ORIGINAL ARTICLE

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Effect of CPAP on Hemocyte Profile C-reactive Protein and Fibrinogen Levels in People with Obstructive Sleep Apnea

Obstrüktif Uyku Apnesi Olan Kişilerde CPAP'ın Hemosit Profili, C-reaktif Protein ve Fibrinojen Düzeyleri Üzerine Etkisi

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ABSTRACT

Aim: Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder characterized by repeated episodes of apnea and hypopnea during sleep. The repetitive hypoxemic and hypercapnic events can lead to increased proinflammatory cytokine production, endothelial dysfunction, oxidative stress, metabolic dysregulation, and insulin resistance in OSAS patients. In previous studies, some of the hemogram values increased in patients with OSAS and a decrease in these increased values was observed with continuous positive airway pressure (CPAP) treatment. CPAP is the most effective method for treating OSAS and alleviating the patients' symptoms. The aim of this study was to assess the effect of three-month CPAP therapy on hemocyte profile in people with OSAS.

Materials and Methods: Forty patients were included in the study. Data including clinical assessment, full previous polysomnography reports, and baseline and after CPAP therapy, complete blood profile (leukocytes, neutrophils, lymphocytes, hemoglobin, hematocrit, platelets, MPV, PDW, MCV, N/L, and P/L, CRP and fibrinogen) of the participants were collected from the electronic medical record.

Results: All patients who completed the study were CPAP compliant (5.53±0.39 h/night). After three months of CPAP treatment, the mean levels of leukocytes, lymphocytes, hemoglobin, hematocrit, MPV, MCV, N/L, and P/L, CRP and fibrinogen were significantly decreased compared to baseline values.

Conclusion: Our study showed significant decrease in hemoglobin, hematocrit, leukocyte, lymphocyte, MPV, MCV, N/L, and P/L, CRP and fibrinogen after three-month CPAP therapy.

Keywords: Obstructive sleep apnea syndrome, CPAP, hemocyte profile, CRP, fibrinogen

ÖZ

Amaç: Obstrüktif uyku apne sendromu (OUAS), uyku sırasında tekrarlayan apne ve hipopne atakları ile karakterize yaygın bir uyku bozukluğudur. Tekrarlayan hipoksemik ve hiperkapnik olaylar, OUAS hastalarında artmış proenflamatuvar sitokin üretimine, endotel disfonksiyonuna, oksidatif strese, metabolik düzensizliğe ve insülin direncine yol açabilir. Daha önceki çalışmalarda OUAS'lı hastalarda bazı hemogram değerlerinde artış olmuş ve sürekli pozitif hava yolu basıncı (CPAP) tedavisi ile bu artmış değerlerde azalma gözlenmiştir. CPAP, OUAS'ı tedavi etmek ve hastaların semptomlarını hafifletmek için en etkili yöntemdir. Bu çalışmanın amacı, OUAS olan kişilerde üç aylık CPAP tedavisinin hemosit profiline etkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 40 hasta dahil edildi. Klinik değerlendirme, önceki tam polisomnografi raporları ve CPAP tedavisi öncesi ve sonrasında tam kan profili (lökositler, nötrofiller, lenfositler, hemoglobin, hematokrit, trombositler, MPV, PDW, MCV, N/L ve P/L, CRP ve fibrinojen dahil olmak üzere) verileri katılımcılarının elektronik tıbbi kayıtlarından toplanmıştır.

Bulgular: Çalışmayı tamamlayan tüm hastalar CPAP uyumluydu (5,53±0,39 h/gece). Üç aylık CPAP tedavisinden sonra, ortalama lökosit, lenfosit, hemoglobin, hematokrit, MPV, MCV, N/L ve P/L, CRP ve fibrinojen seviyeleri başlangıç değerlerine göre önemli ölçüde azaldı.

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Sonuç: Çalışmamız üç aylık CPAP tedavisinden sonra hemoglobin, hematokrit, lökosit, lenfosit, MPV, MCV, N/L ve P/L, CRP ve fibrinojen değerlerinde anlamlı azalma olduğunu göstermiştir.

Anahtar Kelimeler: Obstrüktif uyku apne sendromu, CPAP, hemosit profili, CRP, fibrinojen

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of partial or total collapse of the upper airway during sleep, resulting in nocturnal hypoxia, daytime sleepiness, and fatigue[1]. It is estimated that 4% of both female and male adults suffer from OSAS[2]. Intermittent hypoxia results in increased reactive oxygen species, leading to oxidative stress and systemic inflammation.

OSAS is a low-grade inflammatory disease. In previous studies, elevated inflammatory cytokines, including IL-6, IL-1, C-reactive protein (CRP), and tumor necrosis factor-alpha, have been observed in OSAS patients[3,4]. Recent studies suggest that both WBC and NLR are good indicators of inflammation[5-8]. Some studies reported that platelet was activated and aggregated in patients with OSAS, which was also relevant in inflammatio[9,10]. MPV and PDW are both useful markers of platelet activity. Recently, studies introduce PLR as a novel inflammatory marker[7,8] In recent years, many studies have focused on leukocyte subsets, red blood cell indices, platelet indices, N/L ratio, and/or P/L ratio in patients with OSAS[11-15].

Continuous positive airway pressure (CPAP) remains the optimum therapy for patients with moderate to severe OSAS. Several studies have analyzed the effect of CPAP therapy on a wide variety of biomarkers of oxidative stress and inflammation[16-20].

Therefore, we aimed to explore the effect of CPAP therapy on hemocyte profile in people with obstructive sleep apnea.

MATERIALS AND METHODS

Study Population

We performed a single-center, cross-sectional study on participants attending our sleep laboratory between May 2018 to February 2019, who had previously been diagnosed with OSAS and had three months of CPAP therapy. Demographic characteristics were collected from the electronic medical record, including age, body mass index, and past medical history.

Exclusion Criteria

Patients with diagnosed autoimmune disorders, acute respiratory tract infection in recent one month, liver or kidney disease, malignant tumor, chronic alcoholism, hyperthyroidism or hypothyroidism, inflammatory bowel disease, inflammatory connective tissue disorders, heart disease (such as coronary artery disease and heart failure), cerebrovascular accident, history of recent blood transfusion (within two weeks), or hematologic disorders such as leukemia, anemia, or myelodysplastic syndrome were excluded. Patients using drugs (including non-steroidal anti-inflammatory drugs, steroids, antibiotics, and immunosuppressive medication) and aged <18 years were also excluded.

Study Design

Data including clinical assessment, full previous PSG reports, and baseline and after CPAP therapy complete blood profile (leukocytes, neutrophils, lymphocytes, hemoglobin, hematocrit, platelets, MPV, PDW, MCV, N/L, and P/L, CRP, and fibrinogen) of the participants were collected from the electronic medical records.

CPAP Compliance

CPAP adherence (hours of use) and efficacy were evaluated by CPAP adherence tracking data downloaded from the CPAP device. We defined CPAP adherence as the average use of four or more hours per night over the three-month study.

Biochemical Parameters

Baseline and after CPAP therapy, complete blood profile in all patients was also recorded from the electronic medical record, including leukocytes, neutrophils, lymphocytes, hemoglobin, hematocrit, platelets, MPV, PDW, MCV, N/L, and P/L, CRP, and fibrinogen.

This study was approved by the Local Ethics Committee of Tekirdağ Namık Kemal University Faculty of Medicine with the number: 2019.160.09.20 (date: 24.09.2019).

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA) version 18 software package. All the values were calculated as the mean±standard deviation. We used paired sample t-test to compare the pre-and post-treatment data of the study group. The reported p values are 2-tailed, and a p value <0.05 was considered statistically significant.

RESULTS

A total of 40 patients were included in the study. Descriptive characteristics of OSAS patients are presented in Table 1. The

mean CPAP pressure established by automatic titration was 7.8±2.6 cmH_2O. Comparisons of before and after CPAP therapy parameters are shown in Table 2.

A paired-samples t-test was conducted to evaluate the impact of the CPAP on the hemocyte profile. There was a statistically significant decrease in hemoglobin from Time 1 [M=40.17, standard deviation (SD)=5.16] to Time 2 (M=37.5, SD=5.15), t (29)=5.39, p<0.001 (two-tailed). The mean decrease in FOST scores was 2.67 with a 95% confidence interval ranging from 1.66 to 3.68. The eta squared statistic (0.50) indicated a large effect size.

All patients who completed the study were CPAP compliant (5.53±0.39 h/night). After three months of CPAP treatment, the mean levels of leukocytes, lymphocytes, hemoglobin, hematocrit, MPV, MCV, N/L, and P/L, CRP, and fibrinogen levels were significantly decreased compared to baseline values (Figures 1 and 2). Our study showed a significant decrease in hemoglobin, leukocyte, lymphocyte, hemoglobin, hematocrit, MPV, MCV, N/L, P/L, CRP, and fibrinogen levels.

Table 1. Descriptive characteristics of participants

	Mean±SD	Range
Age; years	53.79±2.61	39-79
Male sex; n (%)	34 (85%)	
BMI; kg/m^2	31.55±1.01	24.6-40.6
AHI (h^{-1}) before CPAP	46.20±5.18	5.8-82.3
AHI (h^{-1}) after CPAP	3.28±0.96	0.2-16.8
Lowest SpO_2, %	76.95±2.13	59-92
Duration of CPAP therapy (h/day)	5.53±0.39	4.1-8
Under SpO_2 90, minute	37.16±16.01	0-275

BMI: Body mass index, AHI: Apnea-hypopnea index, SD: Standard deviation, CPAP: Continuous positive airway pressure

DISCUSSION

This study reinforces the importance of hematological evaluation as an easy complementary tool to the global approach to OSAS patients by showing that hemoglobin, hematocrit, leukocyte, lymphocyte, MPV, MCV, N/L, and P/L, CRP and fibrinogen levels significantly decreased after positive airway pressure (PAP) treatment. These findings suggest that these parameters might be used as the markers of response to treatment.

Sustained hypoxia results in increased expression of erythropoietin-inducing erythropoiesis with a consequent increase in hematological parameters[21,22]. PAP correction of respiratory events and consequent hypoxia and inflammation can translate into a decrease in hemoglobin, and hematocrit as obtained in our study.

Some studies reported that platelet was activated and aggregated in patients with OSAS, which was also relevant in inflammation. MPV and PDW are both useful markers of platelet activity. The tendency to decrease MPV could also be explained by the fact that besides PAP decreasing hypoxia and inflammation, it also improves platelet aggregability[9,10]. Our results showed a significant decrease in MPV after three months of CPAP treatment.

Neutrophils mainly mediate innate immune response by secreting mediators while lymphocytes mediate adaptive immune response by regulating inflammation[22,23]. Recent studies suggest that both NLR and PLR are good indicators of

Table 2. Comparisons of biochemical parameters after 12 weeks of CPAP treatment

n=40	Before CPAP		After CPAP		p
Variable	Mean±SD	Range	Mean±SD	Range	
Hemoglobin	14.61±1.46	10.75-16.50	14.27±1.47	9.82-17.61	0.006
Hct	43.33±4.18	32.7-51.8	42.39±3.94	29.6-49.9	0.018
MPV	8.90±0.82	7.8-10.8	8.70±0.70	7.7-10.4	0.022
Plt (10^9/L)	246.0±49.1	162-294	242.6±49.0	239.1-339	0.219
PDW	15.09±2.08	12.8-20.3	14.85±1.98	12.0-19.3	0.208
Leukocyte (10^9/L)	8.01±2.00	4.4-12.6	7.60±1.70	5.6-10.8	0.037
Neutrophil (10^9/L)	4.14±1.31	2.2-7.0	4.10±1.22	2.6-6.5	0.774
Lymphocyte (10^9/L)	2.95±0.94	1.5-5.2	2.61±0.75	1.7-4.4	0.001
N/L	1.52±0.58	0.59-3.28	1.70±0.66	0.69-3.55	0.017
P/L	91.2±31.5	40-190	98.8±32.7	50-190	0.037
Fibrinogen (mg/dL)	342.80±91.86	259-450	310.93±65.21	206-447	0.018
CRP (mg/dL)	3.50±3.33	1-14	2.16±1.71	0.2-5.6	0.007

Differences among the four groups were examined using a One-Way analysis of variance (ANOVA) or chi-square test according to the characteristics of the data distribution.

CPAP: Continuous positive airway pressure, RDW: Red cell distribution width, SD: Standard deviation, MPV: Mean platelet volume, Hct: Hematocrit, Plt: platelet, N/L: Neutrophils/lymphocytes ratio, P/L: Platelet/lymphocyte, MCV: the Average volume of red blood cells, RDW: Distribution of red blood cells, MPV: Average volume of platelets, PDW: Width of platelet distribution

inflammation[5-8]. Our study demonstrated that a significant reduction of total lymphocyte count, NLR and PLR occurred exclusively in the peripheral blood of OSAS patients who used CPAP therapy for three months. However, there was no significant decrease in neutrophil counts.

Fibrinogen is an acute-phase protein synthesized from the liver in response to infection and inflammation, and inflammatory cytokines modulate fibrinogen biosynthesis[24]. Previous studies in patients with OSAS determined that elevated fibrinogen levels were related to obesity and the

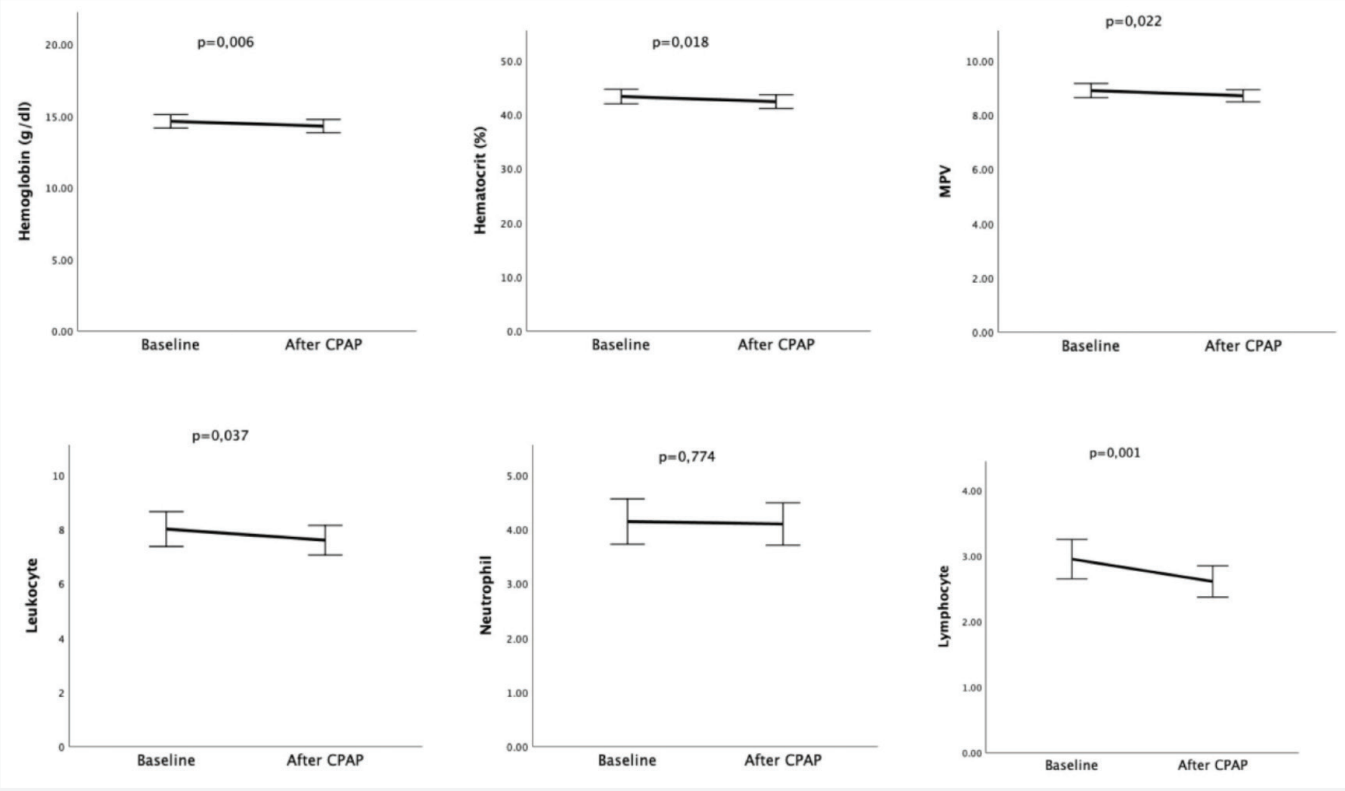

Figure 1. After three months of CPAP treatment, the mean levels of hemoglobin, hematocrit, MPV, leukocytes, neutrophils, and lymphocytes

MPV: Average volume of platelets, CPAP: Continuous positive airway pressure

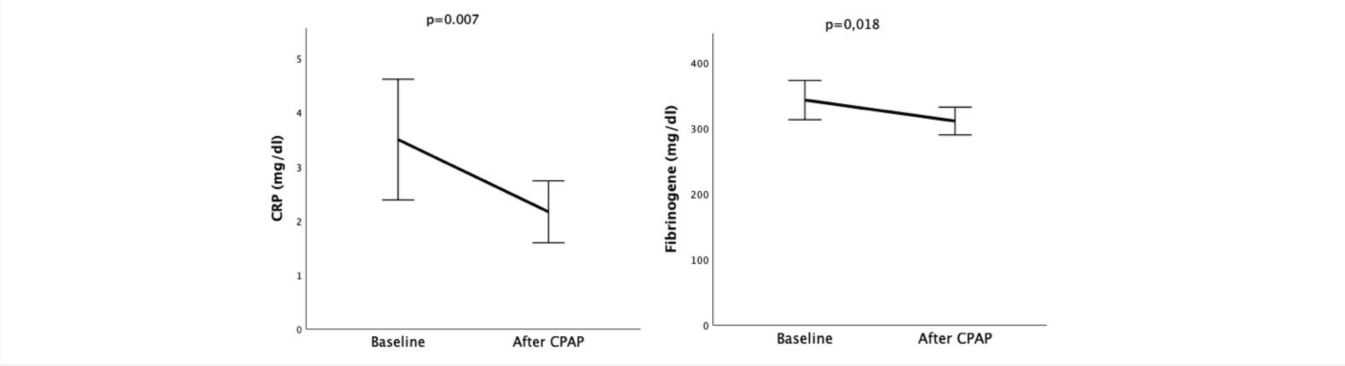

Figure 2. After three months of CPAP treatment, the mean levels of CRP and fibrinogen levels

CRP: C-reactive protein, CPAP: Continuous positive airway pressure

presence of comorbidities such as hypertension and stroke and were improved after CPAP treatment[25]. However, a recent randomized and placebo-controlled crossover trial of OSAS treatment with CPAP did not determine any significant treatment effects on elevated plasma fibrinogen levels[26]. There are inconsistencies between studies on the effect of CPAP therapy on fibrinogen levels in patients with OSAS. This may be because patients with cardiovascular diseases were not excluded from the study in some studies. Our results showed a significant decrease in fibrinogen levels after three months of CPAP treatment.

CRP is an acute-phase protein and plays an important role in innate immunity. It is a sensitive marker of inflammation and an important marker of future cardiovascular risk[27]. Previous studies have presented results, thus denoting the possible beneficial role of CPAP in reducing systemic inflammation and cardiovascular risk in OSAS patients[28-31]. This study also demonstrated that the appropriate use of CPAP therapy could significantly decrease the levels of CRP.

Study Limitations

Our study has some limitations. First, the study was retrospective. And then, our sample size was relatively small. Third, although some hematological indices were considered inflammatory markers, such as NLR and PLR, it was supposed to use classical established inflammatory markers like IL-6 as a reference for comparison during the detection process.

CONCLUSION

Hematological indices are comparatively simple, inexpensive, and practical severity markers of OSAS. Our study has established the importance of hematological evaluation as a complementary tool for diagnosis and treatment response in OSAS patients.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Tekirdağ Namık Kemal University Faculty of Medicine with the number: 2019.160.09.20 (date: 24.09.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.C.M., Concept: L.C.M., Design: L.C.M., Data Collection or Processing: M.Y., Analysis or Interpretation: L.C.M., Literature Search: M.Y., Writing: M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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