerbation frequency, morbidity and mortality [15,16] . Diabetes mellitus is one of the most common metabolic disorder found among COPD patients. There is negative effects on subjects exercise capacity, morbitity and mortality due to metabolic syndromes like diabetes mellitus [17,18] . COPD is considered as a novel risk factor for new onset type 2 diabetes mellitus which occurs through multiple pathophysiological alterations first of all nonspecific low-grade inflammation that occur in the lung and then split over in the whole body, and is responsible for systemic characteristics of the disease [2]. The progression of COPD and the development of insulin resistance is due to systemic inflammation, with elevated markers such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Smoking causes inflammation. Smokers have two times higher risk of developing diabetes mellitus type 2 than nonsmokers [19]. COPD patients are more likely to have impaired glucose metabolism than non-

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COPD patients. Almost half of all COPD patients suffer from medical problems frequently linked to diabetes, such as hypertension and dyslipidemia [20] .

Candida albicans causes oral candidiasis an infection of the oral cavity. Pediatrician Francois Veilleux first described it in 1838. Oral candidiasis is generally obtained secondary to immune suppression, whether a patient's oral cavity has decreased immune function or if it is systemic. This immunosuppression is dose-dependent[21.]. Examples of systemic immunosuppression are very young or very old age, immunocompromising conditions such as HIV/AIDS, and chronic systemic steroid/antibiotic use[22,23] . Local immunosuppression is seen in patients using inhaled corticosteroids used in the treatment of asthma and COPD. Oral candidiasis is caused by the *Candida* species, most commonly *Candida albicans*[24]. When a patient's host immunity becomes disrupted candida can cause oral thrush . This disruption can be local, secondary to inhaled corticosteroid use. Formation of a pseudomembrane is due to overgrowth of the candida fungus. Diagnosis of oral candidiasis is most commonlydone on clinical assessment i.e. based on appearance and risk factors. The appearance of an erythematous, inflamed, and bleeding base after scraping off the plaques aids in diagnosis of oralpharyngeal candidiasis.Oral candidiasis is commonly found in conditions like patients in chemotherapy for malignancies, HIV/AIDS and Type 2 Diabetes Mellitus,.Antimicrobial proteins in the saliva such as lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides and specific anticandida antibodies, interact with the oral mucosa and prevent overgrowth of candida.Drugs such as inhaled steroids have been shown to increase the risk of oral candidiasis by possibly suppressing cellular immunity and phagocytosis[25]. Job FM van Boven et all found in their study that significant and clinically relevant increased number of oral candidiasis in the first year after therapy with ICS[26]. Like many other studies, research published in Turkish Thoracic Journal, High dose and long-term use of ICS caused side effects mostly oral candidiasis[27]. This justifies requirement on check of prevalence of oral candidiasis in patients using ICS. ICS is common treatment modality for COPD and major portion of COPD patients also suffering from other comorbidies like type II DM the risk of developing the oral candidiasis. Regular oral prophylaxis and relevant treatments in such patients have proven effective modality in preventing complications of long-term use of ICS.

Conclusion:

COPD and Type II DM are commonly encountered disease in our daily day to day practise with a number of significant complications. Type 2 DM is very commonly seen in COPD patients. ICS along with other inhaled medications is commonly prescribed for treatment of COPD patients. ICS is commonly associated with oropharyngeal candidiasis. Since COPD and Type2 DM are having a chronic course, both needs a regular long term follow up. In this follow up it is imperative to identify the local complications like oropharyngeal candidiasis due to use of ICS, as this condition is easily diagnosed, preventable and treatable. Preventable strategies include good oral hygiene after use of inhalers, use of spacer, regular oral and dental examination and use of mouthwash. It can be concluded that regular dental follow up and required oral prophylaxis may reduce the incidence of oral candidiasis in patients using ICS.

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