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Side Effects of Long-Term Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objectives: The literature lacks sufficient data on the long-term side effects of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) when used for over a year. In this study, the frequency of potential side effects was investigated in patients with COPD who had been using ICS.

Methods: This single-center and observational study included stable COPD patients diagnosed with spirometry who had been using ICS for at least 1 year. Patient demographic and clinical characteristics and ICS-related side effects were recorded in detail according to the hospital records.

Results: The study enrolled 92 patients, 74 (80.4%) of whom were male, with an mean age of 66.5± 8.4 years. The frequency of potential side effects of ICS, including voice changes, oral candidiasis, bruises, and cataracts, was higher after treatment than before treatment (3 [3.3%] vs. 34 [36.9%], p<0.001; 3 [3.3%] vs. 15 [16.0%], p=0.008; 2 [2.2%] vs. 14 [15.2%], p=0.004; and 9 [9.8%] vs. 25 [27.2%], p=0.009, respectively). However, there was no difference in the frequency of adverse events such as pneumonia, mycobacterial infection, osteoporosis, and diabetes mellitus before and after treatment (20 [21.7%] vs. 19 [20.7%], p=0.860; 8 [8.7%] vs. 2 [2.2%], p=0.109; 4 [4.3%] vs. 8 [8.7%], p=0.388; and 10 [10.9%] vs. 13 [14.1%], p=0.678, respectively).

Conclusion: Recognizing and assessing the side effects of ICS in patients with COPD and evaluating decisions regarding the use of ICS in routine clinical practice based on the benefit-risk ratio may be necessary.

Keywords: Adverse effects, cataract, chronic obstructive pulmonary disease, oral candidiasis, pneumonia

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) causes approximately 3 million deaths worldwide each year.[1] Reducing mortality is one of the most important goals of treatment, which has not yet been achieved to the desired extent. In the 2023, Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report, including pharmacological and non-pharmacological treatment approaches that reduce mortality in COPD, was exciting.[2] The report pointed out two large studies showing that triple therapies, including inhaled corticosteroids (ICS), can reduce mortality in patients with frequently exacerbated COPD.[3,4] ICS are widely used in the maintenance treatment of COPD despite controversy. For the first time in the 2019 GOLD report, treatment recommendations for regimens with ICS are presented more clearly.[5] However, there are still insufficient data and recommendations on how long to continue ICS in patients with treatment response and when to consider withdrawal if the patient is stable. Since the side effects of ICS are generally not followed up for more than 1 year in clinical trials, the most important concern related to long-term use is the side effects of ICS. Despite the in-

haler use, systemic side effects such as increased incidence of pneumonia, cataract, and osteoporosis have also been reported in studies to date.[6,7] In this study, the frequency of long-term local and systemic potential side effects were investigated in patients with COPD who had been using ICS for at least 1 year.

METHOD

This single-center and observational study included 92 stable COPD patients admitted to the chest diseases outpatient clinic between May 2022 and 2023. Patients who had been diagnosed with COPD for at least 1 year, had a confirmed post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <0.7, had a smoking history of at least 10 pack-years, and had been on ICS therapy for at least 1 year were included in the study.[5] Patients who had an exacerbation in the past 4 weeks, lacked a spirometric diagnosis, did not use inhaler medication consistently, had various cognitive impairments, and refused participation were excluded from the study.

The case report form was completed for each patient. This form included information on age, gender, smoking status, smoking pack-years, duration of COPD diagnosis, and grade of COPD (in spirometry the FEV1 value determines the grade as follows: Grade 1 (FEV1 ≥80%), Grade 2 (FEV1 ≥50–<80%), Grade 3 (FEV1 ≥30–<50%), and Grade 4 (FEV1 <30%).[8] The form recorded the number of exacerbations experienced in the previous year, details of inhaler treatments, the duration of ICS use, and any potential side effects of the inhaler medications. It also noted whether these side effects occurred before or during the use of ICS. Modified Medical Research Council (mMRC) and COPD Assessment Test (CAT) scores were recorded for each patient's degree of breathlessness and disease control status.[9] The mMRC scale evaluates a person's perception of dyspnea during daily activities. This scale allows individuals to define their sensation of breathlessness. Dyspnea severity is rated on a scale from 0 to 4, where "0 point" indicates no perception of dyspnea, and "4 points" indicates severe dyspnea perception. The CAT scale is a questionnaire specifically designed for individuals with COPD. Its purpose is to evaluate how COPD affects a person's daily life and to track changes over time. The CAT scores range from 0 to 40, with higher scores indicating a more severe impact of COPD on the patient's life. The mMRC and CAT scores were calculated to assess the potential relationship between the severity of COPD and the likelihood of side effects. The eosinophil counts and percentages of the patients were obtained from the hemogram results performed in the past 6 months during the stable period. Voice changes, oral candidiasis, bruising, pneumonia, cataract, osteoporosis, diabetes mellitus, and tuberculosis were evaluated as possible side effects related with ICS according to patients' self-reports and hospital records.

The data were transferred to the IBM SPSS Statistics 22 program. While evaluating the study data, mean±standard deviation value is used for normal distribution and median (interquartile range) for abnormal distribution of numerical variables and frequency distributions (frequency and percentage) for categorical variables. McNemar test was used to compare the frequency of side effect development before and after ICS treatment. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 92 patients were included in this study. Regarding medication use, 67 (72.8%) patients were treated with ICS+long-acting beta-2 agonist+long-acting muscarinic agonist, while 25 (27.2%) patients were treated with ICS+long-acting beta-2 agonist. Demographic and clinical characteristics of the patients are summarized in Table 1.

The frequency of potential side effects of ICS, including voice changes, oral candidiasis, bruises, and cataracts, was higher after treatment than before treatment ($p<0.001$, $p=0.008$, $p=0.004$, and $p=0.009$, respectively). The frequency of side effects possibly related to ICS use in before and after ICS treatment is summarized in Table 2.

DISCUSSION

In this study, the local and systemic side effects of ICS, which occupy an important position in the treatment of COPD, were investigated. During the use of ICS, the most common side effect observed was a change in voice, affecting 36.9% of patients. This was followed by cataracts in 27.2% patients and pneumonia in 20.7% patients, respectively. Oral candidiasis was observed in 16.3% patients, bruising in 15.2%, diabetes in 14.1%, and osteoporosis in 8.6%. Voice alterations, oral candidiasis, bruises, and cataracts each of which may be associated with the use of ICS were found to be significantly more common during ICS usage compared to the non-use period. In contrast, adverse events such as pneumonia, osteoporosis, and diabetes were reported at similar frequency both before and after the treatment.

The most common local side effects of ICS are encountered in patients with COPD.[7] In the study by Lyseng-Williamson et al., the rate of voice change side effects in COPD patients using inhaled steroids was found to be 3–5%.[10] In a study conducted by Klaus et al., a lower incidence of dysphonia and oral candidiasis was observed in the group receiving long-acting β2 agonists and anticholinergics compared

Table 1. Demographic and clinical characteristics of the patients

	Mean±SD
Age (years)	66.5±8.4
	n (%)
Gender	
Male	74 (80.4)
Female	18 (19.6)
Smoking status	
Active smoker	40 (43.5)
Ex-smoker (smoked and quit)	52 (56.5)
Grade of COPD	
Grade 1	9 (9.8)
Grade 2	7 (51.1)
Grade 3	30 (32.6)
Grade 4	6 (6.5)
Least one exacerbation in the previous year	41 (44.6)
Treated with systemic steroids for 5 days during the exacerbation	30 (32.6)
	Median (IQR)
COPD diagnosis time (years)	10.0 (13.0)
mMRC scale score	2.0 (2.0)
CAT scale score	17.0 (12.0)
Frequency of exacerbations in the previous year	0.0 (1.0)
Duration of ICS use (years)	6.0 (6.0)
EOS (cells/mL)	200.0 (210.0)
EOS (%)	2.1 (2.5)

CAT scale: COPD assessment test scale; COPD: Chronic obstructive pulmonary disease; EOS: Eosinophil count; ICS: Inhaled corticosteroids; IQR: Interquartile range; mMRC scale: Modified medical research council scale; SD: Standard deviation.

to the treatment group receiving inhaled glucocorticoids.[4] Similarly, it was observed that intraoral local side effects occurred in approximately one out of three patients in our study. Encouraging each patient to gargle with water after use may help reduce this local side effect.[11,12]

Oral candidiasis is one of the important local side effects that may develop due to ICS and may affect the patient's quality of life and compliance with treatment.[13] The analysis of 16 randomized controlled trials (RCTs) has shown that the use of ICS tripled the risk of oral candidiasis.[14] In this study, it was observed that while the prevalence of oral candidiasis was 3.3% before the use of ICS, this prevalence increased to 16.3% after the initiation of ICS.

Bruising, one of the systemic side effects of ICS, is observed more frequently, especially in elderly patients and when high doses of ICS are used. This causes anxiety in patients and sometimes leads to unnecessary further investigations. The Lung Health Study 2 reported that easy bruising was significantly increased in patients with COPD using ICS compared to those using placebo (11.2% vs. 3.5%).[15] Similarly, in this study, there was an increase in reports of bruising in COPD patients following ICS use. A low level of awareness of this side effect among both physicians and patients can lead to it being frequently overlooked.

Another undesirable effect associated with ICS use is an increased incidence of cataract.[16] In the study by Nath et al., cataract was detected in 16.2% of COPD patients using ICS and the frequency of cataracts increased with age and the incidence was as high as 27.3% in patients aged 80 years and older. In addition, no cataract development was observed even with low-dose ICS use for more than

Table 2. The frequency of side effects possibly related to ICS use in before and after treatment

	Before ICS Treatment	After ICS Treatment	p
Side effects			
Change in voice	3 (3.3)	34 (36.9)	<0.001
Oral candidiasis	3 (3.3)	15 (16.0)	0.008
Bruising	2 (2.2)	14 (15.2)	0.004
Cataract	9 (9.8)	25 (27.2)	0.009
Pneumonia	20 (21.7)	19 (20.7)	0.860
Mycobacteria infection	8 (8.7)	2 (2.2)	0.109
Osteoporosis or bone fracture	4 (4.3)	8 (8.7)	0.388
Diabetes mellitus	10 (10.9)	13 (14.1)	0.678

ICS: Inhaled corticosteroids.
Data are presented as n (%).
McNemar test.

1 year, whereas the prevalence of cataract was 32.2% and 39.7% in medium- and high-dose ICS use, respectively. It was observed that 36.9% of the patients had cataracts, with only 9.8% patients having a cataract diagnosis before ICS treatment, and 27.2% patients receiving a cataract diagnosis after ICS use in this study. It may be important in terms of preventive medicine to be careful about cataracts and to remind regular eye controls especially in patients with COPD who use high dose ICS.

Increased risk of pneumonia is the most concerning side effect of ICS. The frequency of pneumonia before ICS use was comparable to the frequency during ICS treatment observed in this study. A review indicated a higher risk of pneumonia in COPD patients and smokers, regardless of ICS use.[17] The "Extrafine Inhaled Triple Therapy Versus Dual Bronchodilator Therapy In Chronic Obstructive Pulmonary Disease" study, which compared triple therapy (beclomethasone dipropionae+formoterol fumarate+glycopyrronium) with dual bronchodilator therapy (formoterol fumarate+glycopyrronium) and followed patients for 52 weeks, the ICS arm was not associated with a higher incidence of pneumonia.[18] Similarly, the "Study to Understand Mortality and Morbidity in COPD (SUMMIT)" study, ICS use did not lead to an increased risk of pneumonia, whereas low FEV1, history of exacerbation and body mass index <25 kg/m^2 were associated with an increased risk of pneumonia.[19] In multicenter RCTs including large patient groups, such as the Informing the Pathway of COPD Treatment and Towards a Revolution in COPD Health, it was pointed out that there was an increased risk of pneumonia in the ICS arm, but this risk was acceptable considering the exacerbations it prevented.[3,20] While most of the studies evaluating the side effect of pneumonia included fluticasone-containing treatments, an increased risk of pneumonia was found in a few studies with non-fluticasone ICS.[21,22] Therefore, patients who are started on ICS should also be evaluated in terms of other pneumonia risk factors and high-risk patients should be closely monitored in terms of benefit- risk ratio.

There are conflicting results in the literature that ICS may increase the risk of osteoporosis. Observational studies have shown that high-dose ICS, especially when used for more than three years, decrease bone mineral density (BMD).[23] The low-dose ICS was not associated with BMD loss, while high-dose ICS was found to be associated.[24] It was detected that the addition of low-dose inhaled budesonide to treatment did not affect BMD at 4-year follow-up in patients with COPD.[25] It was not observed an increase in the frequency of osteoporosis in COPD patients during ICS treatment compared to the non-use period in this study. However, in light of the literature, the risk of osteoporosis should be taken into consideration when prescribing ICS-containing regimens and dose preference in patients with COPD.

The results of observational studies indicate that ICS may be associated with an increased risk of mycobacterial infection and tuberculosis in patients with COPD.[26,27] A meta-analysis of RCTs also found an increased risk of tuberculosis in patients with COPD using ICS. On the other hand, in a population-based nested case–control study, ICS use in patients with COPD was associated with non-tuberculous mycobacterial infections but not with pulmonary tuberculosis.[28] Similarly, it was not observed an increase in the frequency of pulmonary tuberculosis during ICS treatment compared to the previous period. The fact that mycobacterial infection is included in the etiology of COPD may explain the higher frequency of mycobacterial infection before ICS than after treatment in our study.

The ICS may increase the risk of diabetes and impair glucose control in patients with diabetes.[29] However, there are studies in the literature showing that high-dose ICS increases the risk of diabetes and impairs glucose regulation, as well as studies that have not found a correlation between ICS use and diabetes.[29-31] No significant difference was found between the percentage of patients with diabetes before treatment and those diagnosed after ICS treatment in this study. Although the results in the literature are contradictory on this subject, evaluating diabetes symptoms, especially in COPD patients using high-dose ICS, and monitoring glucose levels in diabetic patients at each visit may increase experience in this regard.

This study also has some limitations. The first of all is an observational study. Since side effects potentially related to ICS were questioned retrospectively and based on patient self-reports, there is a risk of recall bias. To minimize this impact, we conducted a retrospective review of hospital and pharmacy records to document reported adverse events. Second, our study did not include a control group that was not using ICS. Adverse events possibly related to ICS use were categorized into two groups: those occurring before treatment and those arising after treatment. The frequency of these events was then compared. Side effects may be dose-dependent on ICS; however, due to the small number of patients in our study, grouping based on the ICS doses used could not be performed. Finally, due to the small number of patients and the presence of many confounding factors such as age and comorbidities, a definitive cause-and-effect relationship between side effects and inhaled ICS use cannot be established based on these results.

CONCLUSION

Although this study is observational, it indicates that long-term ICS use in patients with COPD may be associated with numerous local and systemic side effects. Increased awareness of these side effects among physicians and patients will lead to earlier recognition and treatment. In primary health care centers and pulmonology outpatient clinics, interrogation of patients with COPD about both the benefits and side effects of ICS regimens is of great importance in the decision to continue treatment.

Disclosures

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Conflict of Interest: All participants involved in the study provided written informed consent.

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