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THE EFFECT OF INHALED CORTICOSTEROIDS ON ABSOLUTE EOSINOPHILS COUNT

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ABSTRACT: Background: Patients with respiratory diseases are frequently treated with inhaled corticosteroids (ICS) to lower the likelihood of exacerbations. Research to date indicates that ICS treatment has a significant impact on eosinophils counts, which is a phenomenon with wider consequences. Therefore, to maximize the benefits of ICS therapy, it is necessary to investigate the intricate interplay between ICS and eosinophils. **Aim and Objective:** Our research aimed to assess the influence of inhaled corticosteroids (ICS) on eosinophils counts, as well as the safety and adherence of ICS therapy. **Materials and Methods:** The single-centered prospective observational study was conducted over three months with 69 patients. The sociodemographic and clinical information were recorded. The ICS's safety and adverse effects were evaluated using the Inhaled Corticosteroid Questionnaire (ICQ). The Morisky Medication-Taking Adherence Scale-MMAS (4-item) was used to evaluate the medication-taking behavior. Statistical significance was defined as a $P < 0.05$. **Results:** Of 69 patients, 42 were in the study arm (with ICS) and 27 in the control arm (without ICS). The mean age of the study arm was 55.2 years, whereas 54.6 years in the control arm. In both the study and control arms, men predominated. With 37.7% of cases, chronic obstructive pulmonary disease (COPD) was the most prevalent diagnosis. In the study arm, there was a small but statistically insignificant decrease in eosinophils. "Poor Adherence" was visible in the ICS arm. The most prevalent side effects reported in the trial arm were hoarseness of voice and a terrible taste in the mouth. **Conclusion:** Our findings show that short-term ICS treatment did not result in a substantial reduction in eosinophils. Treatment adherence will be improved through effective patient education, and side effects will be reduced using multifaceted patient-specific approaches by clinicians.

INTRODUCTION: A significant global cause of illness and mortality, chronic respiratory disorders affect the airways and other lung components [1, 2]. Chronic lung illnesses, including asthma and chronic obstructive pulmonary disease (COPD), are among the most prevalent chronic respiratory conditions.

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These disease entities have a significant role in the increasing worldwide burden of non-communicable diseases (NCDs) [2]. Chronic respiratory illnesses claimed approximately 4 million lives in 2019, accounting for a whopping 74% of all deaths worldwide.

Asthma, which affected 262 million people in 2019, exemplified the intensity of the condition, accounting for 455,000 deaths. In addition, COPD firmly established itself as the third greatest cause of mortality worldwide in 2019, [2] emerging as the predictor of about 3.23 million fatalities. In India, the prevalence of asthma ranged from 2% to 23%,

demonstrating the widespread nature of these NCDs [3]. The following are common risk factors for chronic respiratory diseases: exposure to outdoor air pollution, exposure to the toxic consequences of biomass fuel use, and smoking, exposing nearly equal numbers of people to the harmful effects of second hand smoke [4]. It is estimated that 4 million premature deaths are attributed to chronic respiratory disorders each year [5]. While occupational respiratory disorders are a well-defined risk factor, their exact magnitude is unknown; based on the scant analyses available, it is estimated that work-related exposures related to respiratory disorders cause about 2 million work-related deaths annually [6].

A common treatment for people with COPD is inhaled corticosteroids (ICS). Their primary effect is to lower the risk of exacerbations; unlike long-acting bronchodilators, their effects on symptoms and lung function are minor and insufficient to be used as a guideline for treatment efficacy. As a result, ICS is used in a "risk-directed" manner, with treatment aimed at individuals who are thought to be at risk of exacerbations due to a history of exacerbations and/or low lung function [7].

The biomarker, eosinophils, which are important participants in the immunological response of the body, have long been studied by concerning a variety of illnesses, including asthma and allergic reactions [8]. Research to date indicates that ICS treatment has a significant impact on eosinophil counts, which is a phenomenon with wider consequences. With time, these effects have prompted a crucial question: may extended use of ICS cause eosinopenia, which is characterized by an absolute eosinophil count (AEC) of less than 100? Because of the urgent need to understand the potential hazards caused by ICS in producing eosinopenia, detailed investigations are imperative.

Surprisingly, whereas ICS has received great attention for their effects on eosinophils, research into eosinopenia caused by ICS is limited. To better comprehend the complex interactions between ICS, eosinophils, and their possible effects on health and disease, more research is needed to fill this intriguing knowledge vacuum. These considerations, which form the basis of our investigation, carefully evaluate the complex consequences between ICS and eosinophils to clarify any potential effects on patient health and clinical judgment.

MATERIALS AND METHODS: The single-centered prospective observational study was conducted in the pulmonology department of Kovai Medical Center and Hospital, a contemporary 850-bed multispecialty hospital in Coimbatore. The approval was given by the ethical committee of the university and was issued on April29, 2023, with approval number EC/AP/1041/04/2023 for this study. With a margin of error of 5% and a 95% confidence interval around the prevalence of COPD, the study population was determined. For each group, a sample size of 49 was established, and used convenience sampling. The study was conducted from April 2023 to October 2023. After being informed about the clinical study, all participating patients gave their informed consent.

This study comprised patients of any gender over the age of 18, prescribed ICS for at least 3 months in the study arm and without ICS in the control arm, with AEC>100 cells at baseline, and willing to participate. This study excluded patients who were treated with systemic steroids for more than 14 days throughout the study period and who were only prescribed short-term therapy that was less than three months.

The patient's data collection form was used to gather the sociodemographic data, and the case reports provided clinical information about the patients. The Inhaled Corticosteroid Questionnaire (ICQ), which has 57 items across 15 domains, was used to evaluate the safety and side effects of the ICS. Response options ranged from 0 (not at all) to 6 (a very great deal), with 1 (a very little), 2 (a little), 3 (a moderate amount), 4 (quite a lot), and 5 (a great deal). To allow domain scores with different item counts to be compared, the 15 domain scores were converted into a score out of 100 ((Raw domain score/ (6 * no. items in the domain)) *100). Average of the 15 domain scores (the sum of the 15 domain scores) determined the overall ICQ score (0–100). The largest side effect is indicated with the highest score. The Morisky Medication-Taking Adherence Scale-MMAS (4-item) was used to evaluate the medication-taking behavior: There are four items in

the MMAS, and the scoring system is "Yes" = 0 and "No" = 1. A range of scores, from 0 to 4, is obtained by adding the components together. Rating: high to low. A high score denotes strong adherence.

Statistical Analysis: The Statistical Package for Social Sciences (SPSS) V 22.0 was used to do the statistical analysis. Percentages are used to show categorical summaries. We used the Wilcoxon Signed Ranks Test to assess changes over time within the same group. To compare several groups, we employed the Mann-Whitney U test. A *p*value of 0.05 or less is regarded as statistically significant.

RESULTS: In this study, 81 patients were included, of whom 69 were continued until the study's completion. Of 69 patients, 42 were in the study arm (With ICS) and 27 were in the control arm (Without ICS). **Table 1** displays the baseline characteristics of the study population. It was found that the study arm's mean age was 55.2 years, while the control arm's mean age was 54.6 years. Males dominated both the study arm and the control arm. Chronic obstructive pulmonary disease (COPD) was the most common diagnosis (37.7%) among the 69 individuals who successfully finished the research. The second most prevalent diagnosis was Bronchial Asthma (30.4%). Pneumonia, Eosinophilia, Chronic Cough, Bronchiectasis, and Obstructive Sleep Apnea were among the other diagnoses. The most often prescribed drug in the control group was Levosalbutamol 50 mcg, while the most often prescribed medication in the study group was Budesonide 200 mcg.

TABLE 1: BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Categories	Control group (n=27)	Study Group (n=42)
Mean age (Years ± SD)	55.26 ± 12.8	54.6 ± 14.7
Gender		
Male (n (%))	18 (66.7)	20(47.6)
Female (n (%))	9(33.3)	22(52.4)
Diagnoses condition		
COPD (n (%))	14(51.9)	12 (28.6)
Bronchial Asthma (n (%))	6(22.2)	15(35.7)
*Others (n (%))	7 (25.9)	15 (35.7)
Drugs prescribed (%)	Formoterol and Glycopyrrolate (3.7%)	Budesonide 200 mcg (66.7%)
	Ipratropium Bromide20 mcg (22.2%)	Budesonide 320 mcg (4.8%)
	Levosalbutamol 50 mcg (48.2%)	Budesonide 400 mcg (2.4%)
	Tiotropium 9 mcg (25.9%)	Fluticasone Propionate 250 mcg (26.1%)

*Other diagnoses included Pneumonia, Eosinophilia, Bronchial Hyperreactivity, Chronic cough, Bronchiectasis, and Obstructive Sleep Apnea.

Table 2 displays the biomarker comparison between the control and study arms. When the initial and follow-up measures in the control arm are compared, it is clear that the WBC and AEC levels have slightly increased from baseline, indicating a noticeable upward trend in biomarkers; nevertheless, statistical significance could not be determined. In the study arm by comparing the baseline and follow-up measures, there has been a little drop in AEC and a slight increase in WBC levels. In terms of statistics, the observed values are not significant.

TABLE 2: COMPARISON OF BIOMARKERS BETWEEN CONTROL AND STUDY ARM

Parameters	Control Arm		Study Arm	
	Baseline	3 Month Follow up	Baseline	3 Month Follow up
AEC (cells/µL)	197.52±97.3	201.70±82.7	193.67±105.8	185.38±69.8
P value	0.285		0.492	
WBC(cells/µL)	8787.1 ± 2836.6	8962.9± 2386.4	8926.5 ± 2273.7	9140.2 ± 1774.5
P value	0.083		0.684	

Table 3 displays the MMAS-4 scores at the 3-month follow-up between the Control and the Study Arm. Notably, we found significant variations in the adherence levels. The Control Group had a balanced distribution of "Good Adherence," with the majority of patients

exhibiting "Moderate Adherence," and no "Poor Adherence." On the other hand, "Moderate Adherence" was considerably more common among the patients in the Study Group, and "Poor Adherence" was visible. Remarkably, the number of patients in both the Control and Study groups who exhibited "Good Adherence" stayed constant. These results imply that there are notable differences in medication adherence between the Control Group and the Study Group, especially when it comes to the use of ICS.

TABLE 3: MMAS-4 SCORE BETWEEN CONTROL AND STUDY ARM

Category	Control Arm		Study Arm	
	Baseline	3 Month Follow up	Baseline	3 Month Follow up
Poor (%)	18.5	0.0	26.2	4.8
Moderate (%)	55.6	51.9	59.5	64.2
Good (%)	25.9	48.1	14.3	31.0
MMAS- 4 score (Mean ± SD)	2.78± 1.1	3.44±0.6	2.31±1.1	3.05±0.9
P value (Baseline)		0.440		
P value (Follow Up)		0.223		

Table 4 displays the ICQ score and safety evaluation of the study and control arm. By using ICQ the potential side effects from both the arm were assessed. The common side effects noted in the study arm were Hoarseness of the voice and a terrible taste in the mouth. Dry eyes were reported in the study arm.

TABLE 4: ICQ SCORE AND SAFETY ASSESSMENT

Category	Control Arm	Study Arm
ICQ score	0.1052±0.105	0.8874±0.806
P value	0.009	
Side Effects		
Mild	100.0%	71.4%
Moderate	0.0	23.8%
Severe	0.0	4.8%

DISCUSSION: This study included 81 patients, 69 of whom completed the study successfully. To compare the effects of ICS on eosinophils, these patients were split into two groups: a study group and a control group. Our study has a background with the worldwide burden of respiratory problems, as indicated by its focus on individuals with chronic respiratory diseases, specifically COPD, bronchial asthma, and other respiratory disorders. For example, the Global Burden of Disease Study highlighted the substantial morbidity and death linked to respiratory disorders, while the Global Asthma Report highlighted the prevalence of asthma globally, impacting millions of people [9, 10]. One of this study's significant findings was the influence of ICE on absolute eosinophil count (AEC) during three months. AEC showed a slight reduction in the study group and a minor increase in the control group. Despite the lack of statistical significance, these alterations suggest that ICS may have some effect on eosinophil levels. Our findings align with previous research [11]. The link between ICS and AEC may not be so obvious. In asthma, eosinophils appear to represent a biomarker of corticosteroid responsiveness. The eosinophil count decreases in response to systemic or inhaled corticosteroids, and this decrease are related to the effectiveness of the corticosteroid treatment. This is not shocking because a decrease in blood eosinophils most likely indicates a reduction in eosinophilic airway irritation. Furthermore, it has been shown that sputum eosinophils in COPD can be considerably suppressed by oral and inhaled corticosteroids [12].

AEC was found to be somewhat decreased in our study because ICS prescriptions decreased the risk of exacerbations. Thus, we hypothesized that the application of ICS may have an impact on AEC, and the alteration of the AEC after ICS treatment could indicate the medication's effectiveness. Our findings are based on the short duration of ICE use. Given these findings, also we must acknowledge that eosinophils are merely one component of a multifaceted immunological and inflammatory response in chronic respiratory illnesses. For a variety of reasons, including some unrelated to ICS therapy, their levels may fluctuate. In respiratory disorders, subpar adherence is frequently observed [13]. It is linked to inadequate management, a higher chance of exacerbations, and a higher need for medical attention, as well as an unwarranted rise in potentially hazardous and/or costly treatments [14]. Our study evaluated Medication adherence in both the control and study

arms. Our investigation's findings demonstrated that the control group's adherence ranged from moderate to good. However, the ICS arm was visible with poor adherence. Our findings are in line with earlier research. Poor adherence with inhaled corticosteroids is a major problem in asthma management. It has been found in 30% to 60% of patients and is associated with poor asthma control and higher mortality [15].

This observation is consistent with broader concerns regarding the problems of assuring patient compliance with treatment regimens. The complicated topic of medication adherence is influenced by several variables, such as side effects, patient education, and the practicality of the recommended course of treatment. Our results highlight the necessity of patient education and counseling to enhance adherence in the ICS group. Since, they were first used to treat asthma thirty years ago, the safety of ICE has been thoroughly studied. Compared to glucocorticoids used orally, ICS has fewer and milder side effects. Nevertheless, given that ICS is likely to be taken for extended periods in newborns, children, and older adults, there are worries regarding the systemic effects of these medications [16]. The Inhaled Corticosteroid Questionnaire (ICQ) was employed in our study to evaluate the adverse consequences of ICS treatment. One frequent side effect that we saw in our research was dysphonia, or "hoarseness of the voice." Our findings are consistent with earlier research. Users of ICS frequently report this symptom, even though it is usually minor and does not provide any long-term hazards. Dysphonia typically lasts for several days to weeks at a period. Depending on the patient demographic, device, dosage, duration of observation, and method of data collection, reported occurrences of dysphonia range from 1 to 60% [18, 19, 20].

Another side effect mentioned was "a terrible taste in the mouth." This may have an impact on the patient's sensory experience, which could make the treatment less bearable and possibly affect adherence. The study arm also reported experiencing "dry eyes" as a potential side effect. This side effect emphasizes the systemic effects of ICS and the need to consider the patient's overall well-being, even though it is not directly related to respiratory symptoms. The long-term use of oral steroids is known to raise the risk of glaucoma, which damages the optic nerve due to elevated intraocular pressure, and cataracts, which cloud the lens of the eye. Inhaled steroids may have the same effect, particularly in elderly persons who are already at high risk of these illnesses [20].

According to a previously published study, inner ocular pressure significantly increased in persons who used inhaled budesonide for at least six months [21]. In a similar vein, it was discovered that those who take large doses for an extended length of time have a higher risk of cataracts than those who take lesser doses [22]. Healthcare professionals can make well-informed decisions about treatment alternatives by having a thorough understanding of side effects and how they affect patients. It also highlights how crucial it is for patients and medical staff to communicate openly to resolve issues and customize treatment programs to meet each patient's needs. Our study's findings show that using ICS for a short period did not significantly lower AEC. These findings underscore the need to take treatment duration into account when evaluating the effects of ICS on eosinophil counts, even though our study did not examine the long-term consequences of ICS use. The study also sheds light on how patients view and feel the adverse effects of ICS and medication adherence. One of the most important components of patient-centered care is being sensitive to side effects. Patients' satisfaction and experience with their care can have a big impact on how well they follow their prescription schedules. Addressing these side effects, even if they are not life-threatening, is critical to ensure that patients can continue with their recommended medical treatments and to expect positive treatment outcomes.

CONCLUSION: Our findings show that short-term ICS treatment did not result in a substantial reduction in AEC. Treatment adherence will be improved through effective patient education, and side effects will be reduced using multifaceted patient-specific approaches by clinicians. The long-term effects of ICS use on eosinophils must be studied using a multi-centered evaluation with a larger sample size to provide clinical direction to healthcare practitioners to optimize ICS use.

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