Inhaled steroids reduce apnea-hypopnea index in overlap syndrome

Fariba Rezaeetalab[1], Fariborz Rezaeitalab[2], Vahid Dehestani[3]

1. Chronic Obstructive Pulmonary Disease Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

2. The Sleep Laboratory of Ebn-e-Sina Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

3. Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence:
Fariborz Rezaeitalab:
Assistant professor, The Sleep Laboratory of Ebn-e-Sina Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
e-mail: RezaeiTalabF@mums.ac.ir

Abstract

Background: *Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are two of the most common chronic respiratory disorders. Co-existence of both conditions, referred as overlap syndrome (OLS), is associated with substantially high rates of mortality and morbidity. The present study aimed to evaluate the effect of inhaled corticosteroids (ICS) on apnea-hypopnea index (AHI), an indicator for diagnosis and identifying the severity of OSA, in overlap syndrome.*
Methods: *We conducted a clinical trial on 60 patients diagnosed with overlap syndrome by employing overnight polysomnography before and after receiving ICS. T student test and Mann-Whitney test were applied to analyze the gathered data including age, AHI, nocturnal oxygen desaturation index and SaO_2 (saturated arterial oxygen), daytime (pressure of arterial carbon dioxide) $PaCO_2$ level, forced expiratory volume in one second (FEV1), body mass index (BMI), and waist and neck circumferences.*
Results: *By 3-month ICS administration, this study demonstrated significant reduction of mean AHI and nocturnal oxygen desaturation index along with remarkable improvement of FEV1, diurnal $PaCO_2$ level and nocturnal SaO_2 ($P< 0.05$). Meanwhile, BMI and waist and neck circumferences measurement showed no noticeable changes.*
Conclusion: *As we have not found any literature demonstrating, this is the first study which has evaluated the effect of ICS on AHI in overlap syndrome. Because of a remarkable improvement in obstructive sleep apneas, this study suggests that ICS might be beneficial in treatment of overlap syndrome.*
Keywords: *Apnea-hypopnea index, COPD, inhaled corticosteroids, obstructive sleep apnea, overlap syndrome*

Rezumat

Steroizii inhalatori reduc indicele de apnee-hipopnee în sindromul overlap
Introducere: *Sindromul de apnee în somn obstructiv (SASO) și bronhopneumopatia cronică obstructivă (BPOC) sunt două dintre cele mai frecvente boli respiratorii cronice. Coexistența a două condiții, menționate ca sindromul overlap (OLS), este asociată cu rate semnificativ crescute de mortalitate și morbiditate. Acest studiu a avut drept scop evaluarea efectului corticosteroizilor inhalatori (CSI) asupra indexului de apnee-hipopnee (IAH), un indicator pentru diagnosticul și identificarea severității SASO, în sindromul overlap.*
Metodă: *Am realizat un studiu clinic pe 60 de pacienți diagnosticați cu sindrom overlap prin polisomnografie nocturnă înainte și după administrare de CSI. Testele T Student și Mann-Whitney au fost aplicate pentru a analiza datele culese, inclusiv vârsta, IAH, indicele de desaturare nocturnă și SaO_2 (saturația arterială în oxigen), nivelul $PaCO_2$ (presiunea arterială a dioxidului de carbon) diurn, volumul expirator maxim într-o secundă (FEV1), indicele de masă corporală (IMC), talia și circumferința gâtului.*
Rezultate: *După 3 luni de administrare de CSI, acest studiu a demonstrat o reducere semnificativă a IAH mediu și a indicelui de desaturare nocturnă, împreună cu îmbunătățirea remarcabilă a FEV1, a nivelului $PaCO_2$ diurn și SaO_2 nocturnă ($P <0.05$). În același timp, IMC și circumferința taliei și gâtului nu au suferit modificări notabile.*
Concluzie: *După ce am căutat în literatură, acesta este primul studiu care a evaluat efectul CSI asupra IAH în sindromul overlap. Datorită îmbunătățirii remarcabile a apneelor în somn obstructive, acest studiu sugerează că administrarea de CSI ar putea fi benefică în tratamentul sindromului overlap.*
Cuvinte-cheie: *Index Apnee-Hipopnee, BPOC, cortcosteroizi inhalatori, apnee în somn de tip obstructiv, sindrom overlap*

Abbreviations: *AHI = apnea-hypopnea index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPAP = continues positive airway pressure; FEV1 = forced expiratory volume at 1 second; ICS = inhaled corticosteroids; OSA = obstructive sleep apnea; syndrome; OLS = overlap syndrome.*

Introduction

Individuals suffering from chronic obstructive pulmonary disease (COPD) are at high risk of developing sleep disorders, among which obstructive sleep apnea (OSA) is of great importance[1,2]. OSA is a common sleep-related breathing disorder characterized by repeated episodes of partial or complete upper airway collapse during sleep[2,3]. Adverse effects including frequent oxyhemoglobin de-saturation, fluctuations in blood pressure and heart rate, cortical arousals and sleep fragmentation are immediate consequences of OSA[4,5]. The main manifestations are respiratory pauses during sleep followed by loud snoring and daytime sleepiness[1,3]. According to International Classification of Sleep Disorders (ICSD-2) published by the American Academy of Sleep Medicine (AASM), OSA is diagnosed with an apnea-hypopnea index (AHI) > 5 accompanied by symptoms of daytime sleepiness, awakening with a chocking feeling and loud snoring[6]. By employing AHI, which is ascertained by mean number of apnea + hypopnea per hour of sleep, OSA is classified to mild (AHI of 5-15), moderate (16-30) and severe (AHI > 30)[6,7].

The co-existence of COPD and OSA is referred as the overlap syndrome (OLS)[2] and occurs in 1% of adults[8]. The prevalence of OSA is 2-4%[4,9] and of COPD is 6-10%[10]. Furthermore, 10-15% of individuals with COPD concurrently have sleep apnea[11].

There is evidence indicating that OLS sufferers have more severe nocturnal hypoxemia and hypercapnia than patients with either COPD or OSA alone1[1,12,13]. Consequently, more pulmonary hypertension and cardiovascular events are represented in overlap syndrome[5,15]. Moreover, OSA patients may face

Table I Measured variables of the studied patients

Variables	Groups (Mean ± SD)		P value
	Before ICS administration	After ICS administration	
AHI	24.40 ± 19.45	11.02 ± 12.44	0.002
BMI (kg/m^2)	31.45 ± 5.37	32.52 ± 6.42	0.487
Nocturnal SaO_2%	68.9 ± 8.9	88.7 ± 4.9	0.01
ODI	37.6 ± 9.2	22.3 ±5.8	0.012
$PaCO_2$ (mmHg)	65 ± 2.32	48 ± 1.22	0.014
FEV1 (liter)	1.05 ± 0.31	1.35 ± 0.24	0.03
Waist circumference (cm)	109.80 ± 15.56	107.83 ± 12.43	0.371
Neck circumference (cm)	39.63 ± 4.51	40.72 ± 4.79	0.371

AHI: Apnea-hypopnea index, BMI: body mass index, FEV1: forced expiratory volume in one second, ODI: oxygen desaturation index

adverse consequences regarding to poor neurocognitive performance as a result of diurnal drowsiness and fatigue which remarkably impair the quality of life[4,16,17,18]. Therefore, investigation for the evidence of sleep apnea like daytime sleepiness in COPD patients is of great value[1]. Excessive daytime sleepiness can be evaluated by Epworth Sleepiness Scale (ESS), a self report questionnaire consisting of 8 multiple choice questions regarding dozing in different passive situations. The scores above 9 are indicative of daytime sleepiness[7].

Variety of therapeutic approaches has been suggested for COPD and OSA syndrome. It has been demonstrated that continues positive airway pressure (CPAP) has beneficial effects on both OSA syndrome and COPD[19]. However, poor adherence to this mode of treatment and its expense are drawbacks in a considerable number of the patients[7,20]. Weight loss can also improve sleep apnea[21,22]. On the other hand, it has been shown that ICS has therapeutic effects in severe to very severe COPD cases[23]. As we found no literature demonstrating the therapeutic effects of ICS on sleep apneas in OLS, we designed this study to examine the association between ICS administration and AHI in OLS patients.

Materials and Methods

We conducted a clinical trial on 60 patients with overlap syndrome from November 2010 to July 2012. Primarily, 673 COPD patients referred to the Pulmonary Disease Clinic of Emam-Reza Hospital in Mashhad were assessed for evidence of sleep apnea. The diagnosis of COPD was made based on spirometric criteria (forced expiratory volume in second 1 [FEV1] and the ratio of FEV1 to forced vital capacity [FVC] after bronchodilation), employing the guidelines of Global Initiative for Lung Disease GOLD[24]. All the patients with pneumonia, ischemic heart disease, lung cancer, heart failure, diabetes mellitus, systemic hypertension and history of taking sedatives were excluded to avoid the interference of ICS with the underlying diseases. The remainders (651 patients) were assessed for the evidence of sleep apnea. All patients had obstructive pattern in pulmonary function test. Among them, 98 subjects with severe to very severe COPD (group C and D GOLD[24]) who had history of loud snoring and excessive day-time sleepiness (ESS>9) underwent overnight polysomnography employing Somnomedics 2008 system. The diagnosis of OSA was made for 69 patients based on the AASM criteria. These patients became candidates for treatment with ICS (Fluticasone: 1000μg/day) over a course of 3 months. All patients were simultaneously treated by CPAP. During this period, 9 patients with recurrent attacks were excluded to eliminate the probable effect of other inflammatory diseases like pneumonia. Diurnal $PaCO_2$ were measured before and after the trial. At the end of the treatment course, polysomnography was performed again to evaluate the effect of ICS on AHI. Other polysomnographic parameters including oxygen desaturation index (ODI), and nocturnal SaO_2 were assessed as well.

Demographic information including weight, height, body mass index (BMI), neck and waist circumferences were measured for all the participants before and after the study. All of the records were kept confidential. Written informed consents were initially obtained from all patients and the study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Statistical analysis

The collected data was checked for normality by Kolmogorov–Smirnov test (K–S test) and was analyzed employing SPSS 11.5 software. The P-value less than 0.05 was considered significant. Numerical data including age, BMI, AHI, FEV1, ODI, neck and waist circumference are presented as mean ± SD. T-test and Mann-Whitney U test were performed to compare the variables.

Results

In this study, 60 patients (25 female and 35 male) with OLS underwent polysomnography before and after receiving ICS. Based on GOLD criteria for severity of airflow limitation, 37 subjects were at stage 3 (severe COPD) and 23 cases were at stage 4 (very severe COPD). In addition, according to AASM criteria, 17 cases out of 60 had mild OSA, 25 had moderate OSA and the remainders suffered from severe OSA. The mean SD of age and BMI (before treatment) were 60±6.37 years and 31.45±5.37 kg/m^2, respectively. According to our data, which is demonstrated in Table 1, ICS administration reduced mean AHI ±SD remarkably from 24.40±19.45 to 11.02 ±12.44 (P: 0.002) and ODI from 37.6 ± 9.2 to 22.3±5.8 (P: 0.012). In addition, mean SaO_2 + SD raised sig-

nificantly from 68.9±8.9% to 88.7±4.9% (P:0.01). Mean diurnal $PaCO_2$+SD was initially 65+2.32 mmHg and of FEV1 was 1.05+0.31 liter which also both improved noticeably to 48 ± 1.22 mmHg and 1.35±0.24 liter after the studied period (P<0.05). At the same time, mean BMI±SD after treatment was 32.52±6.42 which did not significantly alter compared to the mean BMI before treatment (P:0.487). Moreover, mean neck and waist circumferences did not markedly change before and after the study (P>0.05) (Table 1).

Discussion

There has been a body of evidence indicating the beneficial effect of ICS in COPD patients[19,20]. Although a systematic review of randomized placebo-controlled trials revealed that ICS administration reduced the risk of COPD exacerbation, they did not evaluate the impact of ICS therapy on OSA in overlap syndrome[25]. A meta-analysis of eight clinical trials, which included 3715 subjects, revealed that ICS therapy declined the lower airway obstruction assessed by FEV1. They insisted on a potential role for ICS in modifying the long-term nature of COPD[26]. Our study demonstrated that by 3-month ICS administration the mean AHI was reduced from 24.40 (compatible with moderate OSA) to 11.02 (compatible with mild OSA). There was also remarkable improvement in other polysomnographic parameters including oxygen desaturation index, and nocturnal SaO_2. No meaningful alteration of mean BMI, the factor that may influence the AHI, was shown during the course of study. Along with above findings, an increase of FEV1 was achieved which showed the efficacy of ICS in treatment of COPD component in these patients. Therefore, we concluded that the reduction of the AHI during this period may occur as a result of treatment with ICS. This finding is compatible with a study which demonstrated the association between severity of asthma and developing symptoms of OSA in patients suffering from asthma[27].

ICS administration may help OLS patients who do not adhere to CPAP therapy. In particular, OLS patients with mild to moderate OSA may be treated by ICS solely. Further investigation, are essential in this area.

The probable therapeutic effect of ICS on OSA in overlap syndrome patients can lighten questions about the mechanisms through which ICS reduces AHI. Measuring a variety of inflammatory mediators may be beneficial in understanding the effect of ICS on AHI in overlap syndrome and even in OSA patients without COPD.

Conclusion

This study indicated that administration of ICS in OLS patients significantly declined the AHI. While CPAP is the standard treatment in OSA syndrome, ICS may also be beneficial and hence can be applied by OLS patients, particularly who are not candidate for CPAP therapy. The authors suggest that further research with larger study population and employing placebo-treated controls with longer period study will provide more comprehensive information.

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Conflict of Interest

Authors have no conflict of interest. ■

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