

Effects of Particle Size of Inhaled Corticosteroid on the Voice

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Summary: Objectives. The purpose of this study was to determine if inhaled corticosteroid (ICS) particle size influences the development of laryngitis including candida laryngitis, dysphonia, or vocalis muscle atrophy in asthmatic patients.

Study Design. Retrospective analysis.

Methods. Medical records of patients from a quaternary care laryngology practice who have asthma were reviewed retrospectively. Subjects were divided into two groups determined by the particle size of their ICS, small or standard. Each patient only used one type of inhaler. All subjects had been seen in the office for dysphonia evaluation. Statistical analysis was performed on the collected data using χ^2 analysis with Yate's Correction for categorical data and a student *t*-test for means. A *P* value of less than 0.05 was considered significant.

Results. There was a significant difference in vocal fold atrophy rate between groups.

Conclusion. Routine use of standard particle size ICS is associated with more atrophy than small size ICS.

Key Words: Inhaler—Asthma—Particle size—Standard—Small—Vocalis muscle atrophy—Complications.

INTRODUCTION

Asthma is a chronic condition of the lung that results in inflammation of the airways, wheezing, chest tightness, shortness of breath, and coughing. The most effective method for reducing asthma symptoms and asthma exacerbation is daily use of inhaled corticosteroids (ICS).¹

Currently available ICS have different particle sizes due to both formulation and propellant. Steroid inhaler types include metered dose inhalers, dry powder inhalers, jet nebulizers, and ultrasonic nebulizers. The pharmacological substance comes in different particle sizes ranging from 1.1 to 4.5 μm . Smaller particles (around 1.2 μm) usually reach distal airways predominately, while larger particles (>4 μm) often are deposited in the upper airways.¹ Dry powder inhalers such as Fluticasone propionate, Budesonide, and Mometasone furoate, usually release larger particles than the pressurized metered dose inhalers.^{2–4} Pressurized meter hydrofluoroalkane (HFA) suspension inhalers, such as Fluticasone propionate, have larger particle sizes than pressurized metered dose HFA solution inhalers, such as Beclomethasone dipropionate, Flunisolide, and Ciclesonide.^{3,5–7}

The purpose of our study was to determine the effects of particle size of inhaled corticosteroids on patient outcomes. The association between particle size and dysphonia is not known, although clinicians generally have accepted the idea that large particle inhalers have greater effect on the larynx than small particles. This study attempts to confirm or refute

that belief in order to provide better guidance to asthmatic patients with voice concern, as well as their pulmonologist.

MATERIALS AND METHODS

The study was approved by the Medical Institutional Review Board at Drexel University College of Medicine in Philadelphia, Pennsylvania. Data on patients with asthma presenting to the office between years 2015 and 2019 were compiled retrospectively based on their use of ICS. Only patients using either small or standard particle size HFA corticosteroid inhaler (ICS) were included in this study. Small corticosteroid particle size was considered less than 2.0 μm (Alvesco, and Qvar) and standard corticosteroid particle size was considered greater than 2.0 μm (Symbicort, and Flovent).^{2,3,7} All included patients were seen in the office for dysphonia and were followed through April, 2019. Patients were excluded if they had not been diagnosed previously with asthma, had known laryngeal disease, had any laryngeal surgery prior to their first visit, or if they were using more than one corticosteroid inhaler (ICS).

Patients who had been using a small particle size corticosteroid inhaler were compared to those using a standard particle corticosteroid inhaler (Table 1).

Forty patients were included in the study. Statistical analysis was performed on the collected data using χ^2 analysis with Yates Correction for categorical data and a Student's *t*-test for means. A *P* value of less than 0.05 was considered significant.

RESULTS

Records from 2015 through April 2019 were reviewed for patients with asthma who used a single corticosteroid HFA inhaler. Forty patients were identified: twenty had been using a small particle size ICS and twenty had been using a standard particle size ICS. There was a female predominance overall (15 females and 5 males in each group). The median ages of the small particle size ICS and standard particle size ICS groups were 44.15 years and 46.0 years, respectively (Table 1). The mean time of use for ICS was 12.5 years in the

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TABLE 1.
Demographics of Patients Showing Small Versus Standard Particle Size ICS Groups. A Student's t test was Performed on Mean and Age. A χ^2 Analysis with Yates Correction was Performed on Gender. A P value of Less than 0.05 was Considered Significant for Both Analyses

	Small Particle (n = 20)	Standard Particle (n = 20)	P value
Female, no.	15	15	1.00
Male, no.	5	5	1.00
Mean age Yr	44.15	46.00	0.7886

small particle group and 13 years in the standard particle group (P value of 0.772). Data analysis of stroboscopic findings (including erythematous and inflammatory changes, Reinke's edema, varices, stiffness, sulci, scar, nodules, cysts, polyps, vocalis atrophy, candida laryngitis, and oral thrush) was performed using Chi Square analysis with Yates's Correction (Tables 2 and 3). Vocalis muscle atrophy was defined as change in the bulk of vocal fold muscle. Stroboscopic findings were reviewed by three independent and blinded observers. The Cohen's Kappa value of reliability between the reviewers was 0.729 and a percent agreement of 94%. The incidence of vocalis atrophy was 5.0% in the small particle size ICS group compared to 30.0% in the standard particle size ICS group. A significant difference (P value of 0.0375) between the two cohorts was found. Analysis of the incidence of other abnormalities (candida laryngitis, oral thrush, structural, erythema, Reinke's edema, varices, stiffness, sulci, scar, cysts, and polyps) revealed no significant differences between groups (Tables 2 and 3).

DISCUSSION

The prolonged use of ICS has been associated with dysphonia secondary to candida laryngitis and to atrophy of the vocalis muscle.^{8,9} Dysphonia caused by contact inflammation from oral corticosteroid inhalers appears to be frequent.¹⁰ A meta-analysis from El Baou et al revealed no clinically significant differences in efficacy or safety of asthmatic treatment comparing small versus standard particle size ICS.¹ However,

TABLE 2.
Complication Rates in Small versus Standard Particle Size Cohorts. A χ^2 Analysis with Yates Correction was Performed for Each Complication. P value of less than 0.05 was considered significant. Only Vocalis Atrophy was Found to be Statistically Significant

	Small Particle	Standard Particle	P value
Vocalis atrophy	1 (5.0%)	6 (30.0%)	0.0375
Candida laryngitis	1 (5.0%)	2 (10.0%)	0.5483
Oral thrush	1 (5.0%)	0 (0.0%)	0.3122
Structural abnormalities	10 (50.0%)	15 (75.0%)	0.1025

TABLE 3.
Stroboscopic Findings in Small versus Standard Particle Size Cohorts. A χ^2 Analysis with Yates Correction was Performed for Each Complication. A P value of Less than 0.05 was Considered Significant. All Six Stroboscopic Findings Except Atrophy Showed no Statistically Significant Difference between Groups

	Small Particle	Standard Particle	P value
Erythema	11 (55.0%)	11 (55.0%)	1.00
Varices	10 (50.0%)	10 (50.0%)	1.00
Stiffness	6 (30.0%)	6 (30.0%)	1.00
Sulci	8 (40.0%)	6 (30.0%)	0.5073
Scar	5 (25.0%)	4 (20.0%)	0.7050
Reinke Edema	7 (35.0%)	11 (55.0%)	0.2036

there have been no studies investigating the adverse voice effects comparing the two particle sizes. This retrospective analysis has demonstrated small particle size ICS (Alvesco and Qvar) to be associated with less vocal fold atrophy compared to standard particle size ICS (Symbicort and Flovent). This is consistent with the evidence that inhaled corticosteroids of larger particle size tend to deposit more in the upper airway including the vocal folds. However, studies of larger groups with longer follow-up durations should be conducted to confirm or refute these results, and to investigate whether other associations (eg, candida laryngitis) might exist.

Increased use of high dosage ICSs has been observed to cause systematic and local side effects, including possible bruising, skin thinning, issues with calcium and phosphate metabolism, adrenocortical suppression, increased risk of osteoporosis, posterior subcapsular cataracts, and glaucoma. Common local side effects among asthmatic patients using inhaled steroids include hoarseness and pharyngeal discomfort.¹¹ While the exact cause of dysphonia and ICS use is not known, possible reasons are mucosal atrophy, negative effects on muscle due to topical steroids, and irritation of the mucosa from particle deposition in the larynx.¹² Furthermore, Mirza et al reported that patients presented with vascular lesions, dilated blood vessels, varices, hemorrhages, and thickness around the vocal folds following inhaler use.¹³

Chmielewska et al stated that small particle size inhalers increase deposition in the lower respiratory tract, resulting in decreased effect on the larynx. Dry powder inhalers have a larger particle size and are activated by inhalation; and, the effect on the larynx is much greater. The use of inhaled corticosteroids leads to dysphonia in 5%–58% of patients.¹²

Ciclesonide is an inhaled corticosteroid with particle sizes that range from 1.2 to 2.1 μ m. This nonhalogenated ICS has been associated with fewer vocal side effects due to its decreased deposition in the larynx.¹² A study conducted by Nave et al provided 18 healthy individuals with ciclesonide and budesonide via metered dose inhalers. Ciclesonide has an inactive delivery mechanism, which is activated in the lungs

by esterases to form des-CIC. Additionally, ciclesonide has low glucocorticoid receptor affinity. The authors found that ciclesonide had a lower frequency of side effects due to the decreased oropharyngeal deposition of des-CIC compared to budesonide.^{14,15}

HFA-134a (1,1,1,2 tetrafluoroethane) provides a smaller particle size of 0.9 μm in a solution. HFA-BDP has the most even and largest lung deposition of 53% when compared to fluticasone propionate (12%–13%) and chlorofluorocarbon beclomethasone (4%). A randomized 12-week study that compared HFA-BDP to CFC-FP found that patients given HFA-BDP significantly improved asthma symptoms. Thongngarm et al observed that HFA-BDP forms an HFA-134a propellant, which increases lung deposition and has increased deposition in smaller airways.¹⁶ In a double-blind parallel study, participants were given either HFC-134a or chlorofluorocarbon propellants. For 14 days, the subjects administered 4 or 8 inhalations four times a day. After 14 days, they were switched to the other medication. No vocal side effects were encountered in the study.¹⁷

One limitation of our study is that although most patients used only one ICS (88%) a few patients have used different ICS over their lifetime (12%). The average use of current regimen in our study was 9.5 years. When these patients with multiple ICS are excluded in the analysis there is no effect on the results. This introduces a small possibility of error in this retrospective study.

Pulmonologists should consider these results especially when they are taking care of professional voice users with asthma, such as public speakers, teachers, singers, actors, clergy, and others.

CONCLUSION

The routine use of standard particle size corticosteroid inhalers in patients with asthma is associated with more vocal fold atrophy than small particle size corticosteroid inhalers. Further studies are needed to confirm these findings and establish causation. However, at present, the use of small particle size ICS appears preferable for patients concerned about possible voice changes with the use of ICS.

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