Clinical response to withdrawal of Inhaled Corticosteroids in stable mild to moderate chronic obstructive pulmonary disease in a tertiary hospital of central Nepal

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ABSTRACT

Introduction: The mainstay treatment according to the Global Initiative for Chronic Obstructive Lung Disease 2023 guidelines for Chronic Obstructive Pulmonary Disease is combination of long acting bronchodilators with addition of inhaled corticosteroids only in patients with increased exacerbations and an eosinophil count of ≥ 300 cells/μL. Despite the recommendations, inhaled corticosteroids are most commonly overprescribed. So, this study aims to follow patients with mild to moderate cases of this disease who are currently on inhaled corticosteroids combination therapy for clinical efficacy after its withdrawal.

Methods: The study was a prospective interventional study conducted at Dhulikhel Hospital that followed individuals with mild to moderate COPD for eight weeks after a sudden ICS withdrawal. Forced Expiratory Volume in first second, modified Medical Research Council grading, COPD Assessment Tool score and number of exacerbations were assessed with follow-up either by telephone or face to face.

Results: Total of 33 patients were enrolled in the study with mean age 68.9 years and standard deviation 9.3 years. Paired t-test analysis showed no significant mean difference in Forced Expiratory Volume in first second and COPD Assessment Tool values before and eight weeks after the withdrawal of Inhaled Corticosteroids.

Conclusions: Our study supported the conclusion of previous larger studies that withdrawing ICS in stable mild to moderate COPD patients makes no difference in clinical symptoms and spirometry.

Keywords: Chronic Obstructive Pulmonary Disease; Inhaled Corticosteroid

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition having chronic respiratory symptoms like dyspnoea, cough and expectoration due to persistent abnormalities of the airways and/or alveoli.[1] The diagnosis is made if post bronchodilator ratio of Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC) < 0.70.[1] It can be mild, moderate, severe and very severe depending on post bronchodilator FEV1 value (≥80% as mild, ≥50 to <80% as moderate, ≥30 to <50 as severe and <30 as very severe).[1]

Bronchodilators like long acting beta2 agonists or long acting anti-muscarinic (LABA/LAMA) are the mainstay of treatment in stable COPD while Inhaled Corticosteroid (ICS) is added in patient with high eosinophil count.[1] Contrary to the recommendation, ICSs are most often overprescribed and continuation leads to several systemic adverse effects. [2–8]

Hence, withdrawal of ICS in low risk stable COPD patients with blood eosinophil count < 300/μL can be a reasonable

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approach for safe management.[1] We aim to identify and follow-up such patients for clinical efficacy of ICS withdrawal.

METHODS

This was a hospital-based prospective interventional study conducted at Dhulikhel Hospital-Kathmandu University Hospital (DH-KUH) conducted over 12 months from August 2021 to August 2022. Ethical approval was taken from the Institutional Review Committee of Kathmandu University School of Medical Sciences- KUSMS-IRC (18/2021). The patients visiting medicine outpatient department who were spirometry- diagnosed with COPD and met inclusion criteria were enrolled after the informed consent. These patients had been stable in terms of spirometry with FEV1 > 50% baseline and had no exacerbation(s) in the last 12 months. These patients had absolute blood eosinophil counts < 300/µL. Bronchial asthma and Asthma-COPD-Overlap (ACO) were ruled out based on history, clinical examination and spirometry. Baseline dyspnea scale with modified Medical Research Council (mMRC) and COPD Assessment Tool (CAT) was measured.[9,10]

Inhalation and device application techniques were observed using standard seven step observation checklists and if incorrect, they were instructed the correct techniques instantly.[11] Inhalational steroids were withdrawn from the patients meeting these criteria. After stoppage of ICS, patients were followed up verbally by either telephone or face to face at the end of two weeks and face to face at the end of eight weeks. Repeat spirometry and post bronchodilator FEV1 were reassessed at the end of eight weeks. Any patient whose symptoms were stable and FEV1 similar to the measurement before discontinuation were continued with bronchodilators (LABA, LAMA or Combination of LABA+LAMA) only.

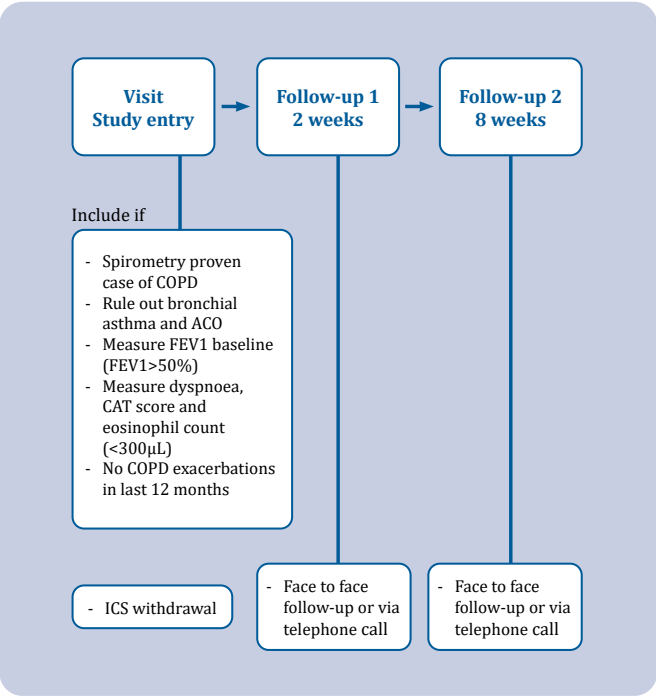

Figure 1: Study design

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; ICS, Inhaled Corticosteroids; ACO, Asthma COPD Overlap; FEV1, forced expiratory volume in first second; CAT, COPD Assessment Tool.

Data obtained on the day of discontinuation, at the end of two weeks and eight weeks were tabulated in Microsoft Excel and statistical analysis was done using Statistical Package for Social Science (SPSS) version 28. Paired t-test was used to compare the pre-and post-intervention data. The results were expressed as count (n), proportion (%), mean and standard deviation (SD). For all analyses, a p-value < 0.05 was considered statistically significant.

RESULTS

Among 50 participants who gave consent for the study, 17 were not able to complete the study due to loss to follow-up and a total of 33 patients were able to complete the study. The mean age of the patients was 68.9 years with a standard deviation (SD) 9.3 years. There were 18 male (54.5%) and 15 female (45.5%) participants. The mean duration of suffering from COPD was 7.5 years with SD of 5.2 years. Nineteen participants (57.5%) were using triple inhalational combination therapy with LABA+LAMA+ICS while the rest of the 14 participants (42.4%) were using LABA+ICS combination therapy. Withdrawing ICS as an intervention, the modified treatment given was LABA (Salmeterol) only to five participants (15.2%), LAMA only to 12 participants (36.4%) and combination of LABA+LAMA to 16 participants (48.5%) as shown (Table 1).

Table 1. Background characteristics of the participants. (n=33)

Characteristics	Frequency (n)	Percentage (%)
Sex		
Male	18	54.5
Female	15	45.5
Age (Mean ± SD)	68.9 ± 9.3	
Duration of COPD (Mean ± SD)	7.5 ± 5.2	
Current treatment		
LABA, ICS	14	42.4
LABA, ICS, LAMA	19	57.5
Modified treatment		
LABA	5	15.2
LAMA	12	36.4
LABA, LAMA	16	48.5

n = Total number of participants throughout the study

SD = Standard Deviation
LABA = Long Acting Beta Agonist
LAMA = Long Acting Muscarinic Antagonist
ICS = Inhaled Corticosteroids

Table 2. Comparison of participant parameters in the beginning of the study and eight weeks after withdrawal of inhaled corticosteroids.

Parameters	In the beginning	8 weeks later	p value *
FEV1 (Mean ± SD)	74.2 ± 8.9	74.0 ± 8.2	0.544
mMRC (Mean ± SD)	1.0 ± 0.7	1.2 ± 0.8	0.006
CAT (Mean ± SD)	11.2 ± 2.3	11.4 ± 2.2	0.058

*paired t-test

FEV1 = Forced Expiratory Volume in one second
mMRC = modified Medical Research Council
CAT = COPD Assessment Tool

Comparison of the parameters in the beginning of the study and eight weeks after withdrawal of ICS was done (Table 2). Paired t-test analysis showed that there was no significant mean difference in FEV1 values and CAT values before and eight weeks after the withdrawal of ICS. The mean mMRC value eight weeks after withdrawal of ICS was found to be significantly higher than the mean value before withdrawal (1.2 compared to 1.0, p value 0.006). A p-value of < 0.05 was considered statistically significant.

DISCUSSION

This study was directed towards the evaluation of patients with mild to moderate COPD receiving therapy with LABA+ICS and LABA+LAMA+ICS to assess if they could manage to stay off ICS after abrupt withdrawal or not. Thirty three patients were included in our study for a full eight weeks excluding the patients who were unable to come to follow-up. Symptoms and clinical impact were assessed by the mMRC dyspnoea scale and/or the CAT.[9,10] Differences in the age, duration of COPD, lung function, mMRC and CAT score before and after the withdrawal of ICS were noted and collated.

According to the ABE Assessment Tool (GOLD Guidelines 2023), the initial pharmacological treatment is recommended to be either a long or short acting bronchodilator in patients with mMRC 0 to 1, CAT <10 and having 0 or 1 moderate exacerbation without hospital admission, which is chosen according to the episode of breathlessness (Group A) whereas combination therapy of LABA + LAMA is recommended for the patients with mMRC ≥ 2, CAT ≥ 10 and having 0 to 1 moderate exacerbations without hospital admission (Group B).[1] However, for the patients with ≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospital admission LABA + LAMA combination is preferred with the addition of ICS if the blood eosinophil count is ≥ 300 cells/μL irrespective of the mMRC and CAT score (Group E).[1] For only a minority of COPD diagnosed as Asthma COPD Overlap (ACO), we use ICS as the mainstay of treatment.[12]

Corticosteroids have various systemic adverse effects including pneumonia, bone fractures, osteoporosis, and new onset diabetes of diabetes progression, cataracts and tuberculosis.[2–8] Ulrik et al. have reported that ICS were prescribed for 76% of mild COPD patients despite the recommendation of ICS for only severe and very severe COPD cases experiencing repeated exacerbation.[1,13] Our study intended to stop prescribing corticosteroids if the number of exacerbations doesn't increase significantly, taking into account the over prescription of corticosteroids against guidelines, systemic adverse effects it causes, and financial burden on patients. A number of past studies from different places have assessed the effect of ICS withdrawal in patients with COPD not meeting the criteria as per the GOLD guidelines and found no significant differences in the number of exacerbations and decrease in lung functions. [2,14]

To make the study manageable, and attainable in a real-life clinical setting of our outpatient department, we did an abrupt withdrawal of ICS with proper monitoring and update afterward. During the follow-up, no significant change in lung function (FEV1) and CAT values were noted but mean mMRC value eight weeks after withdrawal was found to be significantly higher than before withdrawal (1.2 compared to 1.0, p-value 0.006). To our awareness, this kind of study has not been conducted in the hospital and nearby centres in Nepal with long term ICS treatment to assess their capacity to accept abrupt ICS withdrawal. In Nepal, COPD is considered one of the leading causes of morbidity and mortality with a prevalence estimated to be almost 23%,[15] the outcome of the study will be a good reference for practising the management of chronic stable COPD. An observational study in east London also states that ICS cessation was more successful in south-Asian ethnic groups, reduces the cost in general and is well accepted if led by primary care in mild to moderate COPD.[16]

Many studies done in recent years also support that not all patients with COPD will benefit from ICS therapy, particularly if effective dual bronchodilation with LABA and LAMA is maintained.[17] Various other investigations also demonstrated that ICS withdrawal was safe and mainly eosinophil counts > 300 cells/μL were mostly associated with COPD exacerbations (in around 18% of their study patients).[17,18]

The clinical utility of ICS in emphysema variants of COPD is also doubtful as shown in a study by Lee et al.[19] According to the WISDOM trial, patients suffering from severe COPD taking tiotropium plus salmeterol had a similar risk of moderate or severe exacerbations irrespective of continuing or discontinuing inhaled glucocorticoids.[20] The Clinical

Effectiveness Group (CEG) of London has identified 'low risk' COPD to those whose latest predicted FEV1 in last 3 years is ≥ 50% and eosinophils count < 500/µL where withdrawing ICS in these patients can be appropriate.[16]

Hence, discontinuation of ICS in chronic low-risk stable patients with blood eosinophil count < 300/µL can be a reasonable approach for the safe management of clinically stable COPD. In our study, upon comparison of the mean FEV1 scores before and eight weeks after withdrawal of corticosteroids, we found that there was no significant change. Although, there was significant difference in mMRC scores at baseline and eight weeks after withdrawal of corticosteroids, there was no clinically significant change noticed in mean mMRC scores. We also found that there was no significant change in CAT scores from baseline to eight weeks after withdrawal of corticosteroids. None of the patients had any acute increase in symptoms that either needed optimization of treatment or need of hospitalisation during this short period, supporting previous larger studies.

The anonymity of the participants was maintained throughout the research process with proper consent. All the measurements of lung function were performed by a research team under the principal investigator at every follow-up. As we had a limited number of sample sizes, higher number of patients and long term follow up could add more information regarding this study.

CONCLUSIONS

Our study supported the conclusion of previous larger studies that withdrawing ICS in stable mild to moderate COPD patients makes no difference in terms of clinical symptoms and significant difference in spirometry, thereby warranting its discontinuation owing to its unwanted adverse drug effects over clinical benefits.

CONFLICT OF INTEREST:

None

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None

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