Original Article / Çalışma - Araştırma

Voice evaluation in asthma patients using inhaled corticosteroids

İnhaler kortikosteroid kullanan astım hastalarında ses değerlendirmesi

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ABSTRACT

Objectives: This study aims to assess voice changes and laryngeal abnormalities in asthmatic patients using inhaled corticosteroids (ICSs).

Patients and Methods: This study included 30 patients (15 females; mean age 21.3±2.6 years; range, 17 to 26 years and 15 males; mean age 20.7±2.3 years; range, 16 to 27 years) with bronchial asthma treated with ICSs between May 2013 and December 2013. A speech sample from each patient was evaluated by two phoniatricians and the degrees of dysphonia were scored. Each patient's voice was acoustically analyzed using the multidimensional voice program software. Videolaryngoscopy was used to detect laryngeal abnormalities including the vocal folds.

Results: A total of 53.3% of ICSs users had dysphonia; most of them had a mild degree dysphonia. Of patients, vocal folds erythema was present in 56.7%, interarytenoid thickening in 56.7%, vocal folds bowing in 5.3% and vocal fold atrophy in 5.5%. A total of 36.7% patients had manifestations of laryngopharyngeal reflux. The presence of vocal fold bowing and atrophy was significantly related to the duration of ICS use (p=0.048). Soft phonation index values were positively associated with the duration of the ICS use (p=0.013).

Conclusion: Inhaled corticosteroids have abnormally adverse effects both on the function and the structure of the vocal folds.

Keywords: Asthma; inhaled steroid; voice disorder.

ÖZ

Amaç: Bu çalışmada inhaler kortikosteroid kullanan astım hastalarında ses değişiklikleri ve larenks anormallikleri değerlendirildi.

Hastalar ve Yöntemler: Bu çalışmaya Mayıs 2013 - Aralık 2013 tarihleri arasında İKS ile tedavi edilen bronşiyal astımlı 30 hasta (15 kadın; ort. yaş 21.3±2.6 yıl; dağılım, 17-26 yıl ve 15 erkek; ort. yaş 20.7±2.3 yıl; dağılım 16-27 yıl) alındı. Her hastanın konuşma örneği iki foniatrist tarafından değerlendirildi ve disfoni dereceleri skorlandı. Her hastanın sesi çok boyutlu ses programı yazılımı ile akustik olarak analiz edildi. Ses telleri dahil larenks anormalliklerini tespit etmek amacıyla videolarengoskopi kullanıldı.

Bulgular: İnhaler kortikosteroid (İKS) kullananların toplam %53.3'ünde disfoni vardı, bunların çoğunda disfoni derecesi hafifti. Hastaların %56.7'sinde ses tellerinde eritem, %56.7'sinde interaritenoid kalınlaşma, %5.3'ünde ses tellerinde sarkma ve %5.5'inde ses tellerinde atrofi vardı. Hastaların toplam 36.7'sinde larengofarengeal reflü bulgusu vardı. Ses tellerinde sarkma ve atrofi, anlamlı olarak İKS kullanım süresi ile ilişkilendirildi (p=0.048). Yumuşak fonasyon indeks değerleri, İKS kullanım süresi ile pozitif olarak ilişkiliydi (p=0.013).

Sonuç: İnhaler kortikosteroidler ses tellerinin hem fonksiyonu hem de yapısı üzerinde anormal advers etkiye sahiptir.

Anahtar Sözcükler: Astım; inhaler steroid; ses patolojisi.

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Asthma is a widely spread highly heterogeneous disorder that affects persons of all ages. It is an obstructive lung disease characterized by variable degrees of dyspnea caused by airway narrowing and hyperresponsiveness.[1] This hyperresponsiveness is accompanied by enhanced sensory irritability of the airways and increased mucous secretions.[2] Corticosteroid aerosols have proven useful in the treatment of bronchial asthma. Inhaled corticosteroids (ICSs) on a daily and regular routine have a very good clinical effect in the treatment of asthma.[3] There are many types of steroid inhalers-- the dry powder inhaler, jet nebulizer and the ultrasonic nebulizer.[4] Dysphonia (change of voice; voice disorder) has a variety of causes that can be divided into three main groups: organic voice disorders including chemical injury of the larynx, non-organic functional voice disorders and minimal associated pathological lesions (MAPLs).[5] Williamson et al.[6] stated that dysphonia and candidiasis are the most frequent adverse effects associated with ICSs. Dysphonia, particularly with high dose treatment, varies in reported cases from 8 to 58%. Other authors[7,8] found that the incidence of dysphonia among ICSs users occurred in up to 55% of their patients.

Many studies on the subject have been conducted by respiratory physicians, sometimes in collaboration with allergologists and immunologists. However, laryngoscopic and vocal findings have not been mentioned in detail. Few studies have directly investigated voice changes with objective voice analysis and videolaryngoscopy.[9-13] This raised the need to study the different laryngeal manifestations and vocal fold changes in patients using ICSs in a detailed way for better understanding of the nature of the disorders and better management of those patients.

The aim of this study is to assess voice changes and laryngeal abnormalities in asthmatic patients using ICSs. This might help us understand the nature of dysphonia among ICSs users for better assessment and management.

PATIENTS AND METHODS

This study was conducted on thirty patients (15 females, mean age 21.3±2.6 years, range 17 to 26 years; and 15 males mean age 20.7±2.3 years, range 16 to 27 years) with bronchial asthma treated with ICSs between May 2013 and December 2013. All patients were diagnosed as having bronchial asthma by their pulmonary physicians. The patients were recruited in the Phoniatric Clinic of the King Fahd Hospital-Jeddah, KSA for evaluation of the larynx. All patients treated with either beclomethasone dipropionate (BDP) aerosol solution with a dose of 2 inhalations (400 mcg) twice daily or budesonide inhaler, 1 to 2 inhalations (200 mcg to 400 mcg) twice daily. Patients who received concomitant systemic steroids were excluded from the study. Patients with a previous history of voice problems or laryngeal surgery were excluded.

The patients were instructed to rinse their mouth with water after using ICSs to decrease the chance of having oral candidiasis. Minimal duration of treatment was four months. The study protocol was approved by the Sohag University Hospital Ethics Committee. Written informed consent was obtained from each patient. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (KFHJ-21/2013) and with the Helsinki Declaration of 1975, as revised in 2008.

Each patient was subjected to a protocol of voice evaluation that included:

A- Elementary diagnostic procedures

A comprehensive history taking and otorhinolaryngological examination. The history included age, gender, duration of ICSs use, presence of vocal problem, time span between onset of ICSs use and the onset of dysphonia, history of cough, laryngopharyngeal reflux disease (LPRD), smoking, and abusive behaviors. Severity of asthma was stratified according to Global Initiative for Asthma criteria.[14] A speech sample including counting and a conversation about the daily activities was recorded and assessed by two phoniatricians. The degree of dysphonia was assessed auditorily using a modified GRABS scale,[5] and scored on a 4-point scale (0= no dysphonia, 1= mild, 2= moderate, 3= severe).

B- Clinical diagnostic aids

Each patient was assessed with videolaryngoscopy (when possible) using a rigid 70˚ Hopkins rod laryngoscope. A minority of patients could not tolerate this procedure and

Table 1. Distribution of patients as regards age, cough, laryngopharyngeal reflux disease, presence of dysphonia and phonasthenic manifestations

	Male			Female			*Total*		
	n	%	Mean±SD	n	%	Mean±SD	n	%	*p*
Age groups	15	50	20.7±2.3	15	50	21.3±2.6	30	100	0.55
Cough	5	33.3		6	40		11	36.7	0.71
Laryngopharyngeal reflux disease	5	33.3		6	40		11	36.7	0.71
Presence of dysphonia	9	60		7	46.7		16	53.3	0.46
Phonasthenia	6	20		8	26.7		14	46.7	0.61

P-value based on chi square test. The significance level is less than 0.05.

were evaluated with transnasal flexible fiberoptic nasolaryngoscopy. The video images were analyzed systematically by two phoniatricians who looked at seven specific areas; vocal fold edema, erythema, bowing, atrophy, irregular edges, interarytenoid thickening and supraglottic hyperfunction. Each of the previous parameters was scored according to a 4-point scale (0=absent; 1=mild; 2=moderate; 3=severe).

C- Additional instrumental measures

Acoustic analysis was done in a sound-treated room. A four-second voice sample of sustained vowel /a/ was recorded directly into the computerized Speech Lab (CSL model 4150; Kay Pentax, Lincoln Park, NJ, USA) software using a 50 Hz sampling rate and 16 bit quantization. The microphone was placed at a distance of 15 cm from the patients' mouth. Participants were asked to phonate at their natural pitch and loudness level after several trials of trainings. This phonation sample was subjected to analysis using Multidimensional voice program software (Kay Elemetrics Corp., Lincoln Park, NJ, USA). For objective acoustic analysis, the following outcome measures were extracted and analyzed; mean fundamental frequency in Hz (F_0), Jitter %, Shimmer %, Noise to Harmonic Ratio (NHR), Soft Phonation Index (SPI), and Phonatory Frequency Range in Semitones (PFR st).

Statistical analysis

Statistical analysis was done using PASW version 17.0 software program (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov was used to test normality of distribution. Relations between continuous variable were explored using Spearman rho correlations, and the correlation between categorical variables was measured using Kendall tau-b test. Chi square test was used for between group comparisons (categorical variables). Mann-Whitney U test and Kruskal-Wallis test were used to compare differences between groups (categorical and continuous variables). One Sample t test was used to test if the results of acoustic parameters were significantly different from the norms in our calibration. The significance level was $p \leq 0.05$.

RESULTS

Sociodemographic data and history

Table 1 shows the distribution of subjects by age group, cough history, regurgitation history, presence of dysphonia, and presence of phonasthenia (globus sensation, throat dryness, and frequent throat clearing). Fifty-three percent of ICSs users had dysphonia--36.7% with mild and 16.7% with moderate as demonstrated in Figure 1-- and 47% showed phonasthenic symptoms. Regurgitation and cough history were present in 36.7% of the cases.

As demonstrated in Figure 2, 46.7% had mild asthma (males=50%, females=50%), 20% had

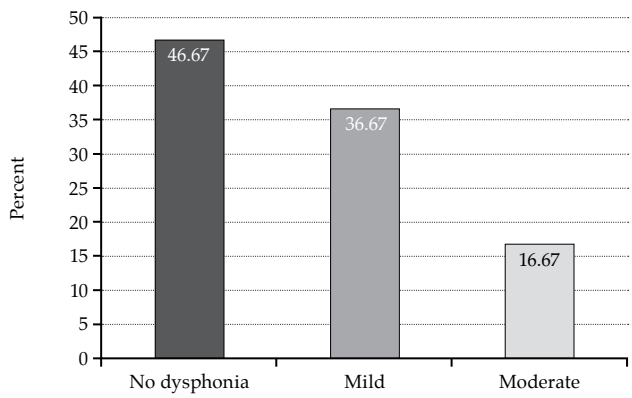

Figure 1. *The distribution of patients according to the degree of dysphonia.*

Table 2. Means and standard deviations of inhaled corticosteroids use duration (in months) and time span between onset of dysphonia and the start of inhaled corticosteroids use (in months)

	Male	Female	
	Mean±SD	Mean±SD	*p*
ICSs use duration	16.4±12.7	24.7±16.9	0.08
Time span	5.6±6.4	4.5±5.7	0.56

SD: Standard deviation; ICSs: Inhaled corticosteroids; P-value based on Mann-Whitney U test. Significant level is <0.05.

moderate asthma (males=33.3%, females=66.7%) and 33.3% had severe asthma (60% males, 40% females).

A Mann-Whitney U test revealed non-significant differences in duration of inhaled steroid use between males (median=8, n=15) and females (median=18, n=15), U=70.5, z= –1.75, p=0.08, r=0.01. Also, there were non-significant differences in time span (the time between the onset of dysphonia and the start of ICSs use) between males (median=5, n=15) and females (median=0, n=15), U=99, z= –0.59, p=0.56, r=0.1 (Table 2).

Kendall tau-b test revealed a positive correlation between ICSs and the presence of dysphonia but it was statistically insignificant (p=0.12, r=0.49). There was moderate degree of significance between ICSs use duration and the dysphonia duration according to Spearman rho correlation test (p=0.41, r=0.02).

Videolaryngoscopy

The video images were analyzed systematically. Seven areas were analyzed;

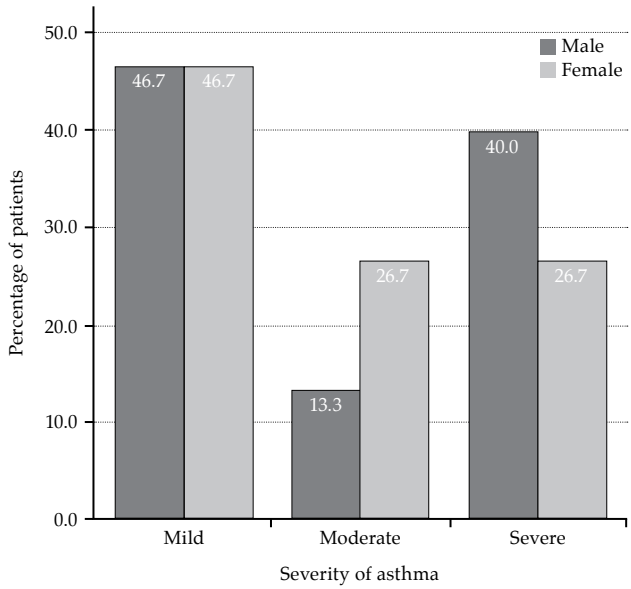

Figure 2. *Distribution of males and females patients stratified by asthma severity.*

vocal fold edema, erythema, supraglottic hyperfunction, vocal fold irregularity, vocal fold bowing, atrophy, and interarytenoid thickening. The most evident laryngoscopic findings in ICS users were interarytenoid thickening (56.7%), vocal fold erythema (56.7%), vocal fold edema (36.7%), supraglottic hyperfunction (53.3%), and irregularity of vocal fold edges (53.3%). Only 5.8% of patients had vocal fold bowing and 3.5% had vocal fold atrophy. The distribution of videolaryngoscopic parameters among asthmatic patients used ICSs is shown in Table 3. The distribution of laryngeal findings according to severity using a 4-point scale (0= no dysphonia,

Table 3. The distribution of videolaryngoscopic findings among inhaled corticosteroids patients

Parameter	Patients with abnormal findings			
	Total	Male	Female	
	%	%	%	*p*
Vocal folds erythema	56.7	23.3	33.3	0.27
Vocal folds edema	36.7	20	16.7	0.71
Vocal folds atrophy	3.5	1.8	1.7	0.76
Vocal folds bowing	5.8	2.8	3.0	0.99
Vocal folds irregularity	53.3	23.3	30	0.46
Supraglottic hyperfunction	53.3	23.3	30	0.46
Interarytenoid thickenings	56.7	26.7	30	0.71

P-value based on Chi square test. The significance level is <0.05.

Table 4. The distribution of laryngeal findings according to severity

	Grade 0 (% of cases)	Grade 1 (% of cases)	Grade 2 (% of cases)	Grade 3 (% of cases)
Erythema	43	16.7	20.3	20
Edema	63	20	7	10
Irregularity of vocal folds	46.7	6.7	16.7	30
Vocal folds bowing	94.7	3.1	2.2	0
Interarytenoid thickening	43.3	16.7	16.7	23.3
Vocal fold atrophy	94.5	3.4	2.1	0
Supraglottic hyperfunction	46.7	13.3	10	30

1= mild, 2= moderate, 3= severe) is shown in Table 4.

A Kendall tau-b test revealed a weak positive significant correlation between ICS duration and presence of vocal fold bowing (r=0.346, n=30, p=0.048).

Acoustic assessments

In the current study normal values on our calibration were used as a reference to reveal the differences between our findings and normal. Jitter % means were significantly higher in men and women compared with normal values (p=0.04, p=0.001). The comparison of shimmer % and NHR mean values between ICSs users and the normal values revealed significant differences in both men and women (for men p=0.003 and p=0.0001) (for women p=0.03 and p=0.004). There was non-significant differences between ICSs users mean values and normal values in males as regard fundamental frequency and soft phonation index (p=0.91, p=0.25). The distributions of acoustic parameters in the study group are shown in Table 5.

When investigating the relationship between ICSs duration and SPI measures using Spearman rho test, there was a moderate positive correlation between the two variables, (r=0.447, n=30, p=0.013). High levels of ICSs durations were associated with high levels of SPI.

DISCUSSION

This study evaluated laryngeal abnormalities, perceptual correlates of dysphonia and acoustic parameters of voice in 30 asthmatic patients using inhaled steroids. Bhalla et al.[15] mentioned the value of inhaled steroids in the management of asthma is unquestioned, but it has long been recognized that their use is associated with oropharyngeal and laryngeal adverse effects.

Also, the impact of ICSs on voice production received considerable research attention. A good number of this research focused on individuals with asthma. The bulk of these studies suggested that ICSs have a negative impact on voice production.[15,16] Other authors[17-19] reported that dysphonia and candidiasis tend to occur with all kinds of ICSs and are probably dose related.

Table 5. Distributions of mean jitter %, shimmer %, noise to harmonic ratio, soft phonation index, phonatory frequency range, and fundamental frequency values among inhaled corticosteroids users

	ICSs users		Normal			
	Means		Means		*p*	
	Male	Female	Male	Female	Male	Female
Jitter %	1.22	1.8	0.69	0.77	0.04	0.001
Shimmer %	4.29	3.64	3.12	2.71	0.003	0.03
Noise to harmonic ratio	1.45	1.04	0.13	0.11	0.0001	0.004
Fundamental frequency	125.87	217.9	126.6	230.7	0.91	0.04
Soft phonation index	7.24	10.5	6.77	8.5	0.25	0.02
Phonatory frequency range	2.98	2.55	2.1	2.37	0.013	0.19

ICSs: Inhaled corticosteroids; The significant level at 0.01 and 0.05 based on one Sample t-test.

However, a study done by Shaw and Edmunds[20] showed no adverse effects of ICSs on voice production. Moreover, Balter and Adams[21] showed an improvement in voice following ICSs. The improvement of voice after short-term use of ICS reported by Barnes[22] stated that the ICS is designed to serve as an anti-inflammatory agent.

The incidence of these local side effects on the larynx and pharynx may vary among different studies. In this study, 53.3% of asthmatic patients used ICS had dysphonia, (36.7% had mild degree and 16.7% had moderate degree). These results are in concordance with the results of Torre and Barlow,[17] who described the presence of dysphonia in 50% and laryngeal abnormalities in 46% of their study population.

In the current study there was a moderate significant relation between the duration of ICSs use and the persistence of dysphonia, as the duration of dysphonia increases by increasing the duration of ICS use. This result is in agreement with those of Ozbilen Acar et al.[23] who studied 12 asthmatic patients and reported dysphonia and laryngeal changes as a result of prolonged use of ICSs.

In this study there was a significant relation between ICS use duration and the duration of dysphonia. This could be explained by the presence of cough and laryngopharyngeal reflux (LPR) in 36.7% of patients. Cough and LPR that are associated with some cases of asthmatic patients play a significant role in voice change due to vocal folds congestion and irritation that may result in mucosal changes. In addition, asthma itself is a factor that affects voice quality as the underlying reduced pulmonary reserve associated with asthma may significantly impact the quality of the voice.

Humbert et al.[24] measured speech segment durations of various lengths in asthmatics compared with healthy controls, and found that the asthmatics had various abnormalities, including increased pause time between the speech segments and fewer syllables per breath. According to Mirza et al.[25] turbulent airflow at the level of the vocal folds may explain the deposition of some inhaler particles on the vocal folds, which in turn leads to mucosal irritation and dysphonia by its chemical effect.

In the current study, we observed laryngeal findings in the larynx of ICSs users ranging from mild to severe. Mild findings include vocal fold erythema, edema and vocal fold atrophy. Severe laryngeal findings include vocal fold irregularity, interarytenoid thickening and supraglottic hyperfunction. Vocal fold bowing was observed in only 5.8% of all cases with a significant positive relation between ICSs use and the degree of vocal fold bowing. The mucosal changes identified as a cause of dysphonia could be due to either a direct ICSs effect on mucosa "an ICSs or propellant effect on the mucous secreting glands" or an ICS or propellant effect on the mucous itself.

Ishizuka et al.[26] performed a simple observational study to evaluate dysphonia in patients with bronchial asthma who were using ICSs. The researchers found that 26% of patients complained of local adverse effects, including throat discomfort, throat irritation, cough and hoarseness. A total of 20% of all patients complained of dysphonia. Moreover, most patients complained of local adverse effects within six months after starting ICSs therapy. Dysphonia was more evident in the high-dose group (20%).

DelGaudio[19] described a condition that is referred to as steroid inhaler laryngitis, a clinical entity that is caused by steroid inhalation and manifested by dysphonia, throat clearing and fullness. The study population consisted of 20 patients with reactive airway disease and dysphonia who were receiving inhaled steroid therapy. The author reported laryngeal findings ranging from mucosal edema, bilateral severe vocal cord and arytenoid hyperemia, thickening, leukoplakia, granulation, and candidiasis. In two cases, the vocal fold changes were severe enough to prompt direct laryngoscopy and biopsy to rule out malignancy. He concluded that steroid inhaler laryngitis is a form of chemical laryngopharyngitis induced by topical steroid administration.

Corticosteroid myopathy is a common complication of prolonged treatment for more than five years with ICSs. Quantitative studies of muscle function in patients on long-term daily steroid therapy frequently show reduction in muscle performance.[27]

In the current study the observed vocal fold bowing could be explained by ICSs induced myopathy or the mucosal atrophy as a result of

chemical injury due to ICSs use. Moreover vocal fold atrophy was related to the duration of ICSs use-- the longer the duration of ICSs use, the more likely the vocal fold bowing.

Krecicki et al.[28] assessed the effect of ICSs on the vocal folds in patients treated for bronchial asthma. Participants consisted of 50 patients who received ICSs for treatment of asthma and a control group of 41 healthy volunteers. All patients were non-smokers and had been receiving ICSs for at least 18 months. The results showed vocal fold atrophy in 20%, atrophy of laryngeal mucosa in 44% and vocal fold bowing in 20%. The authors concluded that the vocal fold pathologies were caused by ICSs.

Babu and Samuel[29] identified vocal fold bowing in five out of 22 studied patients. Their study did not support the postulate that bowing was the result of an ICSs-induced myopathy.

In the current study supraglottic hyperfunction represents 53.3% of patients and may be a musculoskeletal adaptation to laryngeal mucosal changes or due to underlying poor pulmonary reserve. Gallivan et al.[16] examined a total of 38 patients with voice complaints associated with the use of ICSs. Dysphonia was the primary reason reported in these patients. They reported abnormalities included abnormal mucosal wave symmetry/periodicity (60%), phase closure (65%), glottic closure (60%), mucosal wave amplitude/ magnitude (40%), supraglottic hyperactivity (35%) and glottic plane (7%).

Acoustic voice analysis has been proposed as a simple and a non-invasive means of detecting subclinical voice changes. In their study of 40 asthmatic patients to evaluate voice quality, Dogan et al.[30] stated that laryngeal movement disorders may precede organic disorders in the development of dysphonia and such disorders could be detected by acoustic analysis.

The impact of ICS on the larynx was assessed by Dahl[31] using a prospective, cross-sectional blinded study. They recruited 46 volunteers. The researchers concluded that regular ICS users demonstrated significantly more pharyngeal inflammation and throat discomfort than the other two groups. Laryngeal function and vocal performances were also worse in this group than the other two groups and were more likely to have hoarseness, weakness of voice, aphonia and cough.

In the current study most of acoustic parameters (Jitter %, Shimmer %, harmonic to noise ratio, the mean fundamental frequency, soft phonation index and phonatory range) were significantly abnormal when compared to normal values. These results coincide with those reported by Watts et al.[32] who stated that significant changes in vocal fold vibratory behavior were evident during the course of ICSs use. The increase in perturbation values (Jitter %, Shimmer %, harmonic to noise ratio) is attributed to the irritating effects of corticosteroids. Also in the past studies done by Clark et al.[10] and Watkin and Ewanoski[33] reported a rise in fundamental frequency, cycle-to-cycle variation in vocal F_0 (i.e., Jitter) and abnormal amplitude variations in their F_0 (i.e., Shimmer) in association with inhaled steroid use.

In the present study higher soft phonation index was significantly related to ICSs use, indicating that ICSs use may lead to incomplete vocal fold closure. The soft phonation index parameter reflects the approximation of vocal folds. Higher soft phonation index refers to incomplete vocal fold adduction.

Conclusion

- This study showed dysphonia in 53% of patients and abnormal laryngeal findings in the form of interarytenoid thickening, vocal fold irregularity, vocal fold erythema, vocal fold edema and vocal fold bowing.
- Most acoustic parameters of the patient's voice were higher than standard values and inhaled steroids had a non-significant correlation with the presence of dysphonia.
- Changes in vocal folds were independent of ICSs use and might suggest that in addition to steroid use, other factors may have also played a role in the development of dysphonia such as cough, LPRD, and asthma itself.
- The most common side effect of inhaled steroids is dysphonia. This may direct our attention to the importance of introducing vocal hygiene advice for asthmatic patients treated with ICSs.

Declaration of conflicting interests

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