

Research Article



The Effect of Continuous Positive Airway Pressure Therapy on Obese Children with Stable Asthma

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Received: 21 July 2018

Accepted: 19 October 2018

Version of Record Online: 13 November 2018

Citation

Jalou HE, Givan DC, Wiebke J, Slaven JE, Bendy L, et al. (2018) The Effect of Continuous Positive Airway Pressure Therapy on Obese Children with Stable Asthma. J Pulmonol Stud Treat 2018(1): 03-08.

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Abstract

Study objectives: Continuous Positive Airway Pressure (CPAP) therapy is prescribed for children with Obstructive Sleep Apnea (OSA). We hypothesized that using CPAP in obese children with stable asthma and mild OSA will improve their quality of sleep, day time functioning, and asthma control.

Design: Obese children (BMI > 95thtile) with stable asthma and mild OSA were recruited following an overnight polysomnogram. Subjects were randomized to CPAP (8-10 cm H₂O) or Sham (0-1cm H₂O) treatment for 4 weeks. Modified Berlin sleep questionnaire and Asthma Control Test (ACT) were completed pre and post treatment, and CPAP diaries were maintained. Patients were classified into High or Low Risk based upon the Berlin questionnaire. A subscale score for the Berlin questionnaire was employed: a score of 0-4 for snoring, witnessed apnea, fatigue, and day time sleepiness to determine their frequency and severity. Outcomes were analyzed by the post-pretreatment values, with post scores lower than pretreatment indicating improvement.

Setting: The Power Program (Obesity Clinic) and the Pediatric Sleep Clinic at Riley Hospital for Children at Indiana University.

Patients or participants

Interventions: CPAP therapy and sham-CPAP

Measurements and results: Seventeen children 8-17 years old were evaluated; 9 treated with CPAP and 8 with Sham-CPAP. There were no significant differences in demographics or Berlin score between the two groups; however, the CPAP compared to Sham group tended to have lower ACT scores or worse asthma control (p<0.07) at baseline. There was a significant improvement in daytime fatigue for CPAP versus Sham group (p<0.05). There was significantly greater improvement in ACT score for CPAP than Sham group (p<0.01).

Conclusion: Our study demonstrated that 4-weeks of CPAP in obese children with mild OSA and asthma improved daytime fatigue and ACT compared to Sham with a trend for daytime sleepiness in the CPAP group (Table 2).

Keywords

Continuous Positive Airway Pressure; Polysomnography; Sham-CPAP

Abbreviations

ACT	:	Asthma Control Test
AHI	:	Apnea-Hypopnea Index
CPAP	:	Continuous Positive Airway Pressure
OSA	:	Obstructive Sleep Apnea
PSG	:	Polysomnogram

Introduction

The epidemic of childhood obesity and its consequence on physical and psychological wellbeing is an area of great concern [1]. The effects of obesity on the control of breathing, pulmonary mechanics and gas exchange can lead to significant health issues such as Obstructive Sleep Apnea (OSA) [2]. The prevalence of OSA approaches 60% in obese children with a history of snoring, compared to 1-2% in non-obese otherwise healthy children and the prevalence of OSA is 4-6 times higher in obese children and adolescents than non-obese children with increased risk for poor sleep quality in addition to insulin resistance and cardio-metabolic risk [3,4]. Obesity is also a risk factor for developing asthma, with a recent national survey of children showing a 3% increase risk of asthma in obese children compared to their non-obese peers [5,6]. Obese children also report poor sleep quality with short sleep time and sleep disturbances [7]. The constellation of these nocturnal symptoms can lead to daytime dysfunction including daytime sleepiness, poor school performance, and mood disorders [8].

The presence of OSA is characterized by the complete or partial cessation or reduction of airflow during sleep, which can lead to sleep fragmentation and excessive daytime sleepiness or other impairment in daytime functioning. The severity of sleep apnea is usually determined by the Apnea Hypopnea Index (AHI) [3], which is a calculated value of the complete obstructive and partial obstructive (Hypopnea) events per hour during sleep. Continuous Positive Airway Pressure (CPAP) therapy is the mainstay to treat OSA in adult and pediatric patients who have residual OSA post adenotonsillectomy or have contraindication for surgical intervention. CPAP therapy has been found to decrease daytime sleepiness and to enhance quality of life in adults [9]. However, initiating CPAP therapy for OSA in children is based upon the adult criteria of AHI severity (AHI > 5 per hour), which may not be appropriate for children. Mild OSA has been associated with sleep disruptions in addition to impaired executive cognitive function in children [10,11]. In addition to the potential benefit of CPAP for OSA, several studies in adults with asthma have reported that CPAP reduced asthma symptoms or airway reactivity [12-16]. Studies have also found that CPAP therapy improves neurobehavioral outcomes in children with OSA [17]. Therefore, CPAP might not only improve OSA, but also provide a non-pharmacologic treatment of asthma.

The goal of the current study was to evaluate the effects of CPAP therapy on asthma control, sleep quality and daytime function in obese children with mild OSA and clinically stable asthma by comparing 4 weeks of CPAP therapy vs. Sham-CPAP.

Methods

Subjects

CPAP-naïve subjects with a history of stable and controlled asthma (defined as no recent exacerbation in the last one year and systemic steroid in one year) and obesity (defined as BMI > 95th) were recruited from the pediatric obesity clinic and the pediatric pulmonary and sleep medicine clinic at James Whitcomb Riley Hospital for Children [1,18]. Obese children with clinically stable asthma who underwent an overnight Polysomnogram (PSG) for clinical purposes. Their PSG was consistent with mild sleep apnea with an AHI <5 per hour, subsequently; they were enrolled for the study. The study was approved by the Indiana University Institutional Review Board. Informed consent was obtained from the parents and assent was obtained from subjects. Exclusion criteria included a known history of cyanotic congenital heart disease, chronic lung disease, any respiratory symptoms within 4 weeks prior to testing, escalation in asthma medication at time of recruitment, inability to perform pulmonary function testing, pulse oximetry oxygen saturation less than 90% while awake breathing room air, and a baseline forced expiratory flow in one second (FEV₁) <75% predicted.

Treatment

Subjects were randomized to CPAP (8-10 cm H₂O) or Sham (0-1 cm H₂O) treatment for 4 weeks. No overnight PSG was utilized to determine the level of CPAP pressure, pressures were the pressures used empirically given the patient age and weight. Randomization was performed by assigning a random numbers from 1-17 alternating between the treatment and sham subjects. No PSG for CPAP titration was obtained. CPAP pressures were used empirically. Sham-CPAP was a circuit with a leak to minimize CPAP [19,20]. Within one week of initiating treatment, subjects were contacted by telephone to assure tolerance and adherence to the mask and treatment. For both the CPAP and the Sham treatment groups, the parents or subjects older than 12 years of age completed a sleep diary for CPAP or Sham-CPAP use.

During the first visit the parents completed the pediatric modified Berlin sleep questionnaire which consists of three categories related to the risk of having sleep apnea: severity of snoring, daytime symptoms and obesity or hypertension [21]. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories. We developed a subscale score for the Berlin questionnaire, with a score of 0-4

for each symptom of witnessed apnea, fatigue, and daytime sleepiness to determine their frequency and severity. A score of (0) for no symptoms, score of (1) for a symptom 1-2 times per month, score of (2) for a symptoms of 1-2 times per week, score of (3) for a symptom of 3-4 times per week, and score of (4) for daily recurrence of the symptoms. These scores were utilized for evaluating the degree of fatigue, witnessed apnea, and daytime sleepiness. Similarly, we used a score of (0) for no snoring, score of (1) for louder than breathing, score of (2) for as loud as talking, score of (3) for louder than talking and score of (4) for very loud snoring. The parents or subjects (if 12 years or older) also completed the Asthma Control Test (ACT), which is a multi-question test (5 for adolescent and 7 for children less than 12 year-old) that measures the degree of asthma control [22]. The higher the ACT score reflects the better control of the asthma. After completing the 4 weeks of CPAP therapy or Sham treatment, a repeat of the Berlin sleep questionnaires and the ACT were obtained.

Statistical analysis

Data were analyzed to determine if differences existed between treatment groups at baseline and at follow-up. Follow-up outcomes were analyzed by looking at the change over time, as calculated by taking the difference between the follow-up and baseline outcomes. Berlin sub-scales were considered to have

improved if the follow-up outcome had a lower score than the baseline. These outcomes were then analyzed using the Wilcoxon non-parametric rank-sum test for continuous variables, due to the data having a non-Normal/skewed distribution, and with Fisher's Exact test for categorical variables, due to low cell counts. Analyses were also performed adjusting for baseline values if there were significant differences between treatment groups at baseline. Data were analyzed for outliers to determine if any should be excluded. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

Seventeen subjects between 8-17 years of age were evaluated, nine were treated with CPAP and eight were treated with Sham. There were no significant differences in age, gender, BMI, AHI or ACT between the two groups of subjects (Table 1) at study entry, although the CPAP group had a marginally, although non-significant, lower ACT score compared to the Sham treated group (19.6 ± 4.1 vs. 23.1 ± 2.7 ; $p=0.0701$). There were no significant differences in Berlin sub-scales scores at entry to the study (Table 2). Most participants (16/17; 94%), regardless of treatment group, had positive Berlin scales with high risk outcome for OSA at study entry. The improvement with treatment (Post-Pre) in the Berlin score, and its components,

	CPAP (n=9)	Sham (n=8)	p-value
Age	11.11 (2.62); 10 (8, 15)	11.43 (4.39); 8 (8, 17)	0.6725
BMI	33.72 (9.09); 32.2 (24.9, 48.3)	32.74 (8.67); 34.1 (20.6, 43.1)	0.9622
Gender* (female)	6 (66.7%)	5 (62.5%)	1.0000
ACT	19.56 (4.10); 19 (13 - 27)	23.13 (2.70); 23.5 (19 - 27)	0.0701
AHI	1.63 (1.76); 0.8 (0, 4.5)	2.00 (1.84); 1.5 (0, 4.5)	0.6695
AHI REM	4.43 (8.67); 0.9 (0, 26.4)	3.73 (5.11); 0.8 (0, 12.1)	1.0000
AHI >*	4 (44.4%)	5 (62.5%)	0.6372

Table 1: Demographics at Entry to the Study.

[Values are mean (standard deviation); median (range) for continuous variables and frequency (percentage) for categorical variables (*). P-values are from Wilcoxon non-parametric tests and Fisher's Exact tests, respectively.]

Berlin subscale	CPAP (n=9)	Sham (n=8)	p-value
Snoring	1.78 (1.30); 1 (1-4)	1.75 (0.89); 1.5 (1-3)	0.7902
Witnessed Apnea	0.78 (1.39); 0 (0-4)	0.75 (1.04); 0 (0-2)	0.9110
Daytime Fatigue	3.56 (0.88); 4 (2-4)	3.25 (1.16); 4 (1-4)	0.5574
Daytime Sleepiness	1.00 (1.22); 0 (0-3)	0.88 (1.46); 0 (0-4)	0.7895

Table 2: Comparison of Berlin scores at Entry to the Study.

[Values are variables at baseline, presented as mean (standard deviation); median (range) for continuous variables. P-values are from Wilcoxon non-parametric test.]

as well as the change in the ACT score are summarized in table 3. There was a significant decrease in daytime fatigue for the CPAP compared to Sham treated group (88.9% vs. 37.5% improvement; $p=0.0498$). In addition, there was a significant difference in the change of the ACT scores between the CPAP and Sham treatment groups; the CPAP group had a greater increase in ACT score, indicating a greater improvement in asthma control (3.0 ± 2.6 vs. -1.1 ± 2.0 ; $p=0.0102$). Although the CPAP treated group tended to have lower initial ACT scores, the effect of CPAP on the improvement in ACT score remained significant even after adjusting for baseline ACT scores (2.26 ± 1.96 vs. -0.29 ± 1.95 ; $p=.0242$).

children may lead to underutilization of the use of CPAP in treating pediatric obstructive sleep apnea.

Obese children have an increased incidence of asthma; however, the mechanisms remain unclear [27]. Obesity associated asthma may be related to altered mechanical properties of the lung, as decreased lung volume and reduced stretch of airway smooth muscle can increase airway reactivity [28,29]. CPAP can potentially suppress airway reactivity by increasing lung volume and increasing stretch of the airways and airway smooth muscle, as previously demonstrated in isolated tissues, *in vivo* animal models, and adults with asthma [16,30-32]. Inflammation

	CPAP (n=9)	Sham (n=8)	p-value
Snoring *	5 (55.6%)	1 (12.5%)	0.1312
Witnessed Apnea*	3 (33.3%)	1 (12.5%)	0.5765
Daytime Fatigue *	8 (88.9%)	3 (37.5%)	0.0498*
Decreased Daytime Sleepiness*	4 (44.4%)	2 (25.0%)	0.6199
ACT	3.00 (2.60); 3 (-1, 7)	-1.13 (2.03); 1 (-4, 1)	0.0102*

Table 3: Improvement in Berlin and Change in ACT scores.

[The categorical variables (*) reflect the frequency of participants who improved in the Berlin or Berlin sub-scales, with P-values from Fisher’s Exact Test. The continuous ACT variable is the change in ACT from baseline to follow-up, calculated as follow-up minus baseline, so a positive value indicates larger outcomes at follow-up (which indicates an improvement); these data are represented by mean (standard deviation) in first row and median (range) in second row with p-value from Wilcoxon non-parametric test].

Discussion

Our study demonstrated that use of CPAP therapy for one month by obese children with mild OSA and clinically stable asthma revealed a greater improvement in daytime fatigue and sleepiness compared to Sham treated subjects. This finding is significant as these obese children did not qualify for CPAP treatment based upon the currently employed adult criteria to initiate therapy ($AHI > 5$). In addition, our obese subjects with clinically stable asthma demonstrated a greater improvement in their asthma control with CPAP compared to Sham treatment. This finding suggests the potential benefit of CPAP as a non-pharmacologic treatment for obese children with asthma, in addition to treatment of OSA.

The primary use of CPAP is to treat Obstructive Sleep Apnea (OSA), however, several studies have demonstrated that in addition to the effect of CPAP therapy on sleep apnea, CPAP treatment can improve subjective daytime functioning and performance in cognitive tests [23-26]. While these previous studies demonstrated improvement in daytime cognitive function in patients with severe OSA using CPAP for at least 3-6 weeks and up to three months. Our study found improvement in daytime functioning in obese children with mild OSA using CPAP for only one month. These findings suggest that applying the adult criteria to initiate CPAP treatment in obese

is an important component of asthma, as well as obesity [33], and CPAP therapy could potentially minimize airway inflammation by minimizing snoring and mild upper airway obstruction, which may be a chronic irritant of the airways [34]. CPAP treatment may also have additional systemic effects, as it has been demonstrated to reduce post-prandial lipidemia [35], as well as reduce soluble and cellular immune response factors [36-39]. As obesity is associated with multiple chronic systemic diseases, such as hypertension and diabetes [1,40-42], early intervention with CPAP in obese children with mild OSA may minimize the development or progression of these sequelae in adulthood.

Our study has several limitations. The number of subjects evaluated was relatively small, and thus our findings need to be reassessed in a larger population. Utilizing PSG’s and Actigraphy to better quantify the sleep architecture. In addition, a follow-up PSG would provide important insights into whether CPAP improved sleep in these subjects. Lastly, outcomes were limited to questionnaires; a more detailed evaluation of asthma, such as airway reactivity, and more objective evaluations of neurocognitive behavior, as well as evaluation of systemic inflammatory responses will be important.

In conclusion, even though there are significant practice variations in the pediatric sleep medicine where some would

initiate CPAP therapy for an AHI between 1 and 5 per hour if symptomatic. But the current standard of care criteria does not support such practices. And given the fact that we found that one month of CPAP therapy for obese children with mild OSA and clinically stable asthma improved their daytime functioning and asthma control. Therefore, it may be necessary to reexamine the criteria for implementing CPAP therapy in the pediatric population especially obese children.

Funding Source: No other external funding was secured for this study.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Notation of prior abstract publication/presentation: Presented as Poster Discussion Session at American Thoracic Society Conference, MAY 15, 2016 Denver, CO.

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