Studying the effect of inhaled corticosteroids on the larynx in bronchial asthma patients using videostroboscopy

Atef AbdAlla Almaraghy[a], Ahmed Seliem[a] and Rana Ahmed Khalifa[b]

Department of [a]Otolaryngology MD of Phoniatrics, Unit of Phoniatrics and [b]Department of Otolaryngology, Faculty of Medicine, Alazhr University, Cairo, Egypt

Correspondence to Rana Ahmed Khalifa, Unit of Phoniatrics, Faculty of Medicine, Alazhr University, Cairo, Egypt
E-mail: ranakl@yahoo.com

Received 25 January 2012
Accepted 19 May 2012

The Egyptian Journal of Otolaryngology
2012, 28:270–274

Introduction
The frequent use of inhaled corticosteroids (ICS), especially at higher doses, has been accompanied by concern about both systemic and local side effects. The systemic complications of ICS have been extensively studied and are well documented in the literature. There are comparatively few studies reporting on the local complications of ICS. Compared with systemic side effects, the local side effects of ICS are considered to constitute infrequent and minor problems. However, although not usually serious, these local side effects are of clinical importance.

Aim of the work
The aim of this study was to demonstrate the effect of ICS on the larynx using videostroboscopy in patients suffering from bronchial asthma in order to avoid these effects on the patients in further protocols of treatment.

Patients and methods
This study was carried out on 50 patients suffering from bronchial asthma. They were divided into two groups. Group A included 25 patients suffering from bronchial asthma treated using ICS (budesonide) for 1 year at a dose of 1600 μg/day. Group B included 25 patients having bronchial asthma and not receiving ICS. Each patient was subjected to the following protocols of assessment: (i) elementary diagnostic procedures such as (a) patient interviews, (b) auditory perceptual assessment, and (c) laryngeal visualization. (ii) Clinical diagnostic aids: laryngovideostroboscopy was carried out using a digitalized stroboscopy system to examine the vocal fold mobility, congestion, hypertrophy, ventricular folds hypertrophy, glottic gap, and glottic closure. The following acoustic parameters were measured: fundamental frequency, jitter (cycle-to-cycle variation in frequency), shimmer (cycle-to-cycle variation in amplitude), and noise-to-harmonic ratio (N/H). (iii) Additional instrumental diagnostic measures: the acoustic signals were recorded from each patient. The results of this study revealed more laryngeal abnormalities in group A than in group B. Dysphonia was found in 76% of the patients in group A, in which voice was perceived as either strained, leaky, or of rough qualities. The following changes in the glottis were observed in some patients: either localized or diffuse congestion of the vocal folds, hypertrophy in the ventricular bands, incomplete glottic closure, and glottic gap. In addition, there were also decreases in glottic wave and amplitude. Acoustic analysis showed significant increase in the jitter and shimmer values.

Keywords:
bronchial asthma, inhaled steroids, larynx, videostroboscopy

Egypt J Otolaryngol 28:270–274

1012-5574

Introduction

Bronchial asthma is a chronic inflammatory disorder of the airway in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. This inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at night and early in the morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment [1].

Treatment of bronchial asthma comprises multiple measures like supplementation with oxygen, bronchodilators, platelet activation factors antagonists, diuretics, antibiotics, antiallergens, and corticosteroids [2].

The frequent use of inhaled corticosteroids (ICS) has been accompanied by both systemic and local side effects. The systemic complications of ICS have been extensively studied and are well documented in the literature. Systemic complications occur because up to 80% of the dose delivered by a conventional metered-dose inhaler is swallowed [3]. Problems include calcium and phosphate metabolism with subsequent risk of osteoporosis; adrenocortical suppression; bruising and skin thinning; posterior subcapsular cataracts; and glaucoma [4]. However, there are comparatively few studies with the sole objective of reporting the local complications of ICS. It is well known that dysphonia and pharyngeal discomfort are common problems in asthmatic patients using inhalers, especially among those using inhaled steroid preparations. Compared with systemic side effects, the local side effects of ICS are considered to constitute infrequent and minor problems. However, although not usually serious, these local side effects are of clinical importance. They may affect compliance with therapy [5].

Local side effects include perioral dermatitis; tongue hypertrophy; oropharyngeal, laryngeal candidiasis; pharyngeal inflammation; and dysphonia without candidiasis, manifested as bowing of the vocal folds on phonation, cough during inhalation, and a sensation of thirst [6]. Some authors have speculated that a 'residue' from the inhaled substance irritates the pharyngolaryngeal mucosa. Indeed, both the propellant and lubricant components of metered-dose inhaler preparations will have a proinflammatory local effect on the larynx [7].

The fact that anti-inflammatory steroid preparation causes inflammation in the upper airway is probably multifactorial, depending on the following factors: the steroid (e.g. preparation, carrier substance, dose of steroid, and regime), the manner in which it is propelled into the airway (i.e. the inhaler device), intrinsic inflammation of the upper airway in asthmatic patients, mechanical irritation because of cough, the existence of a comorbid inflammatory disease such as rhinitis and postnasal catarrh, and/or the presence of associated inflammatory stimuli (e.g. smoking and noxious agents at the workplace) [8].

Voice problems have been reported in 30–50% of patients being treated with inhaled steroids. They can persist in some cases and, if severe, the only remedy would be, in some cases, discontinuation of inhaled steroid therapy [9].

Aim of the work

The aim of this study was to demonstrate the effect of ICS on the larynx using videostroboscopy in patients suffering from bronchial asthma in order to avoid these effects on the patients in further protocols of treatment.

Patients and methods

This study was carried out on 50 patients suffering from bronchial asthma. They were divided into two groups. Group A included 25 patients treated using ICS (budesonide) for 1 year at a dose of 1600 μg/day. Group B included 25 bronchial asthma patients not receiving ICS. They were recruited from the outpatient and inpatient clinics of Chest and Otolaryngology Departments at Al-Hussein University Hospital during the period from May 2006 to May 2008. They included 29 female patients and 21 male patients (Table 1). The patients fulfilled the criteria for diagnoses of the disease. Patients with any associated etiological factor that might affect the vocal folds were excluded from the study.

Table 1 Age and sex distribution in both groups

Parameters	Sex	*N*	Age range	Mean age ± SD
Group A	Female	14	35–54	47.36 ± 7.90
	Male	11	48–60	52.18 ± 4.06
Group B	Female	15	32–60	48.05 ± 7.80
	Male	10	24–64	48.30 ± 10.96

Methods

Each patient was subjected to examination using the voice assessment protocol used in Ain-Shams University Hospitals [10].This protocol includes the following levels.

Elementary diagnostic procedures

(1) *Patient's interview*: included collection of personal data and analysis of the patient's complaint, phonasthenic symptoms, type and dose of inhaled steroid, and duration of treatment.
(2) *Auditory perceptual assessment*: while listening to the patient's voice, auditory perceptual assessment was performed using the modified GRBAS scale [11], and voice was assessed commenting on the following parameters: (a) overall grade of dysphonia (G): normal (0), slight (1), moderate (2), or severe (3). (b) Character (quality) of voice: strained (S), leaky (L), breathy (B), and irregular 'rough' (I); each character is evaluated from 0 (normal) to 3 (severe). (c) Pitch: normal or decreased. (d) Loudness: normal or decreased.
(3) *Laryngeal visualization*: examination of the larynx by indirect laryngoscopy, flexible nasolaryngoscopy (if needed), and rigid laryngoscopy.

Clinical diagnostic aids

Laryngovideostroboscopy was performed using a digitalized stroboscopy system (Model 9100 B; Kay Elemetrics Corp., Lincoln Park, New Jersey, USA) attached to a rigid endoscope 70° (Model 9105; Kay Elemetrics Corp.) and connected to a CCD camera (Model 9111; Panasonic, Yokohama, Japan) for augmentation, documentation, and examination of the following: Vocal fold mobility, congestion, hypertrophy, ventricular folds hypertrophy, glottic gap, and glottic closure.

Stroboscopy was also used, each patient was asked to sustain the vowel /a/ in phonation. The following parameters were observed: glottic closure, glottic wave (normal, decreased, or absent), amplitude (normal, decreased, or absent), and symmetry in phase and amplitude.

Additional instrumental diagnostic measures

The acoustic signals were recorded from each patient when seated on an examination chair in a quiet room. The patient was instructed to clear his/her throat and to produce a sustained vowel /a/ at a comfortable pitch and loudness for 3–4 s. The acoustic signal was recorded using a dynamic microphone (Shure prologue 14 H) that was positioned at a constant mouth-to-microphone distance of 10–15 cm. The mid-2 s vowel segment was selected and analyzed.

This signal was incorporated into the multi-dimensional voice program model 5105 version 3.1.7 (Kay Elemetrics Corp.) to carry out acoustic analysis. The signals were processed at a sampling rate of 44 100 Hz.

The following acoustic parameters were measured: fundamental frequency, jitter (cycle-to-cycle variation in frequency), shimmer (cycle-to-cycle variation in amplitude), and the noise-to-harmonic ratio.

Results

The present work included a total of 50 patients, 21 male patients (42%) and 29 female patients (58%) with a total female-to-male ratio of 1.3 : 1.

Auditory perceptual assessment

As regards the degree of dysphonia, Table 2 shows the number and percent of patients in group A according to the grade of dysphonia they showed.

As regards the character of voice, Table 3 shows the number and percent of patients in group A with strained voice character. Strained voice: there were 14 patients with grade 0 (56%), seven patients with grade 1 (28%), three patients with grade 2 (12%), and one patient with grade 3 (4%).

As regards leaky voice, Table 4 shows that there were 14 patients with grade 0 (56%), seven patients with grade 1 (28%), three patients with grade 2 (12%), and one patient with grade 3 (4%).

As regards breathy voice, Table 5 shows that there were 23 patients (92%) with grade 0, one patient with grade 1 (4%), and one patient with grade (4%).

As regards rough voice, Table 6 shows that there were 15 patients with grade 0 (60%), eight patients with grade 1 (32%), two patients with grade 2 (8%).

As regards pitch, Table 7 shows that pitch was normal in 12 patients (48%) and decreased in 13 patients (52%).

As regards loudness (intensity), Table 8 shows that loudness was normal in 11 patients (44%) and decreased in 14 patients (56%).

Vocal fold examination

Table 9 shows results of vocal fold examination of group A using continuous light.

Laryngovideostroboscopy

Table 10 shows results of the vocal fold examination of group A using stroboscopy.

Acoustic analysis

Comparison between both groups as regards the acoustic parameters: fundamental frequency, jitter, shimmer, and noise-to-harmonic ratio (Table 11).

Table 2 Number and percent of patients in group A with different grades of dysphonia

Auditory perceptual assessment (grade)	*N* (%)
1-grade 0	6 (24)
2-grade 1	6 (24)
3-grade 2	10 (40)
4-grade 3	3 (12)

Table 3 Number and percent of patients in group A with strained voice character

Strained voice (grade)	*N* (%)
1-grade 0	14 (56)
2-grade 1	7 (28)
3-grade 2	3 (12)
4-grade 3	1 (4)

Table 4 Number and percent of patients in group A with leaky voice character

Leaky voice (grade)	*N* (%)
1-grade 0	14 (56)
2-grade 1	7 (28)
3-grade 2	3 (12)
4-grade 3	1 (4)

Table 5 Number and percent of patients in group A with breathy voice character

Breathy voice (grade)	*N* (%)
1-grade 0	23 (92)
2-grade 1	1 (4)
3-grade 2	1 (4)
4-grade 3	0 (0)

Table 6 Number and percent of patients in group A with rough voice character

Rough voice (grade)	*N* (%)
1-grade 0	15 (60)
2-grade 1	8 (32)
3-grade 2	2 (8)
4-grade 3	0 (0)

Table 7 Number and percent of patients in group A with changes in the pitch

	N (%)
Normal pitch	12 (48)
Decreased pitch	13 (52)

Table 8 Number and percent of patients in group A with changes in the loudness

	N (%)
Normal loudness	11 (44)
Decreased loudness	14 (56)

Table 9 Results of vocal fold examination of group A using continuous light

	N (%)
Localized congestion	10 (40)
Diffuse congestion	5 (20)
Vocal-fold hypertrophy	1 (4)
Ventricular-fold hypertrophy	14 (56)

Significant differences were detected on comparing jitter and shimmer in group A with those in group B.

Discussion

The frequent use of ICS, especially at higher doses, has been accompanied by concern about both systemic and local side effects. The systemic complications of ICS have been extensively studied and are well documented in the literature. There are comparatively few studies reporting on the local complications of ICS [3]. Compared with systemic side effects, the local side effects of ICS are considered to constitute infrequent and minor problems. However, although not usually serious, these local side effects are of clinical importance [5].

Results of the current study revealed more laryngeal abnormalities in group A (patients receiving ICS) than in group B (patients not receiving ICS). Group A showed the following changes in the glottis with different frequencies: congestion of the vocal folds either localized or diffuse, ventricular band hypertrophy, incomplete glottic closure, and glottic gap. In addition, there was also a decrease in glottic wave and amplitude. Furthermore, acoustic analysis showed significant increase in the jitter and shimmer.

Dysphonia was found in 19 patients (76%) of group A; six patients (24%) with dysphonia grade 1, 10 patients (40%) with dysphonia grade 2, and three patients (12%) with dysphonia grade 3, in which voice was perceived either as strained, leaky, or of rough qualities.

This is consistent with a study conducted by Lavy *et al.* [12] on 38 patients with bronchial asthma. They found dysphonia in 34 patients (89%). They cited a degree of variability and reversibility of dysphonia in their patients who did not fit well with the long duration of ICS induced myopathy. It has been suggested that the etiology of dysphonia in some cases is due to steroid myopathy affecting the vocal fold muscles. Consequently, there is bilateral adductor vocal fold deformity with bowing of the vocal folds on phonation [5]. This is thought to be an extremely rare condition, but, in the authors' opinion, a closer examination using flexible laryngoscopy and videostroboscopy reveals varying degrees of myopathy in symptomatic patients. This problem can, however, be reversed when therapy with the inhaled steroid is stopped.

Table 10 Results of the vocal fold examination of group A using stroboscopy

	N (%)
Glottic gap	4 (16)
Glottic wave and amplitude	
Decreased on the right and the left vocal fold	8 (32)
Decreased on the right vocal fold	2 (8)
Decreased on the left vocal fold	5 (20)
Asymetry in phase	14 (56)
Asymetry in amplitude	12 (48)

With regard to voice character, in the present study it was mainly strained and leaky in group A patients. Strained voice of grade 1 in seven patients (28%), three patients with grade 2 (12%), and one patient with grade 3 (4%). Leaky voice of grade (1) in seven patients (28%), grade 2 in three patients (12%), and grade 3 in one patient (4%). Breathy voice of grade 1 in one patient (4%) and grade 2 in one patient (4%). Rough of voice grade 1 in eight patients (32%)and grade 2 in two patients (8%).

The patient's attempt to compensate for the small glottic gap by glottic and supraglottic hyperactivity could explain the appearance of the strained quality, which is analogous to compensatory hyperfunctional elements. These led to a tense voice that was perceived as a strained quality. Voice is also perceived as leaky in addition to strained when the strained voice with increased glottic and supraglottic activity is associated with air escape through the glottal gap. Dogan *et al.* [13] detected impaired voice quality in 14 of 80 patients (17.5%), which is lower than that found in this study.

In the present study, patients in group A showed localized congestion in 40%, diffuse congestion in 20%, vocal fold hypertrophy in 4%, ventricular folds hypertrophy in 56%, and glottic gap in 16%.

Hanania *et al.* [14] reported that these findings could be explained by the irritation of the laryngeal mucosa or by deposits from the inhalation of steroids.

As regards stroboscopic examination of group A patients, glottic wave and amplitude were decreased in both vocal folds in 32%, in the right vocal fold in 8%, in the left vocal fold in 20%, were asymmetric in phase in 56%, and were asymmetry in amplitude in 48%. These results were consistent with those of the study conducted by Lavy *et al.* [12], who described abnormalities in 19 of 38 patients (50%) and concluded that high dose and long duration of ICS were associated with an increased incidence of local side effects.

In the current study, the variables of acoustic analysis, that is jitter and shimmer, showed statistical difference. These significantly affected acoustic parameters could be explained by the fact that the oscillating character and mechanical properties of the vibratory edges of the vocal folds are affected by the resultant pathological effects such as irregularities in the free edge of vocal folds and

Table 11 Comparison between both groups as regards the acoustic parameters: fundamental frequency, jitter, shimmer and N/H ratio

Cases	Fundamental frequency	Jitter	Shimmer	N/H
Group A	191.90 ± 75.66	2.68 ± 3.19	0.882 ± 0.884	0.244 ± 0.191
Group B	148.730 ± 47.81	0.605 ± 0.343	0.358 ± 0.177	0.020 ± 0.006
Significant test*	$P \geq 0.05$ Insignificant	$P \leq 0.05$ Significant*	$P \leq 0.05$ Significant*	$P \leq 0.05$ Insignificant

congestion. These structural changes could lead to disruptive mechanical effects, an abnormal vibratory pattern, asymmetry in vocal fold vibration, and tissue properties with a subsequent affection of the acoustic parameters. It was reported by Kotby [11] that any subtle deviation of acoustic parameters may affect the pathological changes in voice.

These results were similar to the findings of Koike *et al.* [15], who showed that voice pathology can cause increased noise components in the voice signal such as fundamental frequency, turbulent noise, and voice breaks.

Roland *et al.* [16], in their study on the impact of ICS on voice, found an increased incidence of frequency and amplitude perturbation values (jitter and shimmer) in patients who received ICS in high doses and for a long duration.

Local adverse effects have been reported with all ICS preparations, including beclomethasone dipropionate, budesonide and triamcinolone acetonide, but no study has been conducted to compare the prevalence of local adverse effects between different steroid preparations.

Hone *et al.* [17] conducted a study on 20 patients with asthma on a high dose (1000 μg/day) of inhaled steroids for 3 months. Even before commencing treatment with the inhaled steroids, more abnormalities of the vocal folds were found in the asthmatic patients compared with the control group. However this tended to improve rather than worsen during treatment with the inhaled steroids. This study is in contrast with the present study, which showed more local side effects in asthmatic patients on a high dose inhaled steroids [16].

However, inhaled steroids are the most effective controller medications currently available for the management of persistent asthma, and potential adverse effects are generally outweighed by the benefits of treatment. As such, adopting methods to reduce inhaled steroid-related oropharyngeal adverse effects (i.e. rinse mouth, gargling with water after use) or the use of inhaled steroids with an improved safety profile should be the primary tool in asthma management to minimize the impact of adverse effects, while providing the patient with the most effective treatment currently available for asthma [18].

Hazards to voice unrecognized by indirect laryngoscopy or fiberoptic laryngoscopy were identified by paying meticulous attention to laryngovideostroboscopic abnormalities.

Recommendations

It is recommended to examine the larynx thoroughly in patients receiving ICS for bronchial asthma, whether or not they have dysphonia in order to detect early affection of the vocal folds. Use of the lowest effective ICS dose possible is recommended. Laryngovideostroboscopy should be documented as a pretherapy baseline and then repeated in each ICS patient who developed dysphonia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Snapper JR. Inflammation and airway functions. The asthma syndrome (ed). Am Rev Respir Dis 1998; 141:531–533.

2 Barnes PJ. Medical progress: chronic obstructive pulmonary disease. N Engl J Med 2000; 343:269–280.

3 Selroos O, Backman R, Forsén KO, Löfroos AB, Niemistö M, Pietinalho A, *et al.* Local side-effects during 4-year treatment with inhaled corticosteroids – a comparison between pressurized metered-dose inhalers and Turbuhaler. Allergy 1994; 49:888–890.

4 Van der Molen T, Willemse BWM, Schokker S, ten Hacken NHT, Postma DS, Juniper EF. Development, validity and responsiveness of the clinical COPD questionnaire. Health Qual Life Outcomes 2003; 1.

5 Dubus JC, Marguet C, Deschildre A, Mely L, Le Roux P, Brouard J, *et al.* Local side-effects of inhaled corticosteroids in asthmatic children: influence of drug, dose, age and device. Allergy 2001; 56:944–948.

6 Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol 2003; 112:S1–S40.

7 John AV, Henry G, Aijaz A. Voice disorders team approach to evaluation and management. J Voice 2003; 16:202–210.

8 Cerasoli FJ. Developing the ideal inhaled corticosteroid. Chest 2006; 130: (1 Suppl): 54S–64S.

9 Crompton G. Asthma: management. In: Seaton A, Seaton D, Leitch AG, editors. *Crofton and Douglas's respiratory diseases*. 5th ed. London: Wiley-Blackwell; 2000. pp. 973–997.

10 Kotby MN. *Evaluating voice therapy: measuring the effectiveness of treatment*. 1st ed. Singular; 1995.

11 Kotby MN. Voice disorders: recent diagnostic advances. Egypt J Otolaryngol 1986; 3:89.

12 Lavy JA, Wood G, Rubin JS, Harries M. Dysphonia associated with inhaled steroids. J Voice 2000; 14:581–588.

13 Dogan M, Eryuksel E, Kocak I, Celikel T, Sehitoglu MA. Subjective and objective evaluation of voice quality in patients with asthma. J Voice 2007; 21:224–230.

14 Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. Am J Med 1995; 98:196–208.

15 Koike Y, Takahashi H, Calcaterra TC. Acoustic measure for detecting laryngeal pathology. Acta Otolaryngol 1999; 84:105–107.

16 Roland NJ, Bhalla RK, Earis J. The local side effects of inhaled corticosteroids: current understanding and review of the literature. Chest 2004; 126:213–219.

17 Hone SW, Donnelly MJ, Robertson J, Coakley R, O'Neill S, Walsh MJ. Dysphonia and inhalation of corticoids: a prospective study. Rev Laryngol Otol Rhinol (Bord) 1996; 117:331–333.

18 Rachelefsky G. Inhaled corticosteroids and the risk of oropharyngeal adverse events: results from a meta-analysis. J Allergy Asthma Immunol 2006; 117:358.