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Research Article / Araştırma Makalesi

Long-Term Effects of Positive Airway Pressure Treatment on Restless Legs Syndrome Severity in Obstructive Sleep Apnea Syndrome

Obstrüktif Uyku Apne Sendromunda Pozitif Havayolu Basıncı Tedavisinin Huzursuz Bacak Sendromu Şiddeti Üzerindeki Uzun Dönem Etkileri

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Abstract

To research how long-term positive airway pressure (PAP) therapy affects the severity of restless legs syndrome in patients with obstructive sleep apnea syndrome (OSASThe study included 320 individuals that were diagnosed with moderate and severe OSAS using polysomnography (PSG) and under PAP treatment. Among these patients, the demographic data of 72 patients who met the diagnostic criteria of restless legs syndrome (RLS) were analyzed. The patients were evaluated with the International RLS Study Group rating scale (IRLS) before and at the 12th month after PAP in the treatment of OSAS. The mean body mass index of the 72 patients with OSAS and RLS was 31.2 (±5.8), and their mean apnea-hypopnea index was 44.9±27.7. The prevalence of RLS in moderate and severe OSAS was 24%. There was a negative correlation between the IRLS score and mean oxygen saturation all night (r: -0.075), minimum oxygen saturation all night (r: -0.125), time spent below <90% saturation (r: -0.172), and sleep efficiency (r: 0.087) on PSG performed before PAP treatment, as well as a negative correlation between the IRLS score and weekly PAP use hours at the 12th month after PAP treatment (r: -0.316; p<0.001). The data obtained from this study suggest that the coexistence of OSAS and RLS is common and should not be overlooked in the diagnosis of comorbid diseases. Long-term PAP treatment is effective in reducing RLS symptoms. Further studies are needed on this subject.

Keywords: Restless legs syndrome, obstructive sleep apnea syndrome, positive airway pressure treatment.

Özet

Obstrüktif uyku apne sendromunda (OUAS) pozitif hava yolu basıncı (PAP) tedavisinin huzursuz bacak sendromu şiddeti üzerindeki uzun vadeli etkilerini araştırmak. Çalışmaya polisomnografi (PSG) ile orta ve ağır OUAS tanısı konulan ve PAP tedavisi alan 320 kişi dahil edildi. Bu hastalardan huzursuz bacak sendromu (HBS) tanı kriterlerini karşılayan 72 hastanın demografik verileri analiz edildi. OUAS tedavisinde PAP öncesi ve sonrası 12. ayda hastalar Uluslararası HBS Çalışma Grubu Derecelendirme Ölçeği (IRLS) ile değerlendirildi. OUAS ve HBS olan 72 hastanın ortalama vücut kitle indeksi 31,2 (±5,8), ortalama apne-hipopne indeksi 44,9±27,7 idi. Orta ve şiddetli OUAS'ta HBS prevalansı %24 idi. IRLS skoru ile tüm gece ortalama oksijen satürasyonu (r: -0.075), tüm gece minimum oksijen satürasyonu (r: -0.125), <%90 satürasyonun altında geçirilen süre (r: -0.172) ve uyku arasında negatif korelasyon vardı. etkinliği (r: 0,087) ve PAP tedavisi sonrası 12. ayda IRLS skoru ile haftalık PAP kullanım saati arasında negatif korelasyon (r: -0,316; p<0,001) saptandı. Bu çalışmadan elde edilen veriler OUAS ve HBS birlikteliğinin yaygın olduğunu ve yandaş hastalıkların tanısında göz ardı edilmemesi gerektiğini düşündürmektedir. Uzun süreli PAP tedavisi HBS semptomlarını azaltmada etkilidir. Bu konuda ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Huzursuz bacak sendromu, obstrüktif uyku apne sendromu, pozitif hava yolu basıncı tedavisi.,

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1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a disease characterized by recurrent hypoxemia, hypercapnia, and sleep disturbance and occurs due to the partial or the upper airways completely collapsed. In the literature, it has been reported that the prevalence of OSAS in the general population is 13% in men and 6% in women (1,2). As a result of recurrent decreases in oxygen saturation in OSAS, restless legs syndrome (RLS) can be triggered due to central and peripheral hypoxia in addition to neurocognitive, cardiovascular, and metabolic problems with increased sympathetic activity, and it is often observed together with OSAS.

RLS is a chronic movement disorder characterized by unpleasant sensations, such as pain, burning and tingling and usually results in the need to move the legs during rest and at night. RLS is among diseases that impair sleep quality since it can wake individuals up (3). The prevalence of RLS ranges from 9.4 to 15% in the general population, and it is more common in women than in men (4). The disease has two forms: primary and secondary. The primary form can be genetic or idiopathic, while the secondary form can be caused by iron deficiency, Parkinson's disease, pregnancy, renal failure, and certain drugs (antidepressants, antiepileptics, antiemetics, and antipsychotics) (5). The pathophysiology of RLS is considered to related to a decrease in oxygenation secondary to low iron levels, affecting the dopaminergic system and resulting in a hyperadrenergic state (6). In positron emission tomography studies, patients with RLS have been reported to have a decrease in the dopa uptake in the caudate nucleus and putamen. Studies conducted in recent years have shown that dopamine levels decrease when melatonin level peaks in blood at night, suggesting that RLS may be a sensorimotor disorder (7). As a result of recent revisions made to the definitive diagnosis of RLS by the International Restless Legs Syndrome Study Group (IRLSSG), five basic criteria have been identified to question the symptoms of RLS (8) (Table 1). The detection of abnormal leg movements during nighttime on polysomnography (PSG) supports the diagnosis of RLS (9).

Dopamine agonists (pramipexole, ropinirole), levodopa, gabapentin, pregabalin, iron supplements, and opioids can be used in the treatment of RLS. The most frequently preferred drug group in treatment is dopaminergic agents, but they have many side effects, such as nausea, vomiting, anorexia, insomnia, postural hypotension, hallucinations, psychosis, and even increased RLS symptoms when used at high doses (10).

Although positive airway pressure (PAP) is the gold standard treatment in the treatment of moderate-severe OSAS, weight control, avoidance of alcohol and sedatives, intraoral apparatus, and surgical procedures can also be applied (11) In the current study, we aimed to determine the one-year follow-up outcomes of PAP treatment, which increases peripheral and central oxygenation, on RLS symptoms in patients with OSAS and concomitant RLS.

2. Materials and Methods

This prospective study was conducted between June 2021 and June 2022. The volunteers participating in the study were informed by the researchers about the aim and procedures of the study, and their written and verbal informed consent was obtained. The study was approved by the ethics committee of Adana Cıty Training and Research Hospital (1429/2021) and complied with the principles of the Declaration of Helsinki.

Patients aged under 18 years, pregnant and breastfeeding women, patients receiving medical treatment for RLS (such as dopamine, pregabalin, and gabapentin), and those with inflammatory diseases, malignancy, or low blood hemoglobin, iron, and transferrin levels were excluded from the study. Patients who presented to the sleep outpatient clinic with complaints of snoring, witnessed apnea, and excessive daytime sleepiness were evaluated with the Epworth Sleepiness Scale (ESS) and routine blood tests. There were six electroencephalogram (EEG) channels: submental electromyogram, electrooculogram, electrocardiogram, and cardiorespiratory

channels (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1) (nasal flow, breathing effort, pulsoximetry), cardiorespiratory channels (oculogram, electrocardiogram), cardiorespiratory channels (oculogram), cardiorespiratory channels (cardiogram) (bipolar derivations with two electrodes). Before scoring, each recording underwent a clinical evaluation by qualified medical personnel in accordance with the guidelines established by the American Academy of Sleep Medicine (AASM). During the first-night PSG sleep examinations performed at the sleep laboratory, two-channel electroencephalography, two-channel electrooculography, submental electromyography, oronasal airflow, respiratory movements of the thorax and abdomen, snoring severity, body position, arterial oxyhemoglobin saturation, leg movements, and heart rate per minute were recorded. A total of 320 patients were diagnosed with moderate and severe OSAS using PSG [apnea-hypopnea index (AHI): 5-15/hour, mild OSAS; AHI: 15-30/hour, moderate OSAS; and AHI: ≥30/hour, severe OSAS] (12) and were recommended the PAP device for treatment. Of these patients, 72 that met the study criteria were included in the sample. The PAP titration procedure was performed to determine the appropriate device and pressure. These patients were evaluated in terms of RLS using the five diagnostic criteria determined by IRLSSG and revised in 2014. The IRLSSG rating scale (IRLS) was administered to 72 patients who met 5 diagnostic criteria before PAP treatment and at 12 months. IRLS, developed by IRLSSG in 2003, consists of 10 items each scored between 0 and 4. These items aim to question the severity of RLS symptoms and their effect on the activities of daily living. A total score of 1-10 is considered to indicate mild disease, 11-20 moderate disease, 21-30 severe disease, and 31-40 very severe disease (8,13,14).

Statistical analysis

Investigating correlations (if any) between qualitative variables was done using the chi-square test. The arithmetic mean and standard deviation values for the quantitative variables were shown, whereas the numbers and percentages for the qualitative variables were. For the correlation analysis, the Pearson correlation coefficient was calculated. Age and body mass index were taken into account while adjusting the p values (BMI). Statistics were considered significant with P values under 0.05. Statistical software was used to calculate (IBM SPSS Statistics v. 19).

3. Results

The study included 320 patients using PAP with a diagnosis of moderate to severe OSAS. The mean age of the 72 patients diagnosed with RLS + OSAS was 46.9 (±10.2) years, and 25% were female (n = 18) and 75% were male (n = 54). The mean BMI was 31.2 (±5.8). The mean AHI was 44.9 ± 27.7 (median: 46.9, min-max: 16-114). Table 2 presents the data on sleep efficiency, periodic leg movement, mean oxygen saturation, oxygen saturation <90%, and lowest oxygen saturation values evaluated on PSG.

The prevalence of RLS in the patients with moderate and severe OSAS was 24%. The IRLS score on first-night PSG had a positive correlation with AHI (r: 0.113) and a negative correlation with the mean oxygen saturation all night (r:- 0.075), minimum oxygen saturation all night (r: -0.125), time spent below <90% saturation (r:- 0.172), and sleep efficiency (r: -0.087). At the 12th month after PAP treatment, a negative correlation was found between the IRLS score and PAP use (hours) per week (r:-0.316, $p < 0.001$) (Figure 1).

Table 1. International RLS Working Group diagnostic criteria

Basic diagnostic criteria
1. Uncomfortable or unpleasant leg feelings cause or are accompanied by a need to move the legs.
2. The need to move the legs or uneasy feelings start or get stronger while at rest
3. Motion, such as walking and stretching, partially or completely relieves the impulse to move the legs or painful sensations.
4. The impulse to move your legs or uneasy feelings get greater during the day, in the evening, or at night, or only happen at night or in the evening
5. It is not possible to solely attribute the aforementioned characteristics to the major symptoms of other medical or behavioral problems (myalgia, venous stasis, leg edema, leg cramps, and habitual foot tapping).
Supporting clinical features
1. Family history
2. Response to dopaminergic therapy
3. Periodic limb movements (while awake or during sleep)
4. Absence of expected daytime sleepiness

RLS: restless legs syndrome

Table 2. General PSG findings of the study group

Variables	Mean ± SD	Median (min-max)
AHI	**44.9 ± 27.7**	**46.9 (16-114)**
Sleep efficiency %	81.2 ± 14.6	85.7 (26-98.1)
Minimum O_2 saturation%	78.5 ± 10.7	86.6 (51.8-95)
Mean O_2 Saturation%	90.25 ± 6.25	85.3 (57-97.2)
<90% desaturation (min)	66.7 ± 74.7	82.7 (0-280.1)
PLMS Index	34.6 ± 21.6	36.2 (14.9-118.2)

PSG: polysomnography, AHI: apnea-hypopnea index, PLMS; periodic leg movement score

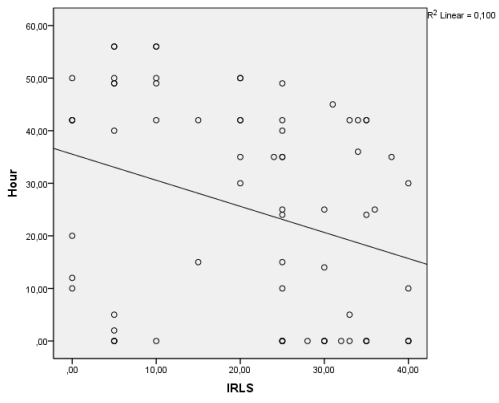

Figure 1. Pearson correlation between RLS severity (IRLS) and hourly PAP use evaluated at the 12th month

4. Discussion

We designed this study under the presumption that the PAP therapy prescribed for OSAS would result in a reduction in the intensity of RLS symptoms. Although OSAS is observed more frequently in men in the general population, recent studies emphasize that its incidence is higher in women describing sleep problems and it should be considered in the

diagnosis of comorbid diseases (15). RLS is a common sleep disorder whose molecular underpinnings and hereditary causes are still poorly understood. RLS is one of the comorbidities that frequently accompany OSAS. In a study conducted in the sleep laboratory of a university hospital, the incidence of RLS was found to be 40.7% in women and 18.1% in men in 589 patients with OSAS (16). In our study, out of 320 moderate and severe OSAS cases, RLS was found in 72 (24%), and of these patients, 25% (n = 18) were female and 75% (n = 54) were male.

Many studies have been conducted on iron deficiency and dopamine imbalance as possible causative factors in the etiopathogenesis of RLS, and this disorder has been found to be nine times more common in those with iron deficiency compared to the general population. In studies conducted in iron-deficient rodents, extracellular dopamine levels were found to be high in the striatum, which was considered to be due to decreases in the membrane-bound dopamine transporter and dopamine 2 receptor density (17,18). This finding has raised questions concerning the accuracy of dopamine treatments, which can cause an increase in the severity of symptoms depending on the dose, frequently observed as a side effect in the treatment of RLS and has led to researchers to seek new treatment methods. Research suggests that in RLS, as a result of decreased transferrin released from oligodendrocytes in brain tissue and hypoxia secondary to iron deficiency, in the substantia nigra, there is an increase in hypoxia-inducible factor-1 (HIF-1) and HIF-2, which show variations in cellular oxygen concentration and are crucial for maintaining oxygen homeostasis as well as endothelial development, which promotes angiogenesis (19). It has also been determined that hypoxia attacks in OSAS cause hyperalgesia after neuronal degeneration as a result of microglia activation and increased mitochondrial reactive oxygen species (20). NLRP3 deficiency, which causes chronic intermittent hypoxia, neuroinflammation, and oxidative stress, has been shown to provides a protective function against neurodegenerative diseases, such as Parkinson's disease by increasing Parkin-dependent mitophagy, a frequently researched topic (21). In addition, myelin synthesis from oligodendrocytes is dependent on iron, and in a study examining the postmortem brain tissues of 11 patients diagnosed with RLS, the levels of myelin basic protein, proteolipid protein and CNPase expression, transferrin, and H-ferritin were found to be decreased in patients diagnosed with RLS compared to controls (22). In a study conducted by screening 1,937 patients, the incidence of RLS was found to be higher in patients with chronic obstructive pulmonary disease compared to the general population (23). In a study by Kaplan et al. evaluating 134 patients with chronic obstructive pulmonary disease (COPD), 39 patients were diagnosed with RLS, and the incidence of RLS was higher in patients with a longer duration of COPD and more severe hypercapnia and hypoxia (24). Consistent with the literature, in our study, we observed that periodic leg movements and the RLS severity score on first-night PSG were correlated with AHI, mean oxygen saturation all night, minimum oxygen saturation all night, and time spent below <90% saturation.

PAP, which is the gold standard method in OSAS, prevents collapse in the upper airways, eliminating apneas and subsequent hypoxemia, thereby treating sleep disorder and daytime sleepiness, improving the quality of life, reducing associated hypertension, cardiovascular events, hemoglobin A1c, postprandial glucose, neurocognitive disorders, motor vehicle accidents, and mortality, and increasing left ventricular ejection fraction (25).

The effects of PAP therapy on the improvement of brain and body functions have been the subject of many studies conducted in recent years. To our knowledge, however, this study is the first to use a prospective design to look at the positive benefits of the PAP device on RLS. Marillier et al. showed that intermittent hypoxia and hypercapnia during sleep cause increased the inhibition of the corticospinal pathway in patients with OSAS, and thus they were able to partially explain the neuromuscular mechanism of extremity muscle dysfunction

in OSAS. Information provided by hypoxic pathway activation and iron deficiency studies on the pathophysiology of RLS indicates the need for new and more effective treatments for this disorder (26). Salminen et al. measured leg oxygen levels during immobilization in patients diagnosed with RLS and detected a significant decrease in oxygen levels in the peripheral veins of the legs ($p < 0.01$). The authors reported a strong correlation between the severity of peripheral hypoxia and the severity of RLS (27). In a retrospective study, Delgado et al. found that in the presence of OSAS and RLS comorbidity, three-month continuous nasal PAP treatment resulted in significant improvement in the scores of ESS ($p < 0.05$), Epworth Sleepiness Scale ($P<0.05$) and Pichot's fatigue/depression questionnaire ($p < 0.01$), and IRLS ($p < 0.05$) scores (28). In another study conducted in a sleep clinic, 28 patients with OSAS and RLS comorbidity were retrospectively screened, and improved RLS symptoms were observed in 20 patients (71.4%) after OSAS treatment (29). In another retrospective study of 434 patients with OSAS with an AHI value of ≥ 5, the improvement in the IRLS scores was found to be better in the PAP-adherent group ($p = 0.045$) than in non-adherent patients ($p = 0.091$) (30). In our study, consistent with the literature, there was a statistically significant improvement in the IRLS scores during the one-year follow-up period of PAP treatment, and a significant correlation was observed between the IRLS score and weekly PAP use hours ($r: -0.316$, $p < 0.001$) (Figure 1).

The study has potential limitations; firstly, patients with mild OSAS were not included in the study because our sample consisted of moderate and severe osas patients who needed pap therapy. Second, our baseline and control severity indexes were subjective based on patients' comments.

5. Conclusion

In this study, the severity of RLS symptoms decreased with the increase in tissue oxygenation after PAP use in patients with the coexistence of OSAS and RLS. There is a need for further studies to measure tissue oxygenation values before and after treatment in these patients and demonstrate that involuntary leg movements are reduced on control PSG

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Adana Cıty Traınıng And Research Hospıtal (Decision no:1429, Date: 02.06.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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