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Research Paper

Effect of Opium Versus Methadone on Polysomnographic Characteristics of Patients With Obesity Hypoventilation Syndrome

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ABSTRACT

Introduction: There are studies about polysomnographic (PSG) characteristics of patients with either obesity hypoventilation syndrome (OHS) or addiction. We aimed to investigate the PSG characteristics of obstructive sleep apnea (OSA) patients with opium addiction, those on methadone maintenance treatment (MMT), and non-addicts for the treatment of addiction.

Methods: In this cross-sectional study, we enrolled 75 patients with OHS in the Bamdad Respiratory and Sleep Research Center affiliated with the Isfahan University of Medical Sciences between January 2020 and February 2021. The patients were categorized into three groups: Opium addicts (OA), MMT, and non-addicts (NA). All patients completed screening questionnaires for OSA. This included the Epworth sleepiness scale (ESS), stop-bang questionnaire, and Berlin questionnaire and the data analyzed by SPSS software, version 24.

Results: A total of 75 OHS patients (54 men [72%] and 21 women [28%]) were studied in three groups, including OA (n=30), MMT (n=15), and NA (n=30). The apnea hypopnea index was not significantly different between the three groups. The longest apnea duration was higher in the OA than in other groups (P=0.001). Central apnea index (P=0.01), longest hypopnea duration (P=0.04), $PaCO_2$ (P=0.04), and time with SpO_2<90% (T_{90}) (P=0.009) were higher in the MMT than in other groups. Furthermore, the minimum SpO_2 was lower in the MMT than in other groups (P=0.03).

Conclusion: Some of the sleep disturbances were worse in the MMT than in the OA group. This suggests the need for further studies to compare the effects of opium and methadone on sleep in OHS patients.

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Highlights

• The severity of obstructive sleep apnea (OSA) in obesity hypoventilation syndrome (OHS) patients on methadone maintenance treatment (MMT) is the same as opium addicts.

• Sleep hypoxia is more severe and prolonged in OHS patients on MMT than opium addicts.

• Sleep hypercapnia is more severe in OHS patients on MMT compared to opium addicts.

Plain Language Summary

In our study conducted in Bamdad Respiratory and Sleep Research Center in Isfahan, we investigated the polysomnographic characteristics of three group of patients with confirmed sleep disordered breathing. These groups included of patients with BMI ≥30, daytime hypercapnia (PCO_2 ≥45) and sleep disordered breathing and opium addiction, treatment with methadone, or none of them. Polysomnography is the standard method for diagnosis of sleep breathing disorders. In this method, several health records including respiration, cardiac, brain and muscle activity are monitored. Methadone has been the approved treatment for opium addiction. The severity of sleep disordered breathing as presented with apnea hypopnea index was not different between groups. However, we found some sleep disturbances including central apnea, duration of sleep with oxygen saturation less than 90%, and the minimum oxygen saturation were worst in under methadone treatment patients. These findings highlight the urgent need for more research on different aspects of methadone treatment.

1. Introduction

Obesity hypoventilation syndrome (OHS) is defined by the triad of obesity (body mass index [BMI] ≥30 kg/m^2), daytime hypoventilation (awake CO_2 ≥45 mm Hg) and sleep-disordered breathing without an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation (Iftikhar & Roland, 2018). The syndrome is often associated with obstructive sleep apnea (OSA), which causes periods of reduced breathing during sleep, resulting in many arousals and awakenings during the night, which results in daytime sleepiness (Kakazu et al., 2020). The treatment of choice for OHS is positive airway pressure therapy in the form of continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV). CPAP consists of one continuous pressure that prevents OSA, but NIV consists of bi-level pressure, including inspiratory and expiratory pressures for additional ventilatory support (Masa et al., 2019).

Methadone, a long-acting μ-opioid agonist, has been recognized as one of the best treatments for opioid addiction. Methadone maintenance treatment (MMT) is a comprehensive treatment program that involves the long-term administration of methadone as a substitute for the opiate, to which the subject has become addicted. (Le et al., 2019). Nowadays, MMT programs are available in both developing and developed countries under the supervision of physicians (Russolillo et al., 2018).

Opium addiction is common in the Iranian population and has been one of the important health issues in recent years. Based on formal reports, 1.8% of the 15–64-year-old population is addicted to opioids in Iran, and some studies have suggested that this value might be as high as 2.8% of the population over the age of 15 years (Aflatoonian et al., 2014; Ekhtiari et al., 2020). On the other hand, methadone usage prevalence is thought to be <0.6% in the Iranian population (Shekarchizadeh et al., 2012).

Methadone and other opioids have various effects on sleep quality and structure in acute and chronic use. Based on previous studies, compared to healthy individuals, these people had more daily drowsiness, and in terms of polysomnographic (PSG) characteristics, these patients had increased waking time and less REM sleep, and in general, sleep disorders, especially central sleep apnea, was more prevalent in these patients (Baldassarri et al., 2020). It has been demonstrated that 75% of patients under treatment with methadone had an apnea-hypopnea index (AHI) above five and there was a correlation between AHI and the daily dose of methadone (McPherson et al., 2019; Finlay et al., 2020) There is a complex bidirectional relationship between sleep and substance abuse (Ara et al., 2016).

So far, various studies have evaluated the prevalence of sleep disorders in patients addicted to opioids or on MMT (Martel et al., 2018, Mubashir et al., 2020). Furthermore, PSG characteristics of OHS patients have been investigated in recent studies. To the best of our knowledge, very few studies have been conducted on this issue and no studies have evaluated the PSG characteristics of these patients in the Iranian population. Considering the prevalence of OHS and also addiction in our region, it is important to study the PSG characteristics of these patients.

2. Materials and Methods

Study design and participants

This is a cross-sectional observational study that was conducted between January 2020 and February 2021 at the Bamdad Respiratory and Sleep Research Center affiliated with the Isfahan University of Medical Sciences. The current study included patients referred to our sleep laboratory with suspected sleep breathing disorders for a PSG investigation.

The inclusion criteria were BMI of more than 30 kg/m^2, daily hypercapnia ($PaCO_2 \geq 45$), confirmed sleep breathing disorder on PSG, and written informed consent to participate in this study. The exclusion criteria were the presence of any known under-treatment neurologic or psychiatric diseases and the consumption of sedative or hypnotic drugs. Inclusion criteria for the OA group were the diagnosis of inhalational opium addiction and for the MMT group, the included patients were on the MMT program for more than three months. Patients were categorized into three groups, including opium addicts (OA), MMT, and non-addicts (NA). The confirmation of addiction was made by an expert psychiatrist.

Data collection

Demographic data of all patients, including age, gender, and past medical histories were collected. All patients completed screening questionnaires for OSA. This included the epworth sleepiness scale (ESS), stop-bang questionnaire, and Berlin questionnaire under the guidance of trained personnel. Standard attended overnight PSG was performed on all patients, and the following variables were monitored: Electroencephalography, electro-oculography, chin and leg electromyography, electrocardiography, oxygen saturation, respiratory effort, oronasal airflow and snoring sounds, and body position (Soltaninejad et al., 2017). Scoring of all PSGs was performed by a certified somnologist according to the American Academy of Sleep Medicine (AASM) scoring manual 2.6 (Jorgensen et al., 2020). The same equipment was used for titration of positive pressure treatment CPAP, bi-level positive airway pressure, and bi-level positive airway pressure with backup rate.

PSG data included AHI, mean SpO_2, minimum SpO_2, central apnea index (CAI), longest apnea, longest hypopnea, and sleep duration with SpO_2 <90%.

Statistical analysis

The statistics analysis was performed using SPSS software, version 24. Non-numerical variables were reported as numbers and percentages and numerical variables as Mean±SD or median and mid-quarter amplitude. Comparison of groups was performed based on quantitative variables using analysis of variance (ANOVA) and quantitative variables were compared using the Kruskal-Wallis-test. Linear and nominal multilevel regression analysis was used to evaluate the effect of treatment in three groups by eliminating the effect of possible confounders. All analyses were performed considering a 5% error level.

3. Results

Demographic characteristics

A total number of 75 OHS patients (54 men [72%] and 21 women [28%]) were enrolled in three groups (OA (30), MMT (15), and NA (30)) based on inclusion and exclusion criteria. The mean age of patients was 55.73±14.47 years and the mean BMI in patients was 37.11±6.73 kg/m^2.

The demographic characteristics of the three groups are shown in Table 1. Among the demographic characteristics, the groups were significantly different only regarding gender (P=0.001). The scores of all OSA screening questionnaires including ESS, stop-bang questionnaire, and Berlin questionnaire were higher in OA patients, although it was non-significant for the Berlin questionnaire (Table 1). Hyperlipidemia was the only comorbidity with significant differences between the groups (P=0.043).

PSG characteristics

The various PSG characteristics of patients in three groups are presented in Table 2. Some variables with significant differences between the groups were CAI, the REM latency, the longest apnea and hypopnea duration,

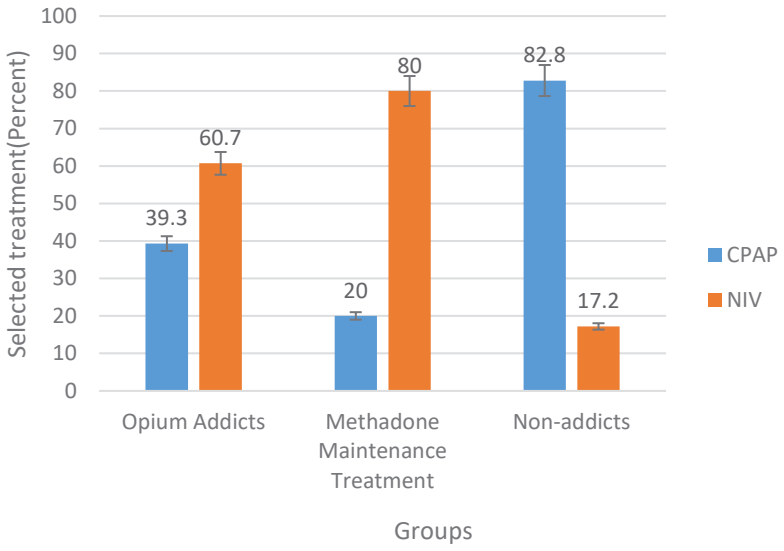

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Figure 1. Treatment modality of OHS patients in the three groups of opium addicts, those on methadone maintenance therapy, and non-addicts

Abbreviation: CPAP: Continuous positive airway pressure; NIV: Non-invasive ventilation.

Note: A treatment modality was selected in a positive airway pressure titration study, the chi-square test was used to compare the differences between groups.

*P=0.001.

T_{90}, and the mean value of $PaCO_2$ ($P<0.05$). In terms of different sleep stages, N1 and N2 sleep stages were significantly different between the groups ($P<0.05$).

Selected treatments

The selected treatment modality based on titration study is illustrated in Figure 1. As shown in Figure 1, the selected treatment modality in the three groups was significantly different (P=0.001).

4. Discussion

To our knowledge, this is the first study on PSG characteristics in patients with OHS and OA or on MMT in the Iranian population. Regarding the relatively high prevalence of all these disorders, simultaneous occurrence of OHS with OA or MMT is possible. Therefore, the evaluation of these patients with intensified problems of ventilation and sleep-disordered breathing is invaluable and useful.

We found significant differences among OHS patients in three groups, including OA, MMT and NA. The OA group had the highest score on the ESS and stop-bang questionnaire compared to other groups. The MMT group had the highest CAI, although the dominant pattern of apnea was obstructive in all groups. The longest apnea was observed in the OA group and the longest hypopnea was observed in the MMT group. Both OA and MMT groups had more sleep time with SpO_2 <90% (T_{90}), lower SpO_2 (lowest SpO_2), and higher CO_2 than the NA group. There were differences in the distribution of N1 and N2 sleep stages, but not in sleep efficiency and N3 and REM stages. Regarding selected treatment, unlike the NA group, which had a higher response rate to CPAP, the OA and MMT groups had a higher response rate to NIV.

The most important finding in our study is more striking and prolonged hypoxia in OHS patients in the OA and MMT groups. The cardiometabolic complications of sleep apnea syndrome are attributed to intermittent hypoxia and secondary activation of inflammatory pathways, the sympathetic system, and oxidative stress (Arnaud et al., 2020; Ryan et al., 2020). Therefore, this group of patients will be at risk for more severe complications and subsequent organ damage. Mediano et al. (2007) reported that OSA patients with higher ESS scores had lower mean and minimum SpO_2 in comparison to OSA patients with lower ESS scores. Similarly, in our study, the OA and MMT groups had higher ESS scores and lower minimum SpO_2 values compared to the NA group,

Table 1. Demographic and clinical characteristics of the three studied groups with obesity hypoventilation syndrome

Variables	Mean±SD/No. (%)			P*
	OA (n=30)	MMT (n=15)	NA (n=30)	
Age (y)	58.22±12.21	57.28±12.92	52.5±16.8	0.28
Male	30(100)	10(66.6)	14(46.6)	0.001
BMI (kg/m^2)	35.9±6.1	37.4±6.5	38.1±7.4	0.44
ESS score	17.75±12.90	12.53±4.37	10.87±5.41	0.01
Stop-bang questionnaire score	6.27±1.20	5.87±1.19	5.07±1.34	0.002
Berlin questionnaire score	7.43±2.47	6.53±2.13	6.53±2.15	0.25
Diabetes mellitus	3(10)	3(20)	8(26.6)	0.25
Hypertension	15(50)	6(40)	12(40)	0.69
Hyperlipidemia	0	3(20)	2(6.6)	0.04
Ischemic heart disease	5(16.6)	3(20)	7(23.3)	0.81
Hypothyroidism	0	0	1(3.3)	0.46

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Abbreviaton: OA: Opium addicts; MMT: Methadone maintenance treatment; NA: Non-addicts; BMI: Body mass index; ESS: Epworth sleepiness scale.

*P<0.05.

but the mean SpO_2 was not different between the three groups (Mediano et al., 2007). This difference can be attributed to the difference between the mean ESS score in the two studies. In our study, the ESS score in the three groups was more than ten, but in the study by Mediano et al. (2007) the ESS score in one group was <10. We found the longest duration for apnea and hypopnea in the OA and MMT groups. This is similar to a previous study by Asadpour et al. who reported prolonged apnea in patients with chronic opium use (Asadpour et al., 2020).

The high prevalence of daytime hypercapnia and chronic respiratory failure in chronic opioid users has been reported previously (Rose et al., 2014). Similarly, in our study, despite the existence of hypercapnia in all patients as a diagnostic criterion of OHS, the mean $PaCO_2$ was higher in the OA and MMT groups than in the NA group. This could be due to the additional respiratory depression effect of these drugs. Hypercapnia has been attributed to adverse consequences of OSA in addition to intermittent hypoxia. Therefore, this finding emphasizes the susceptibility of these groups to more complications.

Similar to our results, in the study by Guilleminault et al. (2010) on a large group of chronic opioid users, OSA was diagnosed, and biphasic positive airway pressure (BiPAP, form of NIV) with backup rate successfully eliminated apnea, desaturation, and related symptoms (Guilleminault et al., 2010). In their study, patients with a BMI of more than 28 kg/m^2 were excluded, but the majority of apnea events in these patients were obstructive. Chronic opioid use is not always associated with CSA. In the mentioned study, the most effective treatment in chronic opioid users was BiPAP with a backup rate, unlike the control group that responded well to CPAP. In our study, the most effective treatment in the majority of cases in the OA and MMT groups was NIV.

Similar to the current study, in the study by Amra et al. opium addiction in OSA patients was associated with lower SpO_2, higher CAI, lower sleep latency, and the same sleep efficiency (Amra, 2015). Unlike our study, opium-addicted patients in that study had higher AHI. The difference could be explained by studied patients, OHS in our study vs OSA in their study.

The typical effect of opioids on sleep architecture included the increase of stage N2, and the decrease of REM and N3 stages has been observed in patients after acute prescription of these drugs and this is not frequently seen in addicted patients (Kay et al., 1979). In our study, the

Table 2. Polysomnographic characteristics of the three studied groups with obesity hypoventilation syndrome

Variables		Mean±SD			P*
		OA (n=30)	MMT (n=15)	NA (n=30)	
AHI		46.9±19.9	39.9±26.6	50.03±26.9	0.43
CAI		3.58±1.2	7.1±3.9	3.4±1.3	0.01
Longest apnea (s)		50.1±4.6	38.6±2.5	27.2±2.7	0.001
Longest hypopnea (s)		64.3±19.5	76.4±15.6	65.8±17.9	0.04
Mean SpO_2 (%)		80.8±16.02	83.4±5.01	86.6±8.3	0.19
Minimum SpO_2 (%)		72.9±11.7	67.08±12.4	76.9±12.9	0.03
T_{90} (%)		71.7±37.7	82.4±23.6	50.4±37.9	0.009
$PaCO_2$		58.8±10.2	59.8±7.08	53.8±8.04	0.04
Sleep efficacy (%)		56.9±18.3	67.5±16.1	62.6±13.7	0.10
Sleep Latency (%)		20.16±11.57	12.47±7.1	23.3±14.6	0.15
REM latency (%)		36±6.1	18.1±3.4	52.9±7.1	0.001
Wake (%)		42.8±17.5	32.5±16.3	38.8±16.2	0.13
Sleep stage (%)	N1	26.1±8.1	20.8±4.5	38.1±8.9	0.01
	N2	22.3±4.9	57.4±8.5	13.9±1.3	0.005
	N3	6.7±1.7	12.2±1.4	8.7±0.9	0.20
	REM	2.3±0.4	1.6±0.3	2.5±0.6	0.87
HR		80.5±15.8	72.4±18.2	78.6±15.1	0.34
PLM index		4.8±0.9	4.8±1.2	3.2±0.6	0.75

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Abbreviation: OA: Opium addicts; MMT: Methadone maintenance treatment; NA: Non-addicts; AHI: Apnea hypopnea index; CAI: Central apnea index; SpO_2: Oxygen saturation measured by pulse oximetry; REM: Rapid eye movement; HR: Heart rate; PLM: Periodic limb movement.

*P<0.05.

duration of N2 was prolonged significantly, but the reduction of N3 and REM stages was not significant in the OA and MMT groups. These differences might be related to a relatively small sample size, especially in the MMT group.

Filiatrault et al. (2016) reported a moderate increase in CAI in chronic opioid users in a systematic review and meta-analysis of seven observational studies. They explained the possible role of confounding factors considering the observational nature of the studies (Filiatrault et al., 2016). In our study, CAI was significantly higher in the MMT group than in other groups. But in the OA group, our finding was different. This finding may be related to the obesity of the studied population. The association between obesity and OSA has been shown in other studies (Jehan et al., 2017). Therefore, this observation in the OA group could be explained.

In another study, the authors evaluated a group of patients under treatment with opioid medications because of pain and reported a higher prevalence of CSA in them compared to the control groups, including subjects with and without pain but without opioid intake (Jungquist et al., 2012). Different results could be explained by the completely different nature of the mentioned study's population. They were prescribed controlled doses of opioids for chronic pain, but our patients were addicted to opium. Additionally, in their study, patients on MMT were excluded. In their study, there was no difference in the minimum SpO_2 between the groups.

The majority of studies on patients with OA or on MMT have assessed sleep apnea syndrome. Studying patients with OHS and OA or those on MMT can be done by the evaluation of sleep characteristics in the presence of two disturbing factors, such as obesity and drugs.

Some limitations in this study should be addressed. The number of patients in all groups, especially in the MMT group was small. The gender distribution of the groups was not similar. The method of categorization was based on the self-report of patients, not laboratory tests. We could not evaluate the exact dose of opium. We did not categorize the patients regarding the dose of opium and methadone. Although all patients in the OA and MMT groups were using the stable dose of these substances, we could not exclude the effect of different doses on the results. We did not consider the duration of opium addiction or methadone treatment beyond three months, which might have affected the final results.

5. Conclusion

Based on the results of this study, AHI was similar among OHS patients in three groups of OA, MMT, and NA. The ESS and STOP-Bang questionnaire scores and the longest apnea duration were higher in the OA group than in the MMT and NA groups. On the other hand, CAI, the longest hypopnea duration, and the minimum SpO_2, T_{90}, and $PaCO_2$ values were higher in the MMT group compared to the OA and NA groups. These results suggest the need for further studies to compare the effects of opium and methadone on sleep in OHS patients.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Isfahan University of Medical Science (Code: IR.MUI.MED.REC.1399.728). Informed consent was obtained from all patients.

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Authors' contributions

Conceptualization, methodology and supervision: Babak Amra; Visualization and validation: Forogh Soltaninejad; Formal analysis: Marjan Mansourian; Software: Mehrzad Salmasi; Data curation and writing the original draft: Hossein Narimani; Review and editing: Forogh Soltaninejad Ingo Fietze: Christoph Schöbel.

Conflict of interest

The authors declared no conflict of interest.

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