

## Effect of Continuous Positive Airway Pressure Treatment on Hemograms of Patients with Severe Obstructive Sleep Apnea in the Lack of Comorbidities

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Received date: April 13, 2017; Accepted date: April 22, 2017; Published date: April 26, 2017

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### Abstract

In this study, we aimed to evaluate the effect of CPAP treatment on hemograms of patients with severe OSA in the lack of comorbidities which might affect the real values of hematological parameters.

This retrospective cohort study patients selected from those whose polysomnography reports were compatible with severe OSAS and who underwent PAP titration in our sleep medicine department. 49 patients were enrolled to the study. The baseline hemograms of the participants were collected from one of the patients' visits before they started to use CPAP devices. The control hemograms were evaluated from one of the control visits in the first six months of treatment. We examined the red cell distribution width (RDW), mean platelet volume (MPV), hemotocrit (Hct) and platelet (Plt) count from the hemograms.

The mean age was 58.2 years  $\pm$  11.3 years, 38.8% were female and 61.2% were male. 69.4% were non-smokers and 30.6% were ex-smokers. The mean body mass index (BMI) was 31.6  $\pm$  5.8 while the mean apnea hypopnea index (AHI) was 50.2  $\pm$  29. The mean duration of CPAP therapy was 4.8 months  $\pm$  3.3 months. The mean RDW, MPV, Hct and Plt count values before CPAP treatment were in normal ranges of laboratory tests. All of the values reduced after CPAP therapy but only the decrease in MPV was statistically significant.

The reduced values supported that CPAP treatment helped to control hypercoagulability and prevented from cardiovascular disorders in OSAS. Hemogram may be a cheap and easily found laboratory test for monitoring the response to CPAP therapy.

**Keywords:** Continuous positive airway pressure; Hemograms; Severe obstructive sleep apnea

### Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of total or partial upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation and arousals from sleep. Intermittent hypoxemia, sympathetic nervous system hyperactivity, oxidative stress, vascular endothelial dysfunction and metabolic dysregulation cause the systemic inflammation that underlies OSAS and its complications. Cardiovascular disorders are the most important cause of morbidity and mortality in OSAS [1]. Hypercoagulability was reported to be associated with cardiovascular complications [2,3]. Mean platelet volume (MPV) indicates platelet activation but does not notice any specific disease [4]. It was found to be significantly higher in patients with severe OSAS [5]. MPV may increase in other diseases such as hypercholesterolemia, diabetes mellitus, hypertension, ischemic stroke, myocardial infarction and smoking [6-8]. Red blood cell distribution width (RDW) is a laboratory measure of size variability and heterogeneity of erythrocytes. Also RDW contributes to platelet activation [9]. In several studies the association between hematological parameters such as RDW, MPV and platelet distribution width (PDW) and OSAS severity has been investigated [10-13]. Since continuous positive airway pressure (CPAP) is accepted as the gold standard

therapy for OSAS, the effect of CPAP treatment on these hematological parameters in OSAS was demonstrated in some studies [14,15]. To our knowledge the comorbidities that might affect the real value of hematological parameters have not been excluded in these recent studies.

In this study, we aimed to evaluate the effect of CPAP treatment on hemograms of patients with severe OSA in the lack of comorbidities which might affect the real values of hematological parameters. In the other hand we tried to find out if a simple and a cheap test as hemogram could be used for monitoring the regular use of CPAP devices in severe OSA patients.

### Methods

This retrospective cohort study protocol was approved by the institutional review committee on clinical research of the Dokuz Eylul University Faculty of Medicine, Turkey. Patients selected from those whose polysomnography reports were compatible with severe OSAS (AHI>30) and who underwent PAP titration in our sleep medicine department. We used the polysomnography and CPAP titration reports which were scored according to the American Academy of Sleep Medicine (AASM). The major inclusion criteria for this study was using the CPAP device for >4 h/day and >5 days/week during at least 1 month. Patients who were non-smokers or ex-smokers for at least 12 months included. Patients with comorbidities such as hypertension, diabetes mellitus, hypercholesterolemia, hematological

diseases, chronic obstructive pulmonary disease and asthma were excluded. We reached the data of 94 severe OSA patients. 35 had several comorbidities. 7 were active smoker. 3 had to use antiagregans for a while. 49 patients were enrolled to the study. Hematological parameters of the patients were collected from the laboratory records of our hospital. The baseline hemograms of the participants were collected from one of the patients' visits before they started to use CPAP devices. The control hemograms of the subjects were evaluated from one of the control visits in the first six months of CPAP treatment. We examined the red cell distribution width (RDW), mean platelet volume (MPV), hemotocrit (Hct) and platelet (Plt) count from the hemograms. We called the patients one by one to be sure if they used their CPAP devices regularly and did not use any drugs such as acetyl salicylic acid, clopidogrel, dipiradamol, heparin, aminophylline, verapamil, nonsteroidal anti-inflammatory drugs, corticosteroids, furosemide, and antibiotics which may affect the platelet function.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 22 software package. All the values were calculated as the mean  $\pm$  standard deviation. We used paired sample t-test to compare the pre- and post-treatment data of the study group.

## Results

Of all the participants, the mean age was 58.2 years  $\pm$  11.3 years, 38.8% (n=19) were female and 61.2% (n=40) were male. 69.4% (n=34) were non-smokers and 30.6% (n=15) were ex-smokers. The mean pack years of cigarette smoking was 30.4  $\pm$  15.8 in ex-smokers. The mean body mass index (BMI) was 31.6  $\pm$  5.8 while the mean apnea hypopnea index (AHI) was 50.2  $\pm$  29.1 and the mean minimum oxygen saturation (Min. SpO<sub>2</sub>) was 74.2  $\pm$  9.8. The mean duration of CPAP therapy was 4.8 months  $\pm$  3.3 months. Demographic and polisomnographic characteristics of the patients are summarized in Table 1.

Variables	n=49 (%)
Age, years (mean $\pm$ SD)	58.2 $\pm$ 11.3
Gender	
Female	19 (38.8)
Male	30 (61.2)
BMI, kg/m <sup>2</sup> (mean $\pm$ SD)	31.6 $\pm$ 5.8
Non-smoker	34 (69.4)
Ex-smoker	15 (30.6)
Pack years of cigarette smoking (mean $\pm$ SD)	30.4 $\pm$ 15.8
AHI, event/h (mean $\pm$ SD)	50.2 $\pm$ 29.1
Lowest SpO <sub>2</sub> , % (mean $\pm$ SD)	74.2 $\pm$ 9.8
Duration of CPAP therapy, months (mean $\pm$ SD)	5.8 $\pm$ 3.3
SD: standard deviation; BMI: body mass index; AHI: apnea hypopnea index; Lowest SpO <sub>2</sub> : minimum oxygen saturation	

**Table 1:** Demographic and polisomnographic characteristics of patients.

The mean RDW, MPV, Hct and Plt count values before CPAP treatment were in normal ranges of laboratory tests. As known, normal range values of Hct between female and male are declared differently in hemograms. Mean Hct values were 39.7%  $\pm$  5.6% (36% to 46%) in female, 41.9%  $\pm$  3.7% (41% to 53%) in male. The mean Hct and Plt values did not show any significant change after CPAP treatment (p>0.05). Normal range values of RDW (11.8% to 14.3 %), MPV (6.9fl to 10.8 fl) and Plt (15610<sup>3</sup>/ $\mu$ l to 373 10<sup>3</sup>/ $\mu$ l) were the same for female and male. Of all patients the mean RDW and MPV values were 14.6%  $\pm$  1.5%, 9.15 fl  $\pm$  1.2 fl before CPAP while the mean RDW and MPV values were 14.4%  $\pm$  1.6%, 8.9 fl  $\pm$  1.3 fl after CPAP. Mean RDW, MPV, Hct and Plt count values reduced after CPAP therapy but only the decrease in MPV was statistically significant (p<0.05). Results of comparison of patients' hematological parameters before and after CPAP treatment are presented in Table 2.

	Before CPAP	After CPAP	p
RDW, % (mean $\pm$ SD)	14.6 $\pm$ 1.5	14.4 $\pm$ 1.6	0.37
MPV, fl (mean $\pm$ SD)	9.15 $\pm$ 1.2	8.9 $\pm$ 1.3	0.02
Hct, % (mean $\pm$ SD)	41.4 $\pm$ 4.5	41.3 $\pm$ 4.2	0.35
Plt count, 10 <sup>3</sup> / $\mu$ l (mean $\pm$ SD)	243.8 $\pm$ 56.8	241.8 $\pm$ 65.4	0.76
CPAP: continuous positive airway pressure; RDW: red cell distribution width; SD: standard deviation, MPV: mean platelet volume; Hct: hemotocrit; Plt: platelet			

**Table 2:** Hematological data of patients before and after CPAP.

## Discussion

In this study, the hematological parameters related to hypercoagulability such as RDW, MPV, Hct and Plt of severe OSA patients without any comorbidity were in normal range values before CPAP treatment. We demonstrated that RDW, MPV (p: 0.02), Hct and Plt count parameters reduced in the first 6 months of CPAP therapy. The reduced values supported that CPAP treatment helped to control hypercoagulability and prevented from cardiovascular disorders in OSAS.

The importance of sleep to health and cardiovascular disease is well known. In several studies it has been shown that repetitive episodes of hypoxia and reoxygenation during sleep provoked platelet activation and/or systemic inflammation and platelet activation might lead to hypercoagulability and cardiovascular disease in OSAS [10,16-19]. Platelets with high volume are metabolically and enzymatically more active and secrete more mediators [20,21]. Varol et al. [5] reported an increase in MPV levels of OSA patients and Erden et al. [13] claimed a positive correlation between MPV and AHI. But Kurt et al. [10] did not find any correlation between MPV and the severity of OSAS. It has been shown that smoking activated platelet function [22]. Also Topcuoglu et al. [23] showed that MPV did not indicate OSAS severity in the absence of comorbidities. Similarly, we did not find an abnormality in the mean MPV of our severe OSA patients without any comorbidity which were claimed to affect platelet activation.

Oxidative stress and inflammation were shown to be linked to RDW [24]. Inflammation is related to ineffective erythropoiesis. Inflammatory cytokine production desensitizes bone marrow erythroid progenitors to erythropoiesis, inhibits red blood cell maturation and promotes anisocytosis [25]. Several studies tried to explain the

association between RDW and the severity of inflammatory diseases such as cardiovascular and pulmonary diseases [26,27]. Ozsu et al. [11] demonstrated that RDW values of OSA patients were higher than controls and they found an association between RDW and severity of OSAS. They reported that RDW associated with cardiovascular disorders in OSA patients. However, Kurt and Yildiz [10] did not show any correlation between RDW and AHI. The mean RDW of our severe OSA patients without comorbidities was in the normal range value before treatment. Our finding supports that the RDW levels increase in the OSA patients with cardiovascular disorders.

Saygin et al. [28] found a significant increase in Plt count with the severity of OSAS. In their study the Plt value correlated with AHI in the patients <40 years old with cardiovascular disease and in the patients  $\geq$  40 years old without cardiovascular comorbidities. Their patients with cardiovascular diseases had higher hematocrit correlated with the severity of OSAS. Hct is expressed as the per cent of a blood sample occupied by intact red blood cell. It affects blood viscosity and platelet aggregation.

Hct may be an indicator of inflammation and oxidative stress in OSAS. Karakas et al. [29] did not find any correlations between AHI and Hct. But the mechanisms of Plt activation in patients with OSAS may be the chronic intermittent hypoxia and high levels of catecholamines which is a result of sympathetic activity [30-32]. Minogluchi et al. [33] reported that the levels of sCD40L and sP-selectin which were known as Plt activation markers increased in patients with moderate and severe OSAS. Hui et al. [19] found a positive correlation between Plt and AHI. The mean values of Hct and Plt count were in normal range in our severe OSA patients. These results might change if they have been compared with a healthy control group. This was one of the limitations of our study.

CPAP therapy is still the most effective treatment for patients with OSAS. CPAP relieves airway obstruction and reduces hypoxia and inflammation [34]. CPAP treatment decreases platelet aggregability [35]. Several studies demonstrated the increase in blood viscosity before and the decrease after CPAP treatment [36,37]. Varol et al. [38] showed that 6 months of CPAP therapy reduced MPV values of severe OSA patients but they found platelet counts higher than baseline. Sokucu et al. [14] reported that 6 months of CPAP therapy significantly decreased MPV value but increased RDW. Feliciano et al. [39] showed that RDW significantly decreased after PAP treatment. We also found a decrease in the mean RDW value of our patients after treatment. Sokucu et al. [14] did not find any significant difference in platelet count between OSA group and controls after 6 months of CPAP treatment. Feliciano et al. [39] also reported a significant decrease in platelet count of 48 male OSA patients (18 mild, 5 moderate, 25 severe) after 6 months of CPAP therapy. Similar to Feliciano et al. the mean platelet count value of our study patients decreased after CPAP treatment but this was not statistically significant. The severity of OSAS is associated with increased Hct but it does not present as polycythemia [40]. Khan et al. [41] showed a significant increase in Hct after 1 year of CPAP therapy in elderly OSA patients. Their claim was that hypoxic stimulation of erythropoiesis might obscure anemia of aging in OSA patients over 65 years, and CPAP treatment restored this anemia. In our patient's average age 58.2, Hct values decreased in the first 6 months of CPAP treatment but it was not at the anemia limit.

There are some limitations of our study such as small sample size and the lack of control group. It was a retrospective study and we observed the hemograms that were analyzed in the first 6 months visit

after CPAP treatment initiation. We standardized the CPAP treatment period at least 1 month.

## Conclusion

The reductions in both MPV and blood viscosity with CPAP may protect from cardiovascular complications associated with OSAS. Hemogram may be a cheap and easily found laboratory test for monitoring the response to CPAP therapy of OSA patients. Further prospective cohort studies with large sample sizes will help to use hemograms in routine controls for CPAP therapy compliance.

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