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Obstructive Sleep Apnea Syndrome and Pain: A Cross-sectional Study

Obstrüktif Uyku Apne Sendromu ve Ağrı: Kesitsel Bir Çalışma

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ABSTRACT

Aim: The present study aims to investigate the relationship between chronic widespread musculoskeletal system pain (CWP) and neuropathic pain (NP) among patients, who were diagnosed with obstructive sleep apnea syndrome (OSAS).

Material and Methods: For this cross-sectional study, the study was carried out in sleep polyclinic of Uşak University's Medical Faculty Hospital between 1 May 2017 and 1 February 2018. The patients, who applied to the sleep polyclinic for the complaint of sleep disorder and were diagnosed with OSAS by using polysomnography (PSG) but haven't had a treatment for this purpose yet, were involved..

Results: Examining the PSG results of participants, mild OSAS was detected in 16 cases, moderate OSAS in 15 cases, and severe OSAS in 26 cases. Pain was detected in minimum 1 region in 89% of the cases, whereas 38.5% of participants were found to have neuropathic pain (NP). NP was found to linearly increase with an increase in degree of OSAS (p=0.049). According to Pittsburgh Sleep Quality Index (PSQI) scores, 54% (n=31) of the participants had poor sleep quality, and according to Health Assessment Questionnaire (HAQ) scale scores, 36% (n=21) of the participants had low quality of life (QoL). When examining the differences between groups, due to the variables not being normally distributed, the Mann Whitney U and Kruskal Wallis-H Tests were utilized. to investigate the relationships among variables that do not follow a normal distribution, Spearman's Correlation Coefficient was employed.

Conclusion: CWP and NP were found to accompany each other among those with OSAS. The prevalence of NP increases with an increase in degree of OSAS. The QoL and quality of sleep among those with OSAS with pain were poorer than those having no pain. Women with OSAS were found to have higher pain and lower QoL when compared to men.

Keywords: Sleep apnea, obstructive, musculoskeletal pain, neuropathic pain

ÖZ

Amaç: Bu çalışma, obstrüktif uyku apne sendromu (OUAS) tanısı alan hastalarda kronik yaygın kas-iskelet sistemi ağrısı (KYKİSA) ile nöropatik ağrı (NA) arasındaki ilişkiyi araştırmayı amaçlamaktadır..

Gereç ve Yöntemler: Bu kesitsel çalışma, 1 Mayıs 2017-1 Şubat 2018 tarihleri arasında Uşak Üniversitesi Tıp Fakültesi Hastanesi uyku polikliniğinde gerçekleştirildi. Uyku polikliniğine uyku bozukluğu şikayeti ile başvuran ve polisomnografi ile obstrüktif uyku apne sendromu tanısı konulan ancak henüz bu amaçla tedavi görmemiş hastalar çalışmaya alındı.

Bulgular: Olguların polisomnografi sonuçları incelendiğinde 16 olguda hafif, 15 olguda orta ve 26 olguda ağır düzeyde obstrüktif uyku apne sendromu saptandı. Olguların %89'unda en az 1 bölgede ağrı saptanırken, olguların %38,5'inde nöropatik ağrı (NA) saptandı. NA'nin obstrüktif uyku apne sendromu derecesi arttıkça lineer olarak arttığı bulundu (p=0,049). Pittsburgh Uyku Kalitesi İndeksi (PUKİ) puanlarına göre olguların %54'ünün (n=31) uyku kalitesi kötüydü, Sağlık Değerlendirme Ölçeği puanlarına göre ise olguların %36'sının (n=21) yaşam kalitesi düşüktü.

Sonuç: Obstrüktif uyku apne sendromu olanlarda KYKİSA ve NA'nın birbirine eşlik ettiği saptandı. Obstrüktif uyku apne sendromu derecesi arttıkça NA prevalansı artmaktaydı. Obstrüktif uyku apne sendromu ile beraber ağrısı olanlarda yaşam kalitesi ve uyku kalitesi skorları daha kötü bulundu. Obstrüktif uyku apne sendromu'lu kadınların erkeklere göre ağrı skorları daha yüksek ve yaşam kalitesi skorları daha düşük bulundu.

Anahtar Sözcükler: Uyku apnesi, obstrüktif, kas iskelet ağrısı, nöropatik ağrı

INTRODUCTION

OSAS is a disorder that is characterized with obstructive apnea, hypopnea, and/or respiratory effort incused by repetitive collapse of the upper respiratory pathway (1). Even though its prevalence varies between the countries, the prevalence is 24% among men and 9% among women (2).

Chronic pain is defined as the pain lasting longer than 3 months (3). Chronic pain is observed in 11-29% of the general population. Among those having chronic pain, 50-89% have poor sleep quality and/or complaints of feeling not refreshed after waking up (4). The relationship between sleep and pain is a bilateral one. The insufficient sleep and consequently the daytime sleepiness cause hyperalgesia (5). The majority of patients with OSAS (37.9-55.4%) have chronic widespread musculoskeletal pain (4,6,7).Chronic widespread musculoskeletal pain is more common in female patients with OSAS (4).

Neuropathic pain (NP) is defined as the pain caused by a dysfunction or primary lesion influencing the somatosensorial system. The sleep quality of patients with NP may be influenced by various factors, such as associated diseases, clinical symptoms, and psychological disorders, which can complicate treatment. Pain sensitivity has a positive relationship with sleeplessness. Thus, degradation was found in pain tolerance of patients having NP and sleep problems (8). It is known that OSAS increases the frequency of neuropathic pain through inflammatory pain pathways and causes hyperalgesia (9,10). In literature, there is limited study examining the NP symptoms among OSAS patients. We think that our study will make important contributions to the literature as it reveals the relationship between OSAS and NP and the factors affecting it.

Common complaints in the primary care system include sleep disturbance, chronic musculoskeletal and neuropathic pain. Obstructive sleep apnea syndrome should also be considered in the differential diagnosis of patients with these complaints.

The present study aims to investigate the relationship between CWP and NP symptoms among the patients, who were diagnosed with obstructive sleep apnea syndrome (OSAS).

MATERIAL and METHODS

The present cross-sectional study was carried out in sleep polyclinic of Uşak University's Medical Faculty Hospital between 1 May 2017 and 1 February 2018. The study sample consisted of all patients who met the inclusion criteria, among those who applied to the sleep outpatient clinic during the study. Upon the ethics committee approval was obtained from Uşak University's Observational Clinical Research Ethics Committee. (Approval date: 07.06.2017, Approval number: 2017-40).

Among those applying to the sleep polyclinic, the ones that have been recently diagnosed with OSAS by using PSG, meeting the inclusion criteria, and volunteering to participate were involved. In accordance with Helsinki Declaration, informed consent forms were obtained from all the participants.

Inclusion criteria; volunteering to participate, newly diagnosed with OSAS, not having had any treatment for OSAS.

Exclusion criteria; having a previous OSAS treatment, having any known inflammatory or/non-inflammatory rheumatic disorder, known lumbar disc hernia, cervical disc hernia, polyneuropathy, meniscopathy, peripheral nerve damage, orthopedic surgical disease, Diabetes Mellitus, known oncological disorder, or oncologic disease history (history of chemotherapy or radiotherapy).

Power Analysis

Before the study, an effect size of 0.48 was determined with 80% theoretical power based on LANSS Scores and 70 patients were targeted. At the end of the study, it was determined that 4 patients had polyneuropathy, 3 patients had lumbar disc herniation, 3 patients had fibromyalgia and these patients were excluded from the study. Since 3 patients refused to participate in the study, the study was completed with a total of 57 patients. At the end of the study, the realised power was 83% with an effect size of 0.48.

Data Collection Tools

Sociodemographic characteristics (age, gender, educational status, height, weight, known diseases) and backgrounds of patients were recorded. Together with a physiotherapist and making use of figure drawn on a 40x55cm laminat-

ed board and designed to illustrate nine segments (neck, shoulders, back, elbows, hips/thighs, knees, ankles/feet) in accordance with Nordic Musculoskeletal Questionnaire, the patients were asked to paint where they feel pain (11). While painting, they were asked to use five different colors (black: very severe, red: severe-moderate, blue: moderate, green: moderate-low, and yellow: mild) representing the severity of pain. After the painting process, the patients were asked to describe the character of pain by the keywords such as blunt, throbbing, burning, freezing, tingling, electrification, electric shock, stinging, or pinprick.

The sleep quality was examined using Pittsburgh Sleep Quality Index(PSQI), whereas The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale and Pain Detect scales were used in analyzing the presence of neuropathic pain, Health Assessment Questionnaire(HAQ) scale was used in analyzing the sleep quality, and visual analogue scale (VAS) was used in order to determine the level of pain.

The single-night sleep values were recorded using PSG (Embla N7000, Ontario, Canada) device. Arterial blood gas measurements were performed using pulse oximeter. Nasal and oral airflows were measured using oronasal thermal sensors. Chest wall movements were observed and recorded. Tracheal voices were recorded using thermistors. Respiratory events were scored using the criteria set by American Academy of Sleep Medicine. Complete stop of oronasal airflow for a minimum of 10 seconds is defined as apnea, waking up and 3% decrease in oxygen desaturation due to 50% decrease in airflow for a minimum of 10 seconds is defined as hypopnea. Diagnosis of OSAS was made if apnea-hypopnea index (AHI) value, which is calculated by dividing the total apnea-hypopnea throughout the night by the hours of sleeping, was 5 or higher. According to AHI, the index values $5 \leq AHI < 15$ per hour suggest mild OSAS, $15 \leq AHI < 30$ suggest moderate OSAS, and $30 \leq$ suggest severe OSAS diagnosis. OSAS levels of patients were recorded with PSG results (4,12,13).

HAQ: It consists of 20 questions in total and questions the daily activities over 8 items. The highest score is 60 points; the quality of life decreases with a decrease in score (14).

VAS: VAS is a pain scale, score of which ranges between 0 and 10 points and in which the patient assesses his/her pain himself/herself. 0 point indicates no pain, whereas 10-points indicates the severest pain level (15).

PSQI: It is a scale quantitatively measuring the sleep quality. It analyses the sleep quality for the last 1 month. Total score of PSQI ≤5 indicates “good” sleep quality, whereas the scores >5 indicate “poor” sleep quality (16).

Statistical Analysis

The data obtained in this study were analyzed with IBM SPSS Statistics Version 22 package program. Shapiro Wilk’s was used because of the unit numbers while investigating the status of the variables coming from the normal distribution. While examining the differences between groups, Mann Whitney U and Kruskal Wallis-H tests were used because the variables did not come from the normal distribution. In the case of significant differences in the Kruskal Wallis-H Test, groups with differences were determined by Post-Hoc Multiple Comparison Test. Spearman’s Correlation Coefficient was used when examining the relationships between variables that do not come from the normal distribution. 0.05 was used as the significance level while interpreting the results; It was stated that there is a significant relationship when $p<0.05$, and there is no significant relationship when $p>0.05$.

RESULTS

The study began with 70 newly diagnosed cases with Obstructive Sleep Apnea Syndrome (OSAS). It was found that 4 patients had polyneuropathy, 3 had lumbar disc herniation, and 3 had fibromyalgia, and these cases were excluded from the study. 3 patients refused to participate, so the study was completed with a total of 57 cases (18 women and 39 men). The mean age ± standard deviation of the cases was found to be 50.8±9.9 years. Examining the educational statuses, it was determined that 26 (45.6%) cases were elementary school graduates, 21 (36.8%) cases were secondary school or high-school graduates, and 10 (17.5%) cases were college or university graduates. Analyzing the PSG results, it was found that 16 (28.7%) cases had mild OSAS, 15 (26.3%) had moderate OSAS, and 26 (45.6%) had severe OSAS. Among the cases recently diagnosed with OSAS and not received treatment yet, the median complaint duration for OSAS was found to be 48 (Min: 1- Max: 240) months.

Pain regions and durations in the musculoskeletal system are shown in Table 1. It was also found that 5 cases had no pain in any region. Pain was found at a minimum of 1 region in 89% of cases. There was no statistically significant relationship between OSAS complaint duration and pain duration.

It was found that 54% (n=31) of participants had PSQI scores higher than 5 points, which indicates poor sleep quality. Thirty-six percent (n=21) of cases had HAQ score higher than 10, which indicates poor QoL. No significant relationship was found between OSAS severity and QoL in the present study (p=0.73).

Table 1. Pain regions, severity, duration, and character .

	n (%)	Duration (Month)	Pain severity (1-5)	Blunt	Burning	Freezing	Tingling	Electrification	Pinprick	Throbbing
Neck	25 (43.8)	48	4	10 (40.0)	12 (48.0)	10 (40)	13 (52)	12 (48)	13 (52)	11 (44)
Shoulder	29 (50.8)	48	4	14 (48.2)	14 (48.2)	14 (48.2)	14 (48.2)	12 (41.3)	11 (37.9)	12 (41.3)
Back	26 (45.6)	36	4	13 (50)	12 (46.1)	13 (50)	12 (46.1)	13 (50)	7 (26.9)	11 (42.3)
Elbow	20 (35)	48	4	11 (55)	8 (40)	9 (45)	8 (40)	11 (55)	9 (45)	11 (55)
Hand-Wrist	15 (26.3)	48	4	5 (33.3)	5 (33.3)	5 (33.3)	5 (33.3)	6 (40)	5 (33.3)	5 (33.3)
Lumbar	36 (63.1)	52	5	19 (52.7)	13 (36.1)	11 (30.5)	14 (38.8)	12 (33.3)	11 (30.5)	13 (36.1)
Hip& Thigh	20 (35)	42	4	8 (40)	7 (35)	6 (30)	7 (35)	7 (35)	9 (45)	7 (35)
Knee	26 (45.6)	48	4	14 (53.8)	9 (34.6)	11 (42.3)	11 (42.3)	11 (42.3)	9 (34.6)	9 (34.6)
Foot-ankle	18 (31.5)	24	3.5	7 (38.8)	9 (50)	4 (22.2)	6 (33.3)	6 (33.3)	4 (22.2)	3 (16.6)

There were 22 cases having LANSS score higher than 12 points and 20 cases having Pain Detect score between 18 and 38. Moreover, there were 20 cases having high scores in both of LANSS and Pain Detect scales. NP was observed in 38.5% of the participants (13.6% of mild OSAS cases, 28.3% of moderate OSAS cases, and 59.1% of severe OSAS cases). NP linearly increased with the increasing degree of OSAS. The presence of minimum 1 of the NP symptoms including burning, stinging, tingling, pinprick, electrification, and freezing was found in 46 patients (80%). The data of pain regions, severity, duration, and character are presented in Table 1.

The relationship between the severity of OSAS and scores HAQ, and PUKI was evaluated, and no statistically significant results were found ($p>0.05$).

The scores of male participants in these four measurements were found to be lower than those if women. The results of LANSS, Pain detect, VAS movement, and HAQ scores by gender are presented in Table 2.

Educational level, age, and OSAS degree were found to have no significant effect on the results ($p>0.05$, $p>0.05$, $p>0.05$).

DISCUSSION

OSAS is one of the widely seen sleep disorders. In the present study, most of OSAS cases were found to have pain in minimum 1 segment of body and more than one-third were found to have NP. The prevalence of NP increases with an increase in severity of OSAS. When compared to male OSAS patients, female OSAS patients have significantly higher level of pain and have lower level of QoL. More than half of OSAS patients were found to have poor sleep quality and more than one-third were found to have poor QoL.

CWP is a common condition, with its prevalence in the United Kingdom identified to vary between 35.0% and 51.3%. In Australia, its prevalence is lower, reaching 17% in men and 20% in women. The prevalence has been found to be 25% in China and 39% in Japan. Factors repeatedly associated with pain include age, gender, depression, and sleep disorders. Studies suggest that smoking, alcohol, and comorbidities may also influence the development of chronic pain (17). The comorbidity of OSAS and CWP is frequently observed. In a study examining the effect of musculoskeletal pain on the sleep architecture of those with OSAS, it was reported that 200 out of 393 OSAS patient had CWP (7). In another study examining 4000 patients having chronic spinal pain and receiving chronic opioid treatment, the prevalence of OSAS was found to be 13.8% (18). There also are studies reporting that OSAS does not directly cause the pain by increases the pain threshold by leading to sleep disorders (19,20). In another study, it was claimed that, contrarily, the increased nocturnal hypoxia among OSAS patients caused an increase in IGFBP-1, one of the proinflammatory cytokines, and it resulted in decrease of pain sensitivity and increase in sensitivity to opioid analgesic (9). Terzi and Yilmaz asserted that the relationship between OSAS and pain may be because of the low oxygen saturation and total myalgia score (21). Aytekin E et al. reported in their

Table 2. The Results of Mann Whitney-U Test for the Difference in Measurement Results by Gender .

	Gender	Median (min-max)	*p**
LANSS	Women**	14 (0-24)	**0.013**
	Men**	5 (0-21)	
	Total**	7 (0-24)	
Pain detect	Women	19 (0-30)	**0.008**
	Men	4 (0-33)	
	Total	7 (0-33)	
VAS Night	Women	3 (0-9)	0.549
	Men	3 (0-10)	
	Total	3 (0-10)	
VAS Resting	Women	4 (0-8)	0.233
	Men	3 (0-10)	
	Total	3 (0-10)	
VAS Movement	Women	7.5 (0-10)	**0.036**
	Men	4 (0-10)	
	Total	5 (0-10)	
HAQ	Women	13.5 (0-40)	**0.002**
	Men	3 (0-35)	
	Total	7 (0-40)	
PSQI	Women	7 (2-13)	0.427
	Men	5 (1-18)	
	Total	7 (1-18)	
OSAS Complaint Duration	Women	36 (1-240)	0.377
	Men	60 (1-240)	
	Total	48 (1-240)	

* Mann-Whitney U testi, ** 18 women, 39 men total 57 participants
LANSS: The Leeds Assessment of Neuropathic Symptoms and Signs pain scale, **Pain detect:** Pain Detect scales, **VAS:** Visual Analogue Scale, **HAQ:** Health Assessment Questionnaire Scale, **PSQI:** Pittsburgh Sleep Quality Index, **OSAS:** Obstructive Sleep Apnea Syndrome.

study that the prevalence of CWP was 55.4% among the OSAS patients. Female OSAS patients were found to have more pain than male OSAS patients (4). OSAS degree was found to have no relationship with pain and degree of pain (4,6). Although a higher level of pain (89%) was observed in the present study when compared to the literature, no relationship was found between severity of OSAS and pain. According to the literature, we think that the reason why more pain levels were observed was the inclusion of patients who had just been diagnosed and had not received any treatment in the study. However, female OSAS patients were complaining about pain statistically significantly more than male OSAS patients. The reason for this is that women have more nociceptive sensitivity than men, and we think that there are differences in gonadal hormones.

In literature, the number of studies investigating the comorbidity of OSAS and NP is very limited. In their meta-analysis examining the relationship between diabetic polyneuropathy (DPN) and OSAS, Fujihara K. et al. reported that DPN patients have OSAS prevalence twice as diabetic patients without neuropathy (22). In their study, Doufas et al. emphasized that, as a result of the inflammatory pathways induced by hypoxia, nocturnal hypoxia independently causes hyperalgesia (9). In a meta-analysis study carried out in year 2020, it was determined that there was a relationship between neuropathic pain and OSAS through the potential inflammatory pathways (10). Similar to the literature, in the presenr study more than a third of the patients with OSAS had NP. The rates of neuropathic symptoms vary depending on the pain regions. The NP linearly increases with increasing severity of OSAS. An increase in nocturnal hypoxia as a result of an increase in the severity of OSAS indicates that it increases NP through inflammatory pathways (23).

In their study, Butner K et al. found no relationship between OSAS severity and QoL and exercise capacity (24). Similarly, in their study, Aytekin E et al. found no significant relationship between OSAS severity and QoL but they found the physical capacity of women, who have CWP, lower than men (4). In a systematic review carried out in year 2021, although it was reported that adult patients with untreated OSAS had poor QoL, this relationship was not reported in the studies set only for the relevant variables (25). Similar to the literature, no significant relationship was found between OSAS severity and QoL in the present study. However, similar to the study carried out by Aytekin E et al., a statistically significant relationship was observed between gender and poor QoL. This is believed to be because women are affected by the CWP and NP more than men due to their lower physical capacity and it causes a decrease in QoL scores.

In various studies, musculoskeletal pain developing in OSAS patient was found to have a significant relationship with poor sleep quality and short sleeping durations (7,26). An increase in the number of painful joints results in a further decrease in sleep quality (26). In another study, the non-restful sleep was reported to be the strongest determinant of newly developing CWP among elderly adults. The recent findings suggest that restful sleep is related with the resolution of pain symptoms (27). Similar to the literature, it was determined in the present that severity of pain increased among those with decreasing sleep quality and the patients had a higher pain perception. The sleep quality was found to be poor in more than half of the cases. Besides VAS used as pain scale, also the colors were used in the present study. It was determined that, when the pain perception is expressed over colors, it was severer in comparison to the VAS. This is believed to be because the use of color scale is more understandable for the cases when compared to the scoring.

Table 3. Correlation Test for the Relationship between Measurement Results .

		LANSS	Pain detect	VAS Night	VAS Resting	VAS Movement	HAQ	PSQI
Pain detect	r	.949**						
	p	0.001						
	n	57						
VAS Night	r	.560**	.567**					
	p	0.001	0.001					
	n	57	57					
VAS Resting	r	.449**	.394**	.384**				
	p	0.001	0.002	0.003				
	n	57	57	57				
VAS Movement	r	.582**	.584**	.512**	.679**			
	p	0.001	0.001	0.001	0.001			
	n	57	57	57	57			
HAQ	r	.373**	.319*	0.157	0.214	.398**		
	p	0.004	0.016	0.244	0.11	0.002		
	n	57	57	57	57	57		
PSQI	r	.391**	.335*	0.217	0.133	.333*	.647**	
	p	0.003	0.011	0.105	0.322	0.011	0.001	
	n	57	57	57	57	57	57	

* A relationship at a significance level of 0.05, ** Indicates a relationship at the 0.01 level of significance.

LANSS: The Leeds Assessment of Neuropathic Symptoms and Signs pain scale, **Pain detect:** Pain Detect scales, **VAS:** Visual Analogue Scale, **HAQ:** Health Assessment Questionnaire Scale, **PSQI:** Pittsburgh Sleep Quality Index.

Table 4: Kruskal Wallis H Test Results Regarding the Difference Between OSAS Severities in Terms of Measurement Values) .

		OSAS Severity			Kruskal Wallis H Test
		n	Mean± SD	Median (min-max)	p
Lanss	Mild	16	6.75±6.47	5.5 (0-21)	0.463
	Intermediate	15	9.33±6.63	6 (0-21)	
	Severe	26	9.77±7.74	10.5 (0-24)	
	Total	57	8.81±7.12	7 (0-24)	
Paindetect	Mild	16	7.69±8.73	3.5 (0-29)	0.335
	Intermediate	15	12.87±11.83	8 (0-33)	
	Severe	26	11.27±9.54	10.5 (0-30)	
	Total	57	10.68±10	7 (0-33)	
HAQ	Mild	16	9.94±12.92	3.5 (0-37)	0.73
	Intermediate	15	8±7.63	7 (0-27)	
	Severe	26	10.54±11.07	8 (0-40)	
	Total	57	9.7±10.73	7 (0-40)	
PUKİ	Mild	16	7.25±4.52	7 (2-18)	0.403
	Intermediate	15	7.27±3.94	8 (1-15)	
	Severe	26	5.81±3.41	5.5 (1-13)	
	Total	57	6.6±3.88	7 (1-18)	

The limitations of present study include monocentric design, limited number of patients, and that no re-assessment was performed after the OSAS treatment of participants.

In conclusion, CWP and NP were observed in most of patients having OSAS. Therefore, we also recommend OSAS screening for patients with CWP and NP diagnoses. The prevalence of NP was higher among those with higher OSAS severity. We propose to an interdisciplinary approach centered on pharmacological treatment for the treatment of neuropathic pain in patients with severe OSAS. In comparison to the participants with no pain, the participants having pain had poorer QoL and poorer sleep quality. In patients with OSAS, appropriate pain therapy (e.g. pharmacological, steroid injections, nerve blocks, physical therapy, CPAP therapy, etc.) planning QoL and quality of sleep can be improved. In comparison to the men, it is more frequently observed among female patients with OSAS and their QoL levels were found to be lower. Interventions to increase physical function in female patients with OSAS (eg: exercising, losing weight, etc.) their QoL levels can be improved. Considering these characteristics for those diagnosed with OSAS might prevent the development of possible complications.

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Author Contributions

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Conflicts of Interest

There is no conflict of interest to declare.

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Ethical Approval

Upon the ethics committee approval was obtained from Uşak University's Observational Clinical Research Ethics Committee (Approval date: 07.06.2017, Approval number: 2017-40).

Review Process

Extremely peer-reviewed.

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