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EFFECT OF CPAP AIRWAY REACTIVITY AND AIRWAY INFLAMMATION IN CHILDREN WITH MODERATE-SEVERE ASTHMA

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Abstract

Background: *Asthma indicates airway hyperactivity and airway inflammation. Previously literature has reported that adults with mild well controlled asthma exhibited a marked decrease in airway reactivity (PC20 increased >2-fold) after using nocturnal continuous positive airway pressure (CPAP) for 1 week. If CPAP has positive effect on suppression of airway activity in children who have been suffering from mild-moderate asthma, the chronic use of corticosteroid would decrease. This non-pharmacological therapy would be beneficial in these children.*

Methods*: Children aged 8–17 years with moderate– severe asthma were treated with 4 weeks of nocturnal CPAP (8–10 cm H2O) or sham CPAP (8-10 cm h_2O). Adherence was monitored with a modem installed in the equipment or by memory cards. Airway reactivity, assessed by methacholine bronchial challenge, was measured prior to and following treatment.*

Conclusion: *Results showed that 4-week treatment with nocturnal CPAP did not produce a twofold suppression of airway reactivity in children with moderate–severe asthma.*

Keywords: *Airway obstruction, mechanical strain, sputum, lung function.*

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INTRODUCTION:

Asthma, which is characterized by repeated episodes of reversible airway obstruction, airway hyperactivity and airway inflammation, is primarily treated with b-adrenergic bronchodilators and anti-inflammatory agents. These therapies are effective in the prevention of symptoms for the vast majority of asthmatics; however, they are limited by high cost, poor adherence and increasing concern about long-term adverse effects. Thus, there is a compelling need for new, safe and effective approaches to the treatment of asthma. The mechanical strain imposed on the lungs during breathing is an important modulator of airway responsiveness in vivo [1]. Deep inspirations and tidal breathing decrease airway responsiveness in healthy adults and animals, while the absence of a deep inspiration or tidal breathing increases airway responsiveness However, in humans, the bronchoprotective effect of acute mechanical strain lasts for only 10–20 min and it is less effective in patients with asthma [2][3]

Mechanical stress imposed on the lungs during breathing is an important way of airway responsiveness in vivo deep inspirations and tidal breathing decrease airway responsiveness in healthy adults and animals. Previously research work has done on animals that prolonged mechanical strain of the airways using continuous positive airway pressure decreased airway reactivity in vivo and ex vivo. In a small clinical trial, results showed that adults with mild well controlled asthma exhibited a marked decrease in airway reactivity after using nocturnal CPAP for 1 week; the methacholine (MCh) concentration to decrease forced expiratory volume in 1 s (FEV1) by 20% more than doubled.[4] Currently, there are no studies evaluating whether CPAP suppresses airway reactivity in children, particularly those with moderate–severe disease, who require chronic use of inhaled corticosteroids (ICS) and systemic corticosteroids for frequent exacerbations. If CPAP markedly suppresses airway reactivity in these children, this non-pharmacological therapy might provide a beneficial alternative or supplemental therapy for children with high respiratory morbidity and risk of steroid associated growth suppression. Recent in vitro studies have also demonstrated that mechanical strain of isolated airway smooth muscle (ASM) suppresses the inflammatory response of ASM to IL-13 stimulation11,12; however, there have been no in vivo studies. Therefore, it has hypothesized that nocturnal CPAP for 4 weeks would markedly suppress airway reactivity, as well as airway inflammation, in children with moderate–severe asthma.

METHODOLOGY:

Inclusion criteria

Children aged 8–17 years with moderate–severe asthma, defined by National Asthma Education and Prevention Program/Expert Panel Report (NAEPP)/EPR III guidelines of treatment steps 4 and 5, were recruited

Exclusion criteria

- Study exclusion criteria included:
- Body mass index (BMI) >95th percentile
- Other chronic lung disease
- History of pneumothorax
- Congenital heart disease
- Obstructive sleep apnoea
- Baseline FEV1 < 70% predicted
- Bronchial challenge test with an MCh concentration > 16 mg/mL to decrease FEV1 by 20% (PC20).

Study design

Subjects had two study visits (V1 and V2). The study was single-blinded (subjects were blinded to treatment group, but not all researchers). The research coordinator who performed the study measurements, as well as instructed subjects on use of the CPAP equipment, was not blinded to treatment.

At V1, qualified subjects were alternately allocated to CPAP (8–10 cm H2O) or sham CPAP (8–10 cm H2O) or sham CPAP (<2cm H2O) treatment and instructed to use the assigned treatment every night for a total of 28 3 days. There was telephone follow-up in the first 3 days to assess if parents had been able to set up the equipment at home, as well as weekly telephone follow-up. Assessment was repeated at V2. Adherence to equipment use was assessed by the machine modem or memory card. For an asthma exacerbation requiring oral corticosteroids during the study period, CPAP or sham was extended for 21 days after the last corticosteroid dose. At V2, a subject was considered adherent with treatment if an average of ≥4 h/ night and ≥5 days/week for all 4 weeks was achieved, and if treatment was used for ≥4 h on the two nights before V2.

Measurements:

Asthma symptom score was assessed using the Asthma Control Test (ACT) ; higher scores indicate better contro [5]l. Exhaled nitric oxide (eNO) was measured using a chemiluminescence analyser. Spirometry was obtained with bronchodilators withheld on the day of evaluation[6]. MCh bronchial challenge was performed using the 5-breath protocol

with quadrupling concentrations starting with 0.0625 mg/mL and continuing until FEV1 decreased by 20% (PC20) or MCh concentration of 16 mg/mL was inhaled.17 Induced sputum was obtained after the MCh challenge and treatment with albuterol to return FEV1 to ≥70% predicted. Subjects inhaled increasing concentrations of hypertonic saline (3%, 4%, 5% and 7%) at 5-min intervals using a breath actuated nebulizer coupled with a device that generates oscillating positive expiratory pressure to improve lower airway clearance. Sputum was processed for total cell count and cell viability was determined by trypan blue exclusion. Only samples with cell viability ≥50% and squamous cells ≤20% were considered acceptable [7] [8]. Cell-free supernatant was frozen for cytokine analysis.

Statistical analysis:

The primary outcome was the change in airway reactivity (PC20) between V1 and V2. Sample size was calculated based on the difference of logPC20 changes between groups using our previous study in adults with mild asthma; there was a difference of change in logPC20 between CPAP and sham groups as 0.41, with an SD of 0.46.13 With this effect size, variability and 10% subject dropout. Secondary outcomes included the changes in airway inflammatory markers, FEV1 (% predicted) and ACT scores. Demographic characteristics and baseline results of CPAP and sham groups were compared using Student's t-tests for continuous normal variables, Wilcoxon–Kruskal–Wallis non-parametric tests for non-normal variables, and chi-square tests for categorical variables. We utilized Generalized Linear Models (GLM) so that the analytic assumptions would be met, even when the data were not normally distributed. We tested the main effects of time (change between V1 and V2) and treatment group (CPAP/sham), as well as their interaction. Missing data were tested to ensure they were missing at random. The level of statistical significance was set at 0.05. Statistical analysis was performed using SAS 9.4

RESULTS:

Subjects:

Eighty-four subjects were approached for the study; 25 were excluded based on screening criteria. Two subjects (one in each group) were lost to follow-up, two (one in each group) did not tolerate the equipment and two (one in each group) did not undergo MCh challenge at V2 due to the presence of asthma symptoms. There were no statistically significant differences in age, sex, race or BMI; however, subjects in the sham group were significantly taller when height was expressed as z-scores. There were no statistically significant differences between groups in baseline FEV1, PC20, eNO and ACT score; however, the CPAP compared to sham group had a greater frequency of subjects in asthma treatment step 5 than in step 4.

Primary outcome:

Both groups tended to have an increase in PC20 (lower airway reactivity) between V1 and V2, but the change did not reach statistical significance (P = 0.083). While there was a tendency for greater increase in PC20 in the CPAP compared to sham group, the difference was not statistically significant (P > 0.5) . The CPAP group used the machine for an average of 27.5 ± 9.4 days, 5.7± 1.2 days/week and 6.8 ±2.2 h/ night, whereas subjects in the sham group had averages of 25.3 ± 6.2 days, 5.8 ± 1.1 days/week and 7.9 ± 1.4 h/night. There were no statistically significant differences in the average number of days or average days/week of machine use (Mann–Whitney U-test, P = 0.397 and P > 0.5, respectively). However, on average, the CPAP group used the machine for significantly fewer hours/night over the course of the study compared to sham group (unpaired t-test, P = 0.031). Eight subjects in the CPAP group (29.6%) and nine subjects in the sham group (32.1%) did not meet the adherence criteria, which was not statistically different (chi-square test, P > 0.5). The primary analysis was repeated adjusting for adherence by excluding the 17 non-adherent subjects, as well as adjusting for total hours of machine use, height z-scores and asthma treatment step. None of the subanalyses significantly altered the results. Adverse events There was no significant difference between groups for subjects with asthma exacerbations treated with oral corticosteroids (5 CPAP:3 sham; Fisher's exact test, P > 0.5). Repeating the primary analysis with the exclusion of these subjects did not significantly alter the results.

Secondary outcomes

The overall success rate in obtaining quality sputum samples was 57%; however, only 12 sham and 10 CPAP subjects had quality samples at both study visits. At V1, there were no significant differences between the two groups in total cell count per gram of sputum (×106) or % eosinophils (3.4 vs 4.6, P > 0.5; and 6.2 vs 3.9, P > 0.5, respectively). While there was a tendency for % eosinophils to decrease in CPAP group and to increase in sham group, the changes for the groups were not significantly different (P = 0.130). Cytokines levels of IL-5, IL-13, IL-8, IL-10, interferongamma (IFN-γ) and TNF-α in the induced sputum supernatant did not change significantly with treatment and there were no significant differences in the changes between

treatment groups. FEV1, eNO and ACT score did not change significantly with treatment and there were no significant differences in the changes between treatment groups

DISCUSSION:

We hypothesized that the 4-week treatment with nocturnal CPAP would markedly suppress airway reactivity, producing a twofold increase in PC20 in children with moderate–severe asthma, similar to that observed in adults with mild well-controlled asthma treated for 1 week but did not find a significant effect of CPAP treatment in children with moderate–severe asthma, although there was a tendency for a greater increase in PC20 compared to sham-treated children. There was also a tendency for a decrease in airway inflammation in CPAP-treated subjects, which also did not reach statistical significance. Findings suggest that the magnitude of suppression of airway reactivity following 1 month of CPAP treatment in children with moderate–severe asthma is much smaller than in adults with mild well-controlled asthma. The sample size for current study's children was based upon our previous adult data with an effect size required to double PC20. A twofold magnitude of suppression of airway reactivity would be of a magnitude observed with pharmacological interventions,20–22 and less than the PC20 variability reported for repeated measurements in children [7]. While 1-month intervention might result in greater variability than 1-week intervention, it might have also produced a greater treatment effect. We observed a much smaller potential effect size in children with moderate–severe asthma, which was not statistically significant with the number of subjects we evaluated. Our results indicate that children with moderate–severe asthma treated with CPAP for 1 month produces a much smaller suppression of airway reactivity than adults with mild wellcontrolled asthma treated for 1 week. The smaller effect size observed in children with moderate–severe asthma compared to adults with mild well-controlled asthma may relate to airway remodelling that often occurs with more severe disease. Airway remodelling may increase airway stiffness, limiting the degree of mechanical strain CPAP delivers to the airways and ASM [8]. This mechanism may also explain the smaller bronchodilating effect produced by deep inspiration in adults with asthma compared to non-asthmatic controls.3 The children in our study also used medium-high dose ICS, which might impair the molecular pathways by which mechanical strain suppresses ASM reactivity. In addition, differences in autonomic modulation between non-asthma and asthmatic children might contribute to suppression of in vivo airway reactivity. Lack of adherence to treatment can contribute to the absence of a treatment effect [8]. A multicentre study evaluating adult subjects with mild well-controlled asthma found that CPAP for 12 weeks suppressed airway reactivity [9]; however, sham treatment had a similar effect. In that study, adherence to treatment was very low and significantly lower in CPAP (36%) versus sham (52%), which may have accounted for the absence of a significant difference between treatment groups. In current study, we had good adherence for both groups (70%), which is higher than 50% adherence reported with regular asthma medications, and our outcomes were similar when adjusted for adherence. However, adherence was defined as >4 h/night, derived from CPAP usage for obstructive sleep apnoea. It remains unclear as to the number of hours/night or length of CPAP treatment required to markedly suppress airway reactivity in subjects with moderate–severe asthma. On observation that CPAP and sham tend to suppress airway reactivity, but did not reach statistical significance, was similar to a larger multicentre study of adults[9]. In both studies, sham was used as the control treatment and no group used neither CPAP nor sham. Therefore, improvements with time may have been secondary to greater adherence with asthma medications during the study, due to the Hawthorne effect, or a potential benefit of nocturnal warm, humidified and filtered air provided by the equipment. Sample size was important for our evaluation of whether mechanical strain suppressed airway inflammation, as observed previously in our in vitro studies. 60% success was obtained rate for good quality sputum samples, similar to previous studies of children [10] [11]; however, only a few children (10–12) had quality sputum at both visits. A strength of current study is that it is the first to evaluate CPAP therapy to suppress airway reactivity and inflammation in children, particularly those with moderate–severe asthma who would greatly benefit if corticosteroid use could be reduced. Another strength was the good adherence to treatment, particularly as we were evaluating children from 8 to 17 years of age. The study had several limitations. As we evaluated only children with moderate–severe asthma, the results cannot be extrapolated to children with mild or moderate asthma. A major limitation of our study was the limited number of subjects we could recruit from a single paediatric centre; however, we were able to evaluate whether this population demonstrated a suppression of airway reactivity of a magnitude similar to what we previously observed in adults with mild well-controlled asthma. Evaluation of airway inflammation was limited to induced sputum rather than bronchoalveolar lavage, which would not have been an acceptable risk in our children. In summary,

4 weeks of CPAP treatment for children with moderate–severe asthma did not markedly suppress airway reactivity, nor did it significantly suppress airway inflammation.

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