Title: Opium Versus Methadone Effects on Polysomnographic Characteristics of Patients With Obesity Hypoventilation Syndrome

Running title: Opium vs. Methadone Effects on OHS

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To appear in: Basic and Clinical Neuroscience

Received date: 2021/12/24
Revised date: 2022/01/27
Accepted date: 2022/02/07
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Please cite this article as:

DOI: http://dx.doi.org/10.32598/bcn.2022.3901.1
Abstract

**Background** 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 OHS patients with opium addiction (OA) and those on methadone maintenance treatment (MMT) for treatment of addiction.

**Methods** In this cross-sectional study, we enrolled 75 patients with OHS in Bamdad Respiratory and Sleep Research Center affiliated to Isfahan University of Medical Sciences between January 2020 and February 2021. The patients were categorized in three groups: OA, MMT, and non-addicts (NA). Demographic and PSG characteristics and obstructive sleep apnea screening questionnaires (Epworth Sleepiness scale, Berlin, and STOP-Bang) of patients were recorded and analyzed by SPSS v.24.

**Results** A total of 75 OHS patients [54 men (72%) and 21 women (28%)] were studied in three groups of OA (30), MMT (15), and NA (30). Apnea hypopnea index (AHI) was not significantly different between three groups. The longest apnea duration was higher in OA than 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$_{SO}$) (P:0.009) were higher in MMT than other groups. Furthermore, the minimum SpO$_2$ was lower in MMT than others (P: 0.03).

**Conclusion** The current study demonstrated that some of the sleep disturbances were worse in MMT than OA group. This suggests the need for further studies to compare the effects of opium and methadone on sleep in OHS patients.

**Keywords:** Polysomnography, Obesity Hypoventilation Syndrome, Opium Dependence, Opiate Substitution Treatment, Surveys and Questionnaires
1. Introduction

Obesity hypoventilation syndrome (OHS) is defined by the triad of obesity (Body Mass Index $\geq 30$ Kg.m$^{-2}$), daytime hypoventilation (awake CO$_2 \geq 45$ mm Hg), and sleep-disordered breathing without an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation. (1) 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. (2) 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 obstructive sleep apnea, but NIV consists of bi-level pressure including inspiratory and expiratory pressures for additional ventilatory support. (3) BiPAP is one of the common forms of NIV.

Methadone, a long-acting $\mu$-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 prescribing of methadone as an alternative to the opioid on which the subject was addicted to opium. (4) Nowadays, MMT programs are available in both developing and developed countries under the supervision of physicians. (5)

Opium addiction is not uncommon in 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 are opioid addicts in Iran, and some studies have suggested that this value might be as high as 2.8% of the population over age 15 years. (6, 7) On the other hand, methadone usage prevalence is thought to be less than 0.6% in Iranian population. (8)

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. (9) It has been demonstrated that 75% of patients under treatment with methadone had AHI above 5 / hour and there was a correlation between AHI and daily dose of methadone. (10, 11) In fact there is a complex bidirectional relationship between sleep and substance abuse. (12)

So far, various studies have evaluated the prevalence of sleep disorders in patients addicted to opioids or on MMT. (13, 14) Furthermore, PSG characteristics of OHS patients have been
investigated in recent studies. Here, we aimed to investigate and compare the PSG characteristics of patients with OHS in three groups of addiction (OA), on MMT and non-addicts (NA). 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 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. Methods and material

2.1. Study design and participants

This is a cross-sectional observational study that was conducted between January 2020 and February 2021 at Bamdad Respiratory and Sleep Research Center affiliated to 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 study protocol was approved by the Research committee of Isfahan University of Medical Sciences. The Ethics committee has confirmed this study (IR.MUI.MED.REC.1399.728). Informed consent was taken from all patients.

The inclusion criteria were body mass index (BMI) more than 30 kg·m⁻², daily hypercapnia (PaCO₂ ≥ 45), confirmed sleep breathing disorder on PSG, and written informed consent to participate in this study. The exclusion criteria were presence of any known under treatment neurologic or psychiatric diseases and consumption of sedative or hypnotics drugs. Inclusion criteria for the OA group were the diagnosis of inhalational opium addiction and for the MMT group, the included patients were on MMT program for more than 3 months. Patients were categorized in three groups including: OA, MMT, and NA. The confirmation of addiction was made by an expert psychiatrist.

2.2. 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, and Berlin questionnaire under guidance of trained personnel. Patients were classified into 3 groups: OA, MMT and NA group. Standard attended overnight PSG was performed on all patients, and following variables were monitored: electroencephalography, electro-oculography, chin and leg electromyography, electrocardiography, oxygen saturation, respiratory effort, oronasal airflow and snoring
sounds, and body position(15). Scoring of all PSGs was performed by a certified somnologist according to the American Academy of Sleep Medicine (AASM) scoring manual 2.6(16). The same equipment was used for titration of positive pressure treatment (Continuous Positive Airway Pressure, Bilevel Positive Airway Pressure, and Bilevel Positive Airway Pressure with backup rate).

PSG data included Apnea Hypopnea Index (AHI), mean SpO\textsubscript{2}, minimum SpO\textsubscript{2}, central apnea index (CAI), longest apnea, longest hypopnea, and sleep duration with SpO\textsubscript{2}<90%.

2.3. Statistical analysis

The statistics analysis was performed using the Statistical Package for Social Sciences (SPSS) version 24. Non-numerical variables were reported as number and percentage and numerical variables as mean and standard deviation (or median and mid-quarter amplitude). Comparison of groups were performed based on quantitative values using analysis of variance and for quantitative variables based on Kruskal-Wallis test. Linear and nominal multilevel regression were used to evaluate the effect of treatment in three groups by eliminating the effect of possible confounders. All analyzes were performed using 5% error level.

3. Results

3.1. 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\textsuperscript{2}.

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

3.2. Polysomnographic characteristics

The various PSG characteristics of patients in three groups are presented in Table 2.
As shown in Table 2, some variables with significant differences between groups are central apnea index, the REM latency, the longest apnea and hypopnea duration, T90, and the mean value of PaCO₂ (P <0.05). In terms of different sleep stages distribution, N1 and N2 were different between groups significantly (P <0.05).

3.3. Selected treatments

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

4. Discussion

To our best knowledge, this is the first study of PSG characteristics in patients with OHS and OA or on MMT in 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.

In this study, we found clear differences between OHS patients in 3 groups of OA, MMT, and NA. The OA group had highest score of ESS and STOP-Bang questionnaires 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 OA and the longest hypopnea in MMT group. Two groups of OA and MMT had more sleep time with SpO₂ <90% (T₉₀), lower SpO₂ (lowest SpO₂) and higher CO₂ compared to NA group. There were differences in the distribution of N1 and N2 sleep stages, but not in sleep efficiency, N3 and REM stages. Regarding selected treatment, unlike the NA group who had higher response rate to CPAP, OA and MMT groups had higher response rate to NIV.

The most important finding in our study is more striking and prolonged hypoxia in OHS patients in OA and MMT groups. The cardiometabolic complications of sleep apnea syndrome was contributed to intermittent hypoxia and secondary activation of inflammatory pathways, sympathetic system, and oxidative stress. Therefore, this group of patients will be at risk for more severe complications and subsequent organ damages. In study of Mediano et al, OSA patients with higher ESS had lower mean and minimum SpO₂ in comparison to OSA patients with lower ESS. Similarly, in our study, the OA and MMT groups had higher ESS score and lower minimum SpO₂ compared to NA group, but the mean SpO₂ was not different.
between three groups. This difference can be attributed to the difference between the mean of the ESS score in two studies. In our study, the ESS score in three groups was more than 10, but in study of Mediano, the ESS in one group was less than 10. We found the longest duration for apnea and hypopnea in OA and MMT groups. This is similar to previous study by Asadpour et al who reported prolonged apnea in patients with chronic opium use.

The high prevalence of daytime hypercapnia and chronic respiratory failure in chronic opioid users have been reported previously. At the same way, in our study, despite the existence of hypercapnia in all patients as a diagnostic criterion of OHS, the mean of PaCO₂ was higher in OA and MMT groups than NA group. This could be due to additional respiratory depression effect of these drugs. Hypercapnia had been attributed to adverse consequences of OSA in addition to intermittent hypoxia. Therefore, this finding emphasizes susceptibility of these groups for more complications.

Similar to our results, in the study of Guilleminault et al. in a large group of chronic opioid users, OSA was diagnosed and BiPAP (form of NIV) with backup rate successfully eliminated apnea, desaturation and related symptoms. In their study, patients with BMI more than 28 were excluded, but the majority of apnea events in these patients were obstructive. Apparently, chronic opioid use is not always associated with CSA. In that study, the most effective treatment in chronic opioid users was BiPAP with back up rate unlike the control group that responded well to CPAP. In our study, the most effective treatment in the majority of OA and MMT groups was NIV.

Same as the current study, in the study of Amra et al, opium addiction in OSA patients was associated with lower SpO₂, higher CAI, lower sleep latency, and the same sleep efficiency. 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 another study.

The typical effect of opioid on sleep architecture included the increase of stage N2 and the decrease of REM and stage N3 has been observed in patients after acute prescription of these drugs and this is not frequently seen in addicted patients. In our study, the duration of N2 was prolonged significantly, but the reduction of N3 and REM stages were not significant in OA and MMT groups. These differences might be related to relatively small sample size especially in MMT group.

Filiatrault et al reported moderate increase in CAI in chronic opioid users in systematic review and meta-analysis of seven observational studies. They explained the possible role of
confounding factors considering the observational nature of the studies. In our study, CAI was significantly higher in MMT group than other groups. But in OA group, our finding was different. This finding may be related to obesity of studied population. The association between obesity and obstructive sleep apnea has been shown in other studies.(26) Therefore, this result in OA group could be explained.

In another study, authors have evaluated the group of patients under treatment with opioid medications because of pain and reported higher prevalence of CSA in them compared to control groups including subjects without pain and with pain but without opioid intake.(27) Different results could be explained by completely different nature of that study population. They have been prescribed controlled dose of opioid for chronic pain, but our patients were addicted to opium. Additionally, in their study patients on MMT were excluded. In their results, there was no difference of the minimum SpO2 between groups.

The majority of studies on patients with OA or on MMT have been performed in sleep apnea syndrome. The study of patients with OHS and OA or on MMT, is the evaluation of sleep characteristics in the present of two disturbing factors; obesity and drugs.

Some limitations in this study need to be addressed. The number of patients in all groups, especially in 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. It is not possible for us to evaluate the exact dose of opium. We did not categorize the patients regarded the dose of opium and methadone. Although all patients in OA and MMT groups were using the stable dose of these substances, but we cannot exclude the effect of different doses on the results. we did not consider the duration of opium addiction or methadone treatment beyond the three months. This factor might have effect on final results.

5.Conclusion

Based on the results of this study, AHI was similar between OHS patients in three groups of OA, MMT, and NA. ESS and STOP-Bang score and the longest apnea duration were higher in OA than MMT and NA group. On the other hand, CAI, the longest hypopnea duration, the minimum SpO2 , T90, PaCO2 were higher in MMT compared to OA and NA group. These results suggest the need for further studies to compare the effects of opium and methadone on sleep in OHS patients.
Conflict of interest

None

References

<table>
<thead>
<tr>
<th>Variables</th>
<th>OA (n=30)</th>
<th>MMT (n=15)</th>
<th>NA (n=30)</th>
<th>P-value</th>
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<tr>
<td>Age (years)</td>
<td>58.22±12.21</td>
<td>57.28±12.92</td>
<td>52.5±16.8</td>
<td>~0.01</td>
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<tr>
<td>Male, n (%)</td>
<td>30 (100%)</td>
<td>10 (66.6%)</td>
<td>14 (46.6%)</td>
<td>0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>35.9±6.1</td>
<td>37.4±6.5</td>
<td>38.1±7.4</td>
<td>~0.44</td>
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<td>ESS</td>
<td>17.75±12.90</td>
<td>12.53±4.37</td>
<td>10.87±5.41</td>
<td>~0.01</td>
</tr>
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<td>STOP-Bang</td>
<td>6.27±1.20</td>
<td>5.87±1.19</td>
<td>5.07±1.34</td>
<td>0.002</td>
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<tr>
<td>Berlin</td>
<td>7.43±2.47</td>
<td>6.53±2.13</td>
<td>6.53±2.15</td>
<td>0.25</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>3 (10%)</td>
<td>3 (20%)</td>
<td>8 (26.6%)</td>
<td>~0.25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (50%)</td>
<td>6 (40%)</td>
<td>12 (40%)</td>
<td>~0.09</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0</td>
<td>3 (20%)</td>
<td>2 (6.6%)</td>
<td>~0.04</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>5 (16.6%)</td>
<td>3 (20%)</td>
<td>7 (23.3%)</td>
<td>~0.81</td>
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<td>Hypothyroidism</td>
<td>0</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>~0.44</td>
</tr>
</tbody>
</table>

Table 1: The demographic and clinical characteristics of three groups of opium addicts, methadone maintenance treatment, and Non-addicts with Obesity Hypoventilation Syndrome

OA: Opium Addicts, MMT: Methadone Maintenance Treatment, NA: Non-addicts, BMI: Body Mass Index, ESS: Epworth Sleepiness Scale. Values are mean± standard deviation, or number of patients (%). p <0.05 indicates the significance value of the test.
Table 2: Polysomnographic characteristics of three groups of opium addicts, methadone maintenance treatment, and Non-addicts with Obesity Hypoventilation Syndrome

<table>
<thead>
<tr>
<th>Variables</th>
<th>OA (n=30)</th>
<th>MMT (n=15)</th>
<th>NA (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (Mean± SD)</td>
<td>46.9±19.9</td>
<td>39.9±26.6</td>
<td>50.0±26.9</td>
<td>0.43</td>
</tr>
<tr>
<td>CAI (Mean± SD)</td>
<td>3.58±1.2</td>
<td>7.1±3.9</td>
<td>3.4±1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Longest apnea(s)</td>
<td>50.1±4.6</td>
<td>38.6±2.5</td>
<td>27.2±2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>longest hypopnea(s)</td>
<td>64.3±19.5</td>
<td>76.4±15.6</td>
<td>65.8±17.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean SpO₂ (%)</td>
<td>80.8±16.02</td>
<td>83.4±5.01</td>
<td>86.6±8.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Minimum SpO₂ (%)</td>
<td>72.9±11.7</td>
<td>67.0±12.4</td>
<td>76.9±12.9</td>
<td>0.03</td>
</tr>
<tr>
<td>T₉₀ (%)</td>
<td>71.7±37.7</td>
<td>82.4±23.6</td>
<td>50.4±37.9</td>
<td>0.04</td>
</tr>
<tr>
<td>PaCO₂ (Mean± SD)</td>
<td>58.8±10.2</td>
<td>59.8±7.08</td>
<td>53.8±8.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Sleep efficacy (%)</td>
<td>56.9±18.3</td>
<td>67.5±16.1</td>
<td>62.6±13.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Sleep Latency (%)</td>
<td>20.16±11.57</td>
<td>12.47±7.1</td>
<td>23.3±14.6</td>
<td>0.15</td>
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<td>REM latency (%)</td>
<td>36±6.1</td>
<td>18.1±3.4</td>
<td>52.9±7.1</td>
<td>0.04</td>
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<tr>
<td>W (%)</td>
<td>42.8±17.5</td>
<td>32.5±16.3</td>
<td>38.8±16.2</td>
<td>0.13</td>
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<tr>
<td>N1 (%)</td>
<td>26.1±8.1</td>
<td>20.8±4.5</td>
<td>38.1±8.9</td>
<td>0.01</td>
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<tr>
<td>N2 (%)</td>
<td>22.3±4.9</td>
<td>57.4±8.5</td>
<td>13.9±1.3</td>
<td>0.005</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>6.7±1.7</td>
<td>12.2±1.4</td>
<td>8.7±0.9</td>
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<tr>
<td>REM (%)</td>
<td>2.3±0.4</td>
<td>1.6±0.3</td>
<td>2.5±0.6</td>
<td>0.87</td>
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<tr>
<td>HR (Mean± SD)</td>
<td>80.5±15.8</td>
<td>72.4±18.2</td>
<td>78.6±15.1</td>
<td>0.34</td>
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<td>PLM index</td>
<td>4.8±0.9</td>
<td>4.8±1.2</td>
<td>3.2±0.6</td>
<td>0.75</td>
</tr>
</tbody>
</table>

OA: Opium Addicts, MMT: Methadone Maintenance Treatment, NA: Non-addicts, AHI: Apnea Hypopnea Index, CAI: Central Apnea Index, SpO₂: Oxygen saturation measured by pulse oximetry, REM: Rapid Eye Movement, HR: Heart Rate, PLM: Periodic Limb Movement, p <0.05 indicates the significance value of the test.
Figure 1: Treatment modality of OHS patients in 3 groups of opium addicts, on methadone maintenance therapy and non-addicts.

Treatment modality was selected in positive airway pressure titration study. CPAP: Continuous Positive Airway Pressure, NIV: Non-invasive Ventilation, Chi-square test was used to compare the frequency between groups, *P:0.001