



## CLINICAL STUDY

# ERITROPOİETİN, HEMATOCRİT SEVİYELERİ VE KIRMIZI KAN HÜCRELERİ SAYILARININ PEDIATRİK OBSTRÜKTİF UYKU APNE HASTALARINDA İNCELENMESİ

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### SUMMARY

**Objective:** We aimed to identify a biochemical marker which can be important for obstructive pathologies creating an important indication for adenotonsillectomy.

**Material and Methods:** A total of 35 patients who had adenotonsillectomy operation with the diagnosis of obstructive adenotonsillar hypertrophy were compared with 35 control patients who had various surgeries for different reasons in terms of blood erythropoietin, hematocrit level and red blood cell count.

**Results:** While mean of erythropoietin values of the study group was 9.46±4.2 mU/ml, this value was found to be 8.92±3.6 mU/ml in the control group. Hematocrit levels and erythrocyte counts of the patients in the study and control groups were very close to each other. It was seen that the differences were not statistically significant when the groups were compared via independent samples T-test.

**Conclusion and Significance:** Even though it is not statistically significant, we believe that higher level of erythropoietin in the study group compared to the control group requires similar studies to be conducted on this subject with groups including larger number of patients and by creating sub-groups.

**Keywords:** Sleep apnea, Erythropoietin, hematocrit, pediatric

### PEDIATRİK OBSTRÜKTİF UYKU APNE HASTALARINDA ERİTROPOİETİN, HEMATOKRİT DÜZEYLERİ VE ERİTROSİT SAYILARININ İNCELENMESİ

#### ÖZET

**Amaç:** Bu çalışmada adenotonsillektomi için önemli bir endikasyon oluşturan tıkaçıcı patolojiler ile ilgili biyokimyasal bir belirtecin bulunması amaçlanmıştır.

**Gereç ve Yöntemler:** Tıkaçıcı adenotonsil hipertrofisi tanısı ile adenotonsillektomi operasyonu yapılan toplamda 35 hasta ile başka sebeplerle farklı cerrahiler geçiren 35 kontrol hastası kan eritropoietin, hematokrit düzeyleri ve eritrosit sayıları açısından karşılaştırıldı.

**Bulgular:** Çalışma grubuna ait eritropoietin değerlerinin ortalaması 9.46±4.2 mU/ml iken, bu değer kontrol grubunda 8.92±3.6 mU/ml olarak tespit edildi. Çalışma ve kontrol grubundaki hastalara ait hematokrit düzeyleri ve eritrosit sayıları ise birbirine yakın değerlerde idi. Bağımsız örneklem T test ile gruplar karşılaştırıldığında aradaki farkların istatistiksel anlam ifade etmediği görüldü.

**Sonuç:** İstatistiksel anlam ifade etmese de çalışma grubundaki eritropoietin seviyelerinin kontrol grubuna göre daha yüksek bulunmuş olmasının konuyla ilgili daha fazla sayıda hasta içeren gruplarla benzer çalışmaların yapılmasını gerekli kıldığı düşüncesindeyiz.

**Anahtar Sözcükler:** Uyku apne, eritropoietin, hematokrit, pediatrik

## INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is seen in childhood age group at the rate of 1-5%. It is known that the most common cause of OSA is adenotonsillar hypertrophy in pediatric age group<sup>1,2</sup>. Having a clinical spectrum from nocturnal snoring to serious apnea attacks is an

important health problem of pediatric group that may cause diseases such as growth failure, pulmonary hypertension and neurocognitive deficits such as poor learning, behavioral problems and attention deficit-hyperactive disorders. Therefore, adenotonsillectomy surgery is one of the most common surgical indications in pediatric group. Although the complaints described by the patient relatives or patients are considered in terms of deciding on surgical indication for recurrent tonsillitis and chronic tonsillitis, we believe that identification of a biochemical marker can be important for a clinician in terms of hypoxic symptoms of obstructive pathology in addition to endoscopic

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examination for obstructive pathologies creating an important indication for adenotonsillectomy.

Erythropoietin is a glycoprotein released from kidneys as a response to hypoxia<sup>3</sup>. It is known that erythropoietin, a growth hormone, increases vascular resistance<sup>4</sup>, tissue renin and angiotensin 2 receptor mRNA expression<sup>5</sup>, endothelin 1 production and swing<sup>6</sup>, angiogenesis<sup>7</sup>. Even though it is mostly known for stimulating reproduction of erythroid stem cell in bone marrow, it is considered that it also appears in etiology of cardiovascular diseases in recent years according to the literature<sup>8</sup>. In some studies, conducted with patients having adult sleep apnea syndrome it has been noted that serum erythropoietin levels increased, and this level was normalized by CPAP treatment<sup>9</sup>. However, it has been seen in the literature review that the relationship between pediatric age group OSA syndrome and erythropoietin has not been examined before.

In addition, the fact that hypoxia increases erythroid count and hematocrit level in the studies conducted by adult age group is presented by the existing literature<sup>10</sup>. As seen in the studies regarding erythropoietin, it has been found that serum hematocrit levels increased, and these levels were normalized by CPAP treatment with adult sleep apnea syndrome patients as well<sup>11</sup>. This parameter has not been studied in the patient group having adenotonsillar hypertrophy which is one of the significant causes of OSA in pediatric age group even though it has been studied in adult group for various times.

Determination of erythropoietin levels, hematocrit values and erythrocyte count in the patient group who had adenotonsillectomy due to upper respiratory tract obstruction complaints and whether these values can be indicators for obstructive pathologies in pediatric cases were examined in this study. Our study has the feature of being the first in the literature with these characteristics.

## MATERIAL and METHODS

In this mono-center prospective study, a total of 35 patients who had adenotonsillectomy operation with obstructive adenotonsillar hypertrophy diagnosis were compared in terms

of blood erythropoietin, hematocrit level and erythrocyte count, which are indicators of hypoxia, with 35 control patients who had various surgeries for different reasons. The research protocol was approved by the SAKARYA University Ethics Committee and performed in accordance with the ethical regulations of the Declaration of Helsinki and Turkish law and regulations. Informed consent was obtained from all individual participants included in the study.

The study group included the patients for whom adenotonsillectomy was planned. Blood samples were drawn from all the patients for analysis between 8 and 9 o'clock in the morning. The control group was selected among the patients whose operations were planned because of different indications and did not have any obstructive complaint. Similarly, with the study group, blood samples for analysis purposes were drawn from these patients between 8 and 9 o'clock in the morning of operations.

The patients who had adenoid smaller than grade 3 or tonsil hypertrophy, pulmonary, cardiovascular, ischemic and renal diseases potentially causing an increase in erythropoietin level, the patients who described obstructive sleeping problem in the control group were not included in the study. Unless the approval of the patients or patient relatives was received, those patients were excluded from the study.

The obtained blood samples were taken into anticoagulant-free tubes to be studied EPO and were sent to the laboratory after being centrifuged. The EPO was measured by automated immunochemiluminometric assay using a commercially available kit (Nichols Institute Diagnostics, San Juan Capistrano, CA). The erythrocyte counts, and hematocrit levels were determined from the blood samples taken into the tubes consisting EDTA by means of Cell-Dyn 3700 SL device.

Statistical analysis was performed using IBM SPSS version 20.0 for Windows statistical software (IBM Corporation, Armonk, New York, USA). Continuous variables were expressed as mean  $\pm$  standard deviation and median (25th-75th percentile), and categorical variables were expressed in percentage. For distribution



normality analyses, Kolmogorov-Smirnov analysis was performed and skewness and kurtosis levels were determined. As a result of these measurements parametric tests were preferred for statistical analysis. Independent samples T test was used for the pairwise comparisons between groups. Chi-square test was used for the comparison of the categorical variables. P values less than 0.05 were accepted as significant.

## RESULTS

The patients in the study group consisted of 19 (54.3%) boys and 16 (45.7%) girls. The mean age was  $5.5 \pm 1.5$ . In control group, there were 12 boys (34.3%) and 23 (65.7%) girls and mean age was  $6.3 \pm 1.9$ . When the groups were compared in terms of gender and mean age through Chi-square and independent samples T-test respectively, it was seen that there was not any statistical difference between two groups and it was considered that the groups were comparable with these data ( $p > 0.05$ ).

All the patients in the study group had witnessed apnea attack and were at least grade 3 adenoid and tonsil hypertrophies in oropharynx and endoscopic nasopharynx examinations. Existence of apnea attack was determined in all the patients by means of video records. The patients in control group consisted of the patients

who were operated with various indications such as ventilation tube placement, inguinal herniation and who did not have obstructive pathology.

While the mean erythropoietin value of study group was  $9.46 \pm 4.2$  mU/ml, this value was found to be  $8.92 \pm 3.6$  mU/ml in the control group. It has been seen that there was no statistically significant between the groups when compared by independent samples T-test ( $p > 0.05$ ).

The patients in both study and control groups had hematocrit levels and erythrocyte count in normal limits. While mean of hematocrit levels of study group was  $38.1\% \pm 2.2$ , this value was found to be  $38.6\% \pm 2.6$  in the control group. When the groups were compared in terms of hematocrit values via independent samples T-test, it was seen that the difference was not statistically significant ( $p > 0.05$ ). While mean erythrocyte count of the study group was  $4.86 \pm 0.4$   $10^6$ /ml, this value was found to be  $4.9 \pm 0.5$   $10^6$ /ml in the control group. When the groups were compared in terms of erythrocyte count via independent samples T-test, it was seen that the difference was not statistically significant ( $p > 0.05$ ). The results of the measurements were summarized in Table 1.

**Table1:** Results of the measurements.

	Study group	Control group
<b>Eritropoietin</b>	$9.46 \pm 4.2$ mU/ml	$8.92 \pm 3.6$ mU/ml
<b>Hematocrit value</b>	$38.1\% \pm 2.2$	$38.6\% \pm 2.6$
<b>Erythrocyte count</b>	$4.86 \pm 0.4$ $10^6$ /ml	$4.9 \pm 0.5$ $10^6$ /ml

## DISCUSSION

There are various studies showing that pediatric age group OSA disease which may cause various neurophysiological complaints such as day time somnolence, learning disability, attention deficit and hyperactivity disorder in addition to nocturnal snoring and apnea

complaints can also cause some serious complications such as growth failure, cardiovascular diseases and pulmonary hypertension and can be rehabilitated after adenotonsillectomy<sup>1,2,12,13</sup>. Therefore, it is clinically crucial to have early diagnosis of the disease affecting pediatric age group in terms of different aspects before the complications.



Although adenotonsillar hypertrophy can be easily diagnosed clinically by oropharynx and endoscopic nasopharynx examinations, it is important, especially for the cases where liminal hypertrophy occurs, to determine whether the pathology causing obstruction causes hypoxia symptom. Despite the fact that the necessity of polysomnography is accepted for the diagnosis of the pediatric OSA disease according to the suggestion of American Academy of Pediatrics, it is only recommended for a limited population by a great number of authors due to the adaptation problems to a test performed by placing a lot of sensors to the body for pediatric age group and the different criterion in the assessment of test results<sup>14,15</sup>. Hence, it has been considered that it would be clinically beneficial to find a simpler and quicker indicator on this matter.

It has been stated in the literature that erythropoietin, produced as a response to hypoxia, can be used in the diagnosis and even in the follow-up phase of the treatment for adult OSA patients<sup>16</sup>. However, its use in pediatric age group was examined for the first time in our study. The recommended blood-collection period for analyzing the erythropoietin levels being in a circadian rhythm even though their certain mechanism was not identified, was between 7:30 on 12:00 in the morning<sup>17</sup>. The samples were taken by considering this circadian rhyme in our study. In the presented study, it was seen that there was not a statistically significant difference when two groups including similar individuals in terms of age and gender were compared by their EPO values. However, it was seen that the values of the study group were higher when the data were compared numerically. Therefore, it was considered that statistical significance might occur in the studies which would be performed with larger populations.

It is known that hematocrit levels, another indicator of hypoxemic cases, are high in the people living in high-altitude places. It has been considered by different authors that it can be observed as a symptom in OSA being a disease progressing with recurrent transient hypoxic attacks during sleep. A positive correlation was found between OSA and high hematocrit levels when these values were

examined in adult OSA patients even though its statistical significance was limited<sup>9,18</sup>. However, a study specifically examining the pediatric OSA patients and hematocrit levels could not be found when the existing literature was reviewed. When the data of our study were analyzed, a statistically significant difference was not found between hematocrit level and pediatric OSA. However, we think that; this result might be a process specific to pediatric age group and different results can be found in further researches by creating groups with more limited age ranges.

EPO is a glycoprotein hormone at the weight of 30.4 kDa and produced mostly from kidneys and livers. Its essential duty is to provide the regulation of blood oxygen level by enabling erythrocyte proliferation. In addition to these effects, it has adverse effects on cardiovascular system especially with its direct vasopressor effect<sup>19</sup>. It has been showed in the studies including the adults that the OSA patients having cardiovascular diseases have higher EPO values<sup>3</sup>. Our study has some limitations as it is the first study about the subject; on the other hand, high EPO values of study group, even though they are not statistically significant, can be a guide for further researches such as examination of EPO value in special groups such as children who have cardiovascular system disease findings like pulmonary HT.

## CONCLUSION

Even though it was not statistically significant, EPO values were found to be higher in the study group compared to the control group in our study. Group numbers could not be kept larger because of the ethical reasons as this was the first study in the pediatric age group about the subject. For this reason, we believe that it would be beneficial to carry out similar studies with groups including larger number of patients and creating special sub-groups both for making surgical decision and for understanding the pathophysiological processes in pediatric OSA patients.

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