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Positive Pressure Ventilation Treatment Based on Daytime and Night-time Titration in Patients with Obesity Hypoventilation Syndrome: A Randomized Controlled Trial

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Abstract

Objectives The aim of the present study was to investigate the improvements of gas exchange and excessive daytime sleepiness in patients with obesity hypoventilation syndrome (OHS) in daytime and night-time split polysomnography (DSPSG and NSPSG).

Materials and Methods In the present randomized controlled trial, patients with OHS were enrolled in two DSPSG (51 patients) and NSPSG (50 patients) groups in the Bamdad respiratory and sleep research center in Isfahan, Iran. In both groups, the diagnostic polysomnography (PSG) and titration were conducted in one session according to the guidelines of NSPSG. SpO2, PaCO2, and the Epworth Sleepiness Scale (ESS), were measured initially and 12 weeks after treatment. Furthermore, the PSG parameters and the type of treatments for the two groups were recorded and analyzed.

Results A total of 101 OHS patients (age: 62.02 ± 12.4 year old; 61 females [60.4%]) were evaluated. There were no significant differences regarding BMI, gender, and AHI between groups ($p > 0.05$). Primary SpO2, PaCO2, and ESS were not significantly different between the two groups. After 12 weeks of treatment by continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP), there were significant improvement of SpO2, PaCO2, and ESS score ($p < 0.001$). The amount of change of these variables was not different between groups. Among all variables, only the lower SpO2 and higher PaCO2 were associated with response to BiPAP.

Discussion There were no significant differences in the number of changes of SpO2, PaCO2, and ESS by treatment in the DSPSG and NSPSG groups. Therefore, DSPSG may be considered as a valuable alternative method for the diagnosis and titration in OHS patients.

Clinical Trials IRCT20170512033930N2

Keywords
- continuous positive airway pressure
- obesity hypoventilation syndrome
- noninvasive ventilation
- polysomnography
- obesity

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Introduction

Obesity hypoventilation syndrome (OHS) is defined as the presence of obesity (body mass index [BMI] $\geq$ 30 kg/m^2) and daytime hypoventilation (PaCO2 $\geq$ 45 mm Hg) in patients without central, pulmonary, neuromuscular, metabolic, or chest wall disease that explains the hypercapnia.[1,2]

The majority of patients with OHS have signs of obstructive sleep apnea (OSA) including witnessed apneas, snoring, nighttime choking, nonrestorative sleep, fatigue, and excessive daytime sleepiness. In contrast to patients with OSA alone, patients with OHS are often hypoxemic, and can have symptoms of cor pulmonale. Plethoric obese patients with hypoxemia, a decreased airway area, increased neck circumference, a prominent P2 (a loud second heart sound) on cardiac auscultation, and leg edema, as determined by physical examination, are at risk of having OHS. OHS is an examination of exclusion.[3] Other causes of hypoventilation, such as chronic obstructive pulmonary disease (COPD), severe interstitial lung disease, mechanical respiratory limitation, myopathies, neurological diseases, and congenital causes, should be ruled out.[4]

Overnight polysomnography (PSG) or respiratory polygraphy and titration study are necessary to clarify the pattern of sleep-disordered breathing and the optimal treatment. The use of continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) as two therapeutic options in patients with OHS are recognized as safe and effective.[3] CPAP consists of a continuous pre-set pressure during the respiratory cycle to limit obstructive apneas and hypopneas but unlike noninvasive ventilation (NIV), it does not grant additional ventilatory support. Nonetheless, CPAP can allow the unloading of carbon dioxide accumulated during long-lasting total or partial obstructive events during sleep.[5] There is no clear explanation of the superiority of either mode of PAP therapy and, therefore, in practice, it usually depends on various factors including, but not limited to, the predominance of respiratory disturbances during sleep (obstructive events or hypoventilation), adjustment complexity, and cost. Both PAP modalities attempt to correct sleep hypoxemia, obstructive events, and hypercapnia. Despite the chosen modality, PAP titration during sleep is strongly recommended.[6] Polysomnography is expensive and inconvenient, and split-night PSG was presented as an acceptable alternative.

Overnight PSG and titration is an expensive procedure and with few resources in many countries. Also, night shift is laboring for sleep laboratory personnel and stressful for patients with sleep disturbances. A long waiting list for PSG is an obstacle for early initiation of proper treatment. These problems were intensified during the COVID-19 pandemic due to the impairment the activities of sleep laboratories.[7] Furthermore, excessive daytime sleepiness is one of the common symptoms in OHS patients.[5,8] We aimed to evaluate daytime split PSG (DSPSG) and night-time split PSG (NSPSG) regarding the improvement of gas exchange and excessive daytime sleepiness in a group of patients with OHS.

Material and Methods

In the present randomized controlled trial study, data were gathered from a total of 101patients with OHS, who were referred to the Bamdad Respiratory Research Center, which is affiliated to the Isfahan University of Medical Sciences, Isfahan, Iran. The inclusion criteria were a PaCO2 $>$ 45 mm Hg, BMI $\geq$ 30 kg/m^2, and age $>$ 18 year. The exclusion criteria included any evidence of obstructive or restrictive lung disease including in pulmonary function tests or lung imaging, neuromuscular and skeletal disorders, and heart failure (ejection fraction [EF] $<$ 30%). To rule out lung disease, spirometry was performed for patients with suspicious symptoms or signs or history of smoking. To evaluate neuromuscular and skeletal disorders, all patients were examined by a physician. Furthermore, participants underwent a cardiac examination and were referred to a cardiologist if indicated. The arterial partial pressure of carbon dioxide ($PaCO_2$) was measured using blood gas analysis before PSG in awake state. All patients completed the Epworth Sleepiness Scale (ESS) questionnaire. Demographic characteristics such as gender, age, and BMI were recorded. Then, the patients were randomly allocated to NSPSG or DSPSG. Polysomnography in both groups was performed according to standard guidelines.[9] In the DSPSG group, the study was performed after sleep deprivation at the morning. The scoring of PSG was performed by an expert somnologist based on the AASM guideline. The minimum duration of the diagnostic PSG was 2 hours with AHI $\geq$ 20. In the titration part of the PSG, the minimum duration of the study was 3 hours if the selected treatment could eliminate apnea and hypopneas and improves oxygen desaturation.[10–13]

After 12 weeks, patients were re-examined in both groups. The compliance with treatment was assessed using a memory card. Device use for at least 4 hours at night was considered good compliance for treatment.[14] In all patients, the hours of use of the device and PaCO2 and SaO2 were recorded. Patients completed the ESS questionnaire again.

Approval to conduct the study was obtained from the Ethics Committees of the Isfahan University of Medical sciences (Ethical code: IR.MUI.MED.REC.1399.008).

All data were checked by the investigator for consistency and accuracy before data entry for analysis. Statistical analysis was performed using PASW Statistics for Windows, version 18, (SPSS Inc., Chicago, IL). We examined it using tables, graphs, and statistical indicators. First, the distribution status of the variables was investigated using the Kolmogorov-Smirnov test. To compare the mean of quantitative data between the groups, the independent *t*-test with repeated measures analysis of variance (ANOVA) was used. Qualitative variables are reported as frequencies and percentages. Logistic regression was used to assess the risk factors predicting the need for BiPAP and the odds ratio (OR) index was reported. A *p-value* $<$ 0.05 was considered to prove statistical significance.

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Results

A total of 101 patients with OHS (age: 62.0 ± 12.4 year; female: 61[60.4%]; BMI: 36.3 ± 6.0 kg/m^2) were enrolled in two groups: DSPSG and NSPSG. The PaCO2 and SpO_2 of patients were 53.2 ± 5.8 and 85.4 ± 4.9 mm Hg, respectively. There were no statistically significant differences between groups regarding demographic characteristics, comorbidities, and AHI except for age (►**Table 1**). The patients in both groups had good compliance to PAP therapy based on the assessment of the memory cards of the devices (> 4 hours/day). As shown in ►**Table2**, although there are no significant differences between mean values of SpO_2, $PaCO_2$, and ESS before treatment ($p > 0.05$), the changes of three variables after treatment within each group were significant ($p < 0.001$). In other words, in both groups, treatment resulted in an increase of SpO_2, and a decrease of $PaCO_2$ and ESS.

Data analysis for the identification of the associated factors with need for BiPAP showed that only SpO_2 and $PaCO_2$ were the predictive factors. Therefore, the lower SpO_2 and higher $PaCO_2$, were associated with more possibility of need for BiPAP (►**Table3**). As shown in ►**Fig. 1**, patients who needed BiPAP had lower SpO_2 and higher $PaCO_2$ before and after treatment in both groups.

In the DSPSG group, 34 (66.7%) patients responded to BiPAP, and 13 (26%) patients responded to BiPAP in the NSPSG group,

Discussion

The results of the present study showed the significant increase in SpO_2 and the decrease of $PaCO_2$ and ESS score after 12 weeks treatment in both groups. There was no significant difference in the values of the improvement in the mentioned variables in DSPSG and NSPSG groups.

In previous investigations of daytime PSG in comparison with standard night-time PSG, the accuracy and usefulness of daytime PSG for diagnosing OSA were suggested.[15–17]

The similarity and adequacy of titration time in daytime titration studies is consistent with the results of a previous study of daytime CPAP titration in the USA. Based on their results, there was sufficient amount of REM and non-REM sleep in the daytime titration study.[18] Regarding the high ESS score that indicated excessive daytime sleepiness in OHS patients, this result is to be expected. In line with our study, in the evaluation of daytime titration studies in patients with severe OSA in Canada, there was similar improvement of sleepiness as nighttime titration group after three months.[19] Although in that study the follow-up PSG was performed and showed the residual AHI, and the nadir of SpO2 same as nighttime titration group. In another study with 93 patients with severe sleep apnea in Spain, researchers compared daytime manual, automatic, and night-time CPAP titration. They reported similar CPAP compliance and decrement of sleepiness after three months in the three groups.[20] Our results regarding the same effect of treatment on sleepiness in both groups at follow-up was consistent with their results.

One of the studies that is in line with the present study is the investigation of daytime PSG and titration in 90 hospitalized patients with OSA in Saudi Arabia. They concluded that this method is useful as night-time PSG and titration in some groups, including OHS patients.[21]

In addition, the effect of daytime titration in increasing CPAP adherence in patients with OSA has been suggested.[22,23]

Table 1 Baseline demographic and clinical characteristics of patients with obesity hypoventilation syndrome in both groups

Variables	Daytime SPSG group ($n = 50$)	Night-time SPSG group ($n = 51$)	*p-value*
Age; year	64.9 ± 17.13	59.08 ± 12.22	**0.05**
BMI; kg/m^2	36.06 ± 5.99	36.55 ± 6.16	0.68
Gender; female	27(52.90%)	34 (68.0%)	0.15
DM	18 (35.3%)	21 (42.0%)	0.54
HTN	12 (23.5%)	19 (38.0%)	0.11
HFpEF	7 (13.7%)	6 (12.0%)	0.58
IHD	13 (25.5%)	5 (10.0%)	0.04
Opium addiction	9 (17.6%)	6 (12%)	0.42
SpO_2; %	83.90 ± 8.70	86.92 ± 8.62	**0.08**
$PaCO_2$; mmHg	54.21 ± 5.36	52.19 ± 6.22	0.08
ESS	11.41 ± 5.60	12.02 ± 5.57	0.58
AHI	37.14 ± 21.94	42.82 ± 27.19	0.25

Abbreviations: AHI, apnea hypopnea index; DM, diabetes mellitus; ESS, Epworth Sleepiness Scale; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; IHD, ischemic heart disease; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, oxygen saturation measured by pulse oximetry; SPSG, split polysomnography.
Data presented as mean ± SD, and *n (%)*.

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Table 2 Pairwise comparison of SpO2, PCO2, and ESS before and after treatment in two groups of obesity hypoventilation syndrome

Variables	Time	Daytime SPSG ($n = 51$)	Night-time SPSG ($n = 50$)	*p-value*
SPO2; %	Before treatment	83.90 ± 8.70	86.92 ± 8.62	0.08
	After treatment	89.92 ± 3.24	91.60 ± 3.06	0.54
	Change	6.02 ± 2.45	4.68 ± 4.04	0.17
p-value		< 0.001	< 0.001	
PaCO2; mmHg	Before treatment	54.21 ± 5.36	52.19 ± 6.22	0.08
	After treatment	47.95 ± 5.64	46.82 ± 5.54	0.31
	Change	$- 6.26 \pm 6.51$	$- 5.38 \pm 5.49$	0.50
p-value		< 0.001	< 0.001	
ESS	Before treatment	11.41 ± 5.60	12.02 ± 5.57	0.58
	After treatment	6.23 ± 4.31	6.84 ± 4.35	0.48
	Change	$- 5.17 \pm 3.66$	$- 5.18 \pm 4.58$	0.67
p-value		< 0.001	< 0.001	

Abbreviations: ESS, Epworth Sleepiness Scale; SpO_2, oxygen saturation measured by pulse oximetry; SPSG, split polysomnography.

Table 3 Assessment of risk factors associated with need for BiPAP in patients with obesity hypoventilation syndrome

Variables	OR	95%CI	*p-value*
Sex			
Female	Reference		0.89
Male	0.916	0.257–3.269	
Age; years old	1.027	0.979–1.077	0.27
BMI; kg/m^2	1.040	0.953–1.134	0.37
Comorbidities			
DM	0.992	0.095–1.777	0.81
HTN	1.349	0.392–4.642	0.63
CHF	1.766	0.386–8.076	0.46
IHD	1.041	0.262–4.146	0.95
Addiction	3.974	0.859–18.385	0.07
AHI	0.989	0.965–1.013	0.37
PaCO2	1.104	1.025–1.189	0.009
SPO2	0.771	0.681–0.872	0.001
ESS	0.953	0.887–1.024	0.19

Abbreviations: AHI, Apnea Hypopnea Index; BMI, Body Mass Index; CHF, Congestive Heart Failure; CI, Confidence Interval; DM, Diabetes Mellitus; ESS, Epworth Sleepiness Scale; HTN; Hypertension, IHD; Ischemic Heart Disease; OR, Odds Ratio; SpO2, Oxygen Saturation Measured by Pulse Oximetry; PaCO2; Partial Pressure of Arterial Carbon Dioxide.

In contrast with the present study, the titration time was significantly shorter in some studies of afternoon or daytime titration group than night-time titration.[24] However, in those studies, outcomes including the residual AHI and CPAP compliance were similar between the two groups.

The present study is the first to our knowledge to compare DSPSG and NSPSG in a group of OHS patients. All of the studies of daytime titration were conducted in patients with OSA, and in some of them, a proportion of patients had met the criteria of OHS.

The present study had some limitations, including the differences in some variables between the two groups, lack of comparative NSPSG in the DSPSG group for comparison of the selected treatment, and follow-up PSG for the comparison of residual AHI in two groups.

The results of the present study indicate that DSPSG could be considered as an effective and useful alternative method for initiating treatment in patients with OHS. This method decreases the long waiting list of these patients for sleep laboratory especially in situations such as the COVID-19 pandemic.

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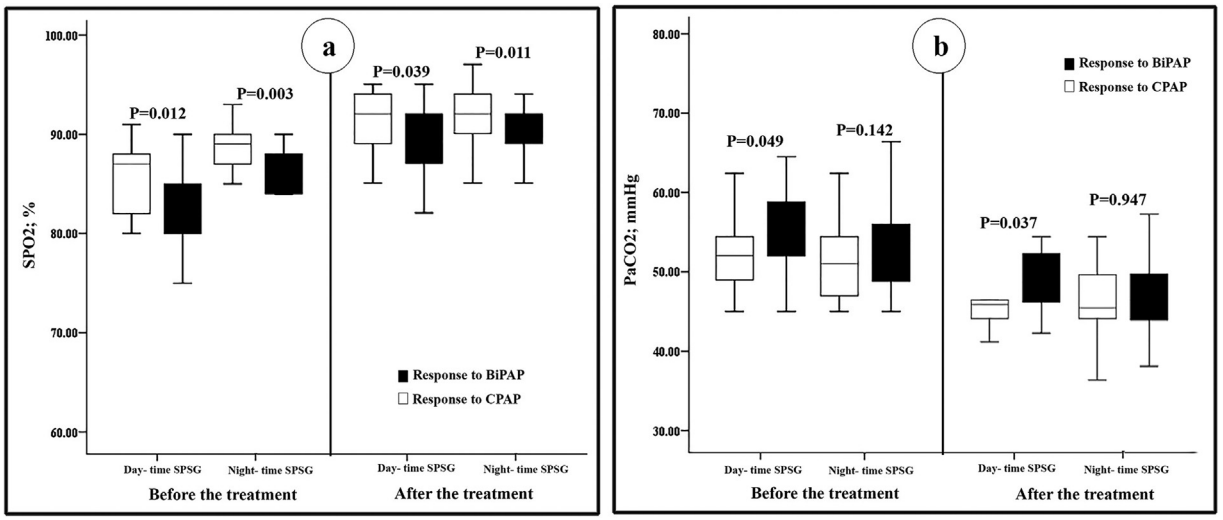

Fig. 1 The association of a) SpO2 and b) PaCO2 with response to BiPAP before and after the treatment. CPAP; Continuous Positive Airway Pressure, BiPAP; Bilevel Positive Airway Pressure.

Ethics Committee Number
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Conflict of Interests
The authors have no conflict of interests to declare.

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