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Structural and vocal effects of combined inhalational therapies in obstructive lung disease: A review

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Abstract

English:

Obstructive lung diseases (OLD), such as chronic obstructive pulmonary disease (COPD) and asthma, rely heavily on combined inhalational medications, including inhaled corticosteroids (ICS) and bronchodilators, for management. While these therapies target airway inflammation and obstruction, their localised effects on the larynx remain insufficiently characterised. This review synthesises evidence on laryngeal consequences, focussing on structural alterations and dysphonia as adverse effects of combined ICS-bronchodilator regimens. We explore histopathological changes, clinical manifestations and the underexplored potential of vocal assessment as a diagnostic and monitoring tool. By integrating pulmonary and otolaryngological perspectives, we highlight gaps in current knowledge and propose directions for future research to optimise patient outcomes in OLD.

Keywords

Dysphonia • Inhalational therapies • Asthma • Budesonide • Quality of life

Efectele structurale și vocale ale terapiilor inhalatorii combinate

Rezumat

Romanian:

Gestionarea bolilor pulmonare obstructive (BPO), precum boala pulmonară obstructivă cronică (BPOC) și astmul, se bazează în mare măsură pe combinații medicamentoase cu administrare inhalatorie. Deși aceste terapii vizează inflamația și obstrucția căilor aeriene, efectele lor localizate asupra laringelui rămân insuficient caracterizate. Această recenzie sintetizează dovezile privind consecințele la nivelul laringelui, concentrându-se pe modificările structurale și disfonia ca efecte adverse ale regimurilor combinate CSI-bronhodilatator. Explorăm modificările histopatologice, manifestările clinice și potențialul încă puțin explorat al evaluării vocale ca instrument de diagnostic și monitorizare. Prin integrarea perspectivelor pneumologice și ORL, evidențiem lacunele din cunoștințele actuale și propunem direcții pentru cercetări viitoare în vederea optimizării rezultatelor la pacienții cu BPO.

Cuvinte-cheie

Disfonie • Terapii inhalatorii • Astm • Budesonid • Calitatea vieții

Introduction

Obstructive lung diseases (OLD), encompassing chronic obstructive pulmonary disease (COPD) and asthma, affect over 500 million people worldwide, imposing a substantial health and economic burden (1, 2). COPD, characterised by chronic bronchitis and emphysema, and asthma, marked by reversible airway obstruction, share an inflammatory

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pathophysiology managed primarily with inhalational therapies (3, 4). Combined regimens, such as inhaled corticosteroids (ICS) with long-acting beta-agonists (LABAs), are standard for reducing exacerbations and improving lung function (5). However, the upper airway, particularly the larynx, is exposed to these medications during inhalation, leading to potential adverse effects (6).

Dysphonia, reported in 5%–58% of ICS users, is a well-documented side effect, yet its mechanisms, prevalence with combined therapies and long-term laryngeal impact are poorly understood (7, 8). Structural changes, including vocal cord atrophy and inflammation, further complicate the clinical picture (9, 10). Despite the larynx's anatomical proximity to the treatment target, vocal assessment remains underutilised in OLD management (11). This review examines the effects of combined inhalational medications on the larynx, emphasising structural changes and advocating for vocal assessment as a critical research and clinical tool.

Pathophysiology of OLD and treatment rationale

Overview of COPD and asthma

COPD is a progressive disease driven by chronic inflammation, oxidative stress and airway remodelling, often linked to smoking and occupational exposures (12, 13). Asthma, conversely, involves allergic inflammation and bronchial hyperresponsiveness, with prevalence rising in urban settings (14, 15). Both conditions impair airflow, necessitating bronchodilators and anti-inflammatory agents (16).

Role of combined inhalational therapies

ICS, such as budesonide and fluticasone, suppress airway inflammation, while LABAs relieve bronchoconstriction (17). Combined therapies enhance efficacy, reducing exacerbation rates in moderate-to-severe OLD (18). However, their delivery via pressurised metered-dose inhalers or dry powder inhalers results in particle deposition in the oropharynx and larynx, influenced by particle size and inhalation technique (19, 20).

Mechanisms of laryngeal involvement

Particle deposition and local effects

Inhalational medications deposit particles in the upper airway, with smaller particles ($<5\ \mu m$) penetrating deeper but still affecting the larynx (19). ICS exert local immunosuppressive effects, increasing susceptibility to infections such as candidiasis, which can extend to the laryngeal mucosa (21, 22). Bronchodilators may enhance irritation by altering airflow dynamics, thereby amplifying the effects of ICS in combined regimens (6).

Histopathological changes

Animal studies demonstrate corticosteroid-induced vocal cord atrophy, oedema and epithelial thinning (23). Chronic ICS use is associated with steroid inhaler laryngitis (SIL), characterised by mucosal inflammation and collagen disruption (24). These changes impair vocal fold vibration, contributing to dysphonia (25).

Structural changes in the larynx

Clinical observations

Videostroboscopy reveals vocal fold erythema, oedema and reduced mucosal wave amplitude in OLD patients using ICS (9). Mirza et al. (6) found bowing of the vocal folds and mucosal irregularities in users of combined Inhaled Corticosteroid and Long-Acting Beta-Agonist (ICS-LABA) therapy, suggesting a synergistic effect. Abumossalam et al. (10) reported vocal cordopathy – inflammation or ulceration – in asthma patients, correlating with ICS duration.

Histopathological evidence

Salturk et al. (23) observed corticosteroid-induced muscle atrophy and collagen disarray in the vocal cords, which become irreversible with prolonged exposure. Secondary infections, such as laryngeal aspergillosis, may lead to granulomatous lesions and scarring, further altering the laryngeal structure (26). These findings underscore the need for longitudinal studies to assess progression.

Infection-related complications

ICS-related immunosuppression predisposes patients to oral and laryngeal candidiasis, with prevalence higher for fluticasone than beclomethasone (21). Saha et al. (26) reported primary laryngeal aspergillosis in an ICS user, highlighting rare but severe structural consequences. These complications exacerbate dysphonia and structural damage (27).

Dysphonia as a clinical manifestation

Prevalence and risk factors

Dysphonia affects up to 58% of ICS users, with higher rates in combined therapy cohorts (6, 7). Williamson et al. (7) noted voice problems and cough in 5%–20% of patients using aerosolised ICS. Risk factors include duration of use, particle size and smoking history, with tobacco exacerbating laryngeal damage in COPD (28, 29).

Acoustic and perceptual changes

Saeed et al. (11) found that 40% of OLD patients exhibited voice disorders, with hoarseness and reduced fundamental

frequency detected via acoustic analysis. Kim et al. (8) reported short-term dysphonia in asthmatics using budesonide, resolving with cessation. Combined therapies may amplify these effects, though data are limited (6).

Impact on quality of life

Dysphonia impairs communication, particularly in voice-dependent professions, reducing quality of life (25). Chang et al. (30) linked chronic cough – an ICS side effect – to vocal strain, compounding laryngeal stress. These findings highlight dysphonia's broader implications in OLD.

Vocal assessment: An emerging tool

Current evidence

Vocal assessment tools, including videostroboscopy, acoustic analysis and patient-reported outcomes (e.g., Voice Handicap Index), detect laryngeal dysfunction in ICS users (9, 19). Almaraghy et al. (9) used videostroboscopy to identify vocal fold changes in asthma patients, advocating its routine use. Vance et al. (19) correlated smaller ICS particle sizes with reduced vocal impact, suggesting a modifiable risk factor.

Gaps in application

Despite its potential, vocal assessment is rarely integrated into management of OLD (11). Santos et al. (28) found tobacco-related dysphonia was worsened by ICS; yet, vocal studies remain scarce. Standardised protocols are lacking, limiting clinical adoption (31).

Proposed framework

We propose a multi-modal vocal assessment framework for OLD patients: (1) videostroboscopy for structural visualisation, (2) acoustic analysis for functional metrics, and (3) patient-reported outcomes for subjective impact. This approach could identify at-risk patients and guide therapeutic adjustments (9, 11).

Clinical implications

Management strategies

Spacer devices and smaller-particle ICS formulations may reduce laryngeal deposition (19). Rinsing the mouth after inhalation helps mitigate the risk of candidiasis(27). For dysphonia, dose reduction or speech therapy may be effective, though evidence is anecdotal (32).

Monitoring and screening

Routine vocal screening could detect early laryngeal changes, particularly in long-term users of combined therapies (31). High-risk groups – smokers, females and lower socioeconomic status patients – may benefit most, given their elevated OLD burden (33, 34).

Future research directions

Longitudinal studies

Long-term studies tracking laryngeal changes with combined therapies are needed, using advanced imaging (e.g., high-resolution Computed Tomography (CT)) and histopathology (23). Comparative trials of ICS versus ICS-LABA regimens could clarify differential effects (6).

Vocal assessment integration

Incorporating vocal assessment into clinical trials could validate its utility as a biomarker of treatment tolerance (11). Gender and comorbidity interactions (e.g., alcohol use, occupational exposures) should be explored (13, 35).

Mechanistic insights

Investigating particle deposition dynamics and the molecular pathways of laryngeal injury could help inform the design of safer inhalers(19). The role of anti-leukotrienes as alternatives to ICS warrants further study (18).

Conclusion

Combined inhalational medications are vital for OLD management but pose significant risks to the larynx, including structural changes and dysphonia. Histopathological and clinical evidence reveal inflammation, atrophy and infection as key mechanisms, exacerbated by combined ICS-bronchodilator use. Vocal assessment emerges as a promising yet underutilised tool to monitor these effects, offering a bridge between pulmonary and otolaryngological care. As OLD prevalence grows, addressing laryngeal consequences through research and clinical innovation will be critical to enhancing patient outcomes and quality of life.

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