TITLE OF STUDY: Efficacy of Auto-adjustable Positive Airway Pressure (APAP) in pediatric patients with obstructive sleep apnea (OSA).

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1. ABSTRACT:

Obstructive sleep apnea syndrome (OSAS) is a disease associated with significant morbidity and is likely under-recognized in the pediatric population. It is characterized by upper airway obstruction leading to partial or complete limitation of airflow while asleep. Sequelae may include nocturnal hypoxemia, hypoventilation, arousals from sleep, and sleep disruption which may predispose the patient to increased risk of cardiovascular disease and neurocognitive impairment. Continuous positive airway (CPAP) is commonly used to treat OSA by delivering a predetermined amount of positive pressure to the patient's upper airway in order to reduce the collapsibility of airway structures during sleep. The commonly accepted method for determining the appropriate pressure setting for children with OSAS is through an in-hospital overnight CPAP titration study. Another commonly used treatment modality in adults with OSAS is auto-adjustable positive airway pressure (APAP), in which airway patency is maintained by adjusting pressure delivery through the night depending on the needs of the patient as determined by the device. Benefits of APAP compared with CPAP include the ability to initiate therapy without an inpatient CPAP titration study, resulting in more prompt establishment of treatment and cost-savings. Patient adherence may also be significantly improved as the pressure delivered is appropriate for sleep stage and patient position, resulting in greater patient comfort. Utility and efficacy of APAP compared to CPAP have never been evaluated in the pediatric population. The aim of this study is to establish APAP as an effective means of assessing CPAP pressure for OSAS in children, and to determine if APAP therapy confers better treatment adherence and quality of life compared to traditional CPAP. We hypothesize that APAP can effectively approximate the pressure determined by CPAP titration study, that APAP is superior to fixed CPAP in terms of treatment success, and that adherence to therapy will be improved with APAP compared to CPAP.

Forty patients aged 5-20 years will be enrolled in the study. These subjects will be recruited from the pediatric pulmonary or pediatric sleep clinic at CCHMC. Patients who are suspected of having OSA will be referred in the usual manner to the sleep center for diagnostic sleep study (PSG). Following the establishment of OSAS diagnosis and subsequent enrollment in the study, the subject will begin therapy with APAP which will continue for 4 to 8 weeks. In that period of time the clinically ordered in-hospital CPAP titration study will be completed. The subject will then be randomized to either traditional fixed pressure CPAP at the pressure determined by in-hospital titration or APAP. The subject will receive 4 weeks of treatment in the randomized group (CPAP or APAP) then crossover to 4 weeks in the alternate group (CPAP or APAP). Both patient and researcher will be blinded to the randomization of pressure modality. The total study period will range from 14-18 weeks.

Appropriate statistical analyses will be used to evaluate two primary outcomes which are (1) the optimal pressure derived from APAP versus CPAP titration study and (2) the adherence to APAP versus fixed pressure CPAP. Other secondary outcomes will be compared between APAP and fixed pressure CPAP including the change in the score of Michigan Pediatric Sleep Questionnaire, Epworth Sleepiness Scale, Pediatric Quality of Life Inventory and CPAP Follow up Questionnaire.

2. PURPOSE OF THE STUDY:

The aim of this study is to establish APAP as an effective treatment modality for OSAS in the pediatric population. We hypothesize that APAP can effectively approximate the pressure determined by PSG CPAP titration as measured by the average 90th pressure percentile and average CPAP pressure delivered to the patient. The in-hospital CPAP titration PSG following initial diagnosis of OSA is the current standard of therapy. APAP would potentially bridge the gap between the time of diagnosis and the follow up PSG for CPAP titration, allowing for more prompt intervention. The other purpose of the study is to determine how APAP therapy compares with traditional CPAP in terms of treatment adherence and quality of life. We hypothesize that APAP is superior to fixed CPAP in terms of treatment success measured by quality of life and symptom reporting by patients or their parents. Additionally, we hypothesize that adherence to therapy will be improved with APAP compared to CPAP as measured by therapy usage hours downloadable from the machine.

3. BACKGROUND:

OSAS is a disease characterized by prolonged partial upper airway obstruction, intermittent complete obstruction (obstructive apnea), intermittent partial obstruction (obstructive hypopnea), or a combination thereof while asleep[1]. Sequelae include nocturnal hypoxemia, hypoventilation with CO2 retention, and/or sleep disruption, which may predispose the patient to increased risk of cardiovascular disease and neurocognitive impairment. Daytime sleepiness or hyperactivity with or without inattentiveness frequently results, which can contribute to short term memory and concentration impairment. Systemic hypertension has been reported in children with OSA. Pulmonary artery hypertension may also result from intermittent hypoxemia or chronic hypoventilation. There is limited normative date for the apnea hypopnea index (AHI) in children, although an AHI greater than 1-2 per hour is used as a cutoff for diagnosis of OSA based on expert consensus. An AHI greater than 5 is considered to be consistent with a moderate degree of OSA and CPAP is commonly offered as one of the treatment options for those patients. OSAS is likely under-recognized in the pediatric population, but according to a recent meta-analysis, has an estimated prevalence between 1 and 4%[2]. The pathophysiology of OSAS is likely multifactorial and involves the anatomic structure of the airway, neuromotor tone, and inflammation. An overall increase in upper airway resistance occurs during sleep under normal circumstances, however, with any anatomic airway narrowing or impairment of neuromotor control, collapsibility is pronounced, and therefore airflow resistance is increased. Once the obstruction occurs, gas exchange is impaired and hypoxemia and hypercapnia ensue, resulting in increased respiratory effort and arousal from sleep. The cycle repeats frequently through the night causing recurrent hypoxemia and sleep fragmentation[3]. Many children instead experience prolonged partial airway obstruction through the night resulting in obstructive hypoventilation.

Surgical and non-surgical treatment modalities exist and often tonsillectomy and adenoidectomy (T&A) is the first line of treatment in the pediatric population. CPAP is frequently employed if T&A is contraindicated or if symptoms persist following surgery, and is a common treatment option for both adults and children with OSAS. CPAP delivers a predetermined amount of positive pressure to the patient's upper airway in order to reduce the collapsibility of upper airway structures during sleep. The commonly accepted method of determining the appropriate pressure setting for children with OSAS is through an overnight CPAP titration study done in the hospital. Another commonly used treatment modality in adults with OSAS is APAP, in which airway patency is maintained by adjusting pressure delivery through the night depending on the needs of the patient as determined by the device. Benefits of APAP compared with CPAP include the ability to initiate therapy without an inpatient CPAP titration study, resulting in more prompt establishment of treatment and cost-savings. Patient adherence may also be significantly improved as the pressure delivered is adjusted appropriately for the airflow detected during each breath, which may vary according to patient position and stage of sleep, resulting in greater patient comfort. Although APAP has never been evaluated in the pediatric population, several adult studies have demonstrated similar treatment effects with APAP compared to CPAP. In one double-blind randomized controlled trial of adults with OSAS, 1 month of APAP treatment was equivalent to 1 month of CPAP in terms of improvement in daytime sleepiness, quality of life and respiratory disturbance during sleep. The majority of patients in that study preferred treatment in the auto-adjusting mode[4]. Another adult study evaluating the efficacy of APAP as a means of titration, using the same device we intend to use (REMstar Auto), showed similar efficacy of automatic titration compared with manual titration in terms of AHI and quality of sleep. Both studies occurred over 2 consecutive nights in the hospital. For those patients receiving APAP titration on the first night, better sleep quality, as measured by total sleep time and sleep efficacy, was demonstrated for APAP compared with traditional CPAP[5].

4. STUDY DESIGN:

The proposed study is a prospective, double-blind, randomized crossover trial. We will only recruit patients who receive care from the pediatric pulmonary or pediatric sleep clinic at CCHMC. Following diagnosis of OSAS, patients who meet inclusion criteria will be enrolled in the study and treated with APAP delivered via the Respironics REMstar Auto device for 4 to 8 weeks. During that period, an in-hospital CPAP titration study will be completed and average 90th pressure percentile and average CPAP pressure derived from the device will be compared to the CPAP pressure determined by CPAP titration PSG. For subjects who are clinically placed on APAP prior to enrollment, they may be recruited into the study up to two months after initiating APAP. The patient will then be randomized in a double blind fashion to either continue on APAP or to change treatment to fixed CPAP at the pressure determined by CPAP titration study for 4 weeks. The subject will crossover to the alternate modality for an additional 4 weeks. The Michigan Pediatric Sleep Questionnaire (PSQ), Pediatric Quality of Life Inventory (PedsQL) and Epworth Sleepiness Scale (ESS) will be administered at the time of enrollment, and following completion of each randomization period to compare quality of life and symptom scores between modalities. A CPAP Follow-Up Questionnaire (CFQ) will also be given after each randomization period to score the comfort and side-effects of treatment. Finally, therapy usage hours downloaded from the

device will be used to compare treatment adherence of APAP compared to fixed CPAP. For subjects recruited after clinically starting APAP, once informed consent has been obtained, all clinical information after initiation of APAP will be included into the research data.

5. DURATION:

The study duration for each patient will be 12-16 weeks. The protocol will remain open to enrollment for 12 months. Total study duration will be 24 months, allowing for 8 months of data analysis.

6. SELECTION AND RECRUITMENT OF PARTICIPANTS:

A. Number of participants

Forty-five subjects will be enrolled in the study, allowing for a 15% drop-out rate. When the total sample size is 40, the study design will have greater than 80% power to detect a difference in means of 1.000 (from published data, the difference between an APAP 90th pressure percentile of 10.4, SD = 1.4 and a mean CPAP titration of 9.4, SD = 1.9)[5]. In the crossover portion of the study, when the sample size in each sequence group is 20 (total sample size of 40), a 2 x 2 crossover design will have 80% power to detect a difference in means of 35.000 (from published data, the difference between an APAP mean minutes of use of 306, SD = 114 and a CPAP mean minutes of use of 271, SD = 115)[6] using a two group t-test (Crossover ANOVA) with a 0.05 two-sided significance level.

B. Inclusion criteria

Patients aged 5 to 20 years, male or female, of any race and any socioeconomic background with moderate OSA defined as an AHI of ≥5 or obstructive hypoventilation, determined by a measured end tidal carbon dioxide level >50 for more than 25% of total sleep time will be included.

Exclusion criteria

Those patients with significant cranio-facial abnormalities, chromosomal abnormalities that would affect compliance, cerebral palsy, significant neurological disease or neuromuscular disease will be excluded from the study.

C. Recruitment

Patients seen by pulmonary or sleep providers in the CCHMC pulmonary or sleep clinics who are suspected of having OSA based on history and physical exam will be referred in the usual manner to the sleep center for a diagnostic sleep study. Those patients who meet inclusion criteria will be referred by their provider for enrollment in the study. Standard practice is for the patient to return to sleep clinic approximately 2 weeks after diagnostic PSG for follow-up and to discuss treatment options. Patients will be recruited for enrollment during that clinic visit.

D. Vulnerable populations

Subjects younger than 18 years old are considered vulnerable to coercion or undue influence and additional safeguards will be used to protect that population. Assent will be obtained after age-appropriate explanation of the study. The child will only participate voluntarily and will have the opportunity to withdraw at any time for any reason, independent of their parent or guardian. Assent will be reaffirmed before study procedures are performed.

7. PROCESS OF OBTAINING CONSENT:

Informed consent for study participation will be obtained by the principle investigator or CCHMC research nurse during the patient's initial clinic visit following diagnostic PSG. The consent form will be reviewed in detail with the patient and his or her parent or guardian, and any of their questions regarding the study will be answered. Subjects aged 11 through 17 will sign their assent. Parents of subjects aged 5 through 17 will sign the consent/parental permission form. Those subjects aged 18 through 20 will sign their own consent for study participation. All those signing consent will receive a copy of the signed consent form. No study-related procedures will be initiated until informed consent is signed.

8. STUDY PROCEDURES:

Once the patient has been enrolled in the study at the time of the first clinic visit following diagnostic PSG, the subject and/or parent will complete the Michigan Pediatric Sleep Questionnaire (PSQ), Pediatric Quality of Life Inventory (PedsQL) and Epworth Sleepiness Scale (ESS). This is standard practice for all patients seen in sleep clinic at each visit. The enrolled subject will be fitted with an appropriate CPAP interface (mask apparatus) by an experienced sleep technologist, and will be trained on use of the Respironics REMstar Auto device which will be set to APAP. The subject will continue to use the device at home every night for 4 to 8 weeks. During that period of time the subject will return for an in-hospital CPAP titration study. The CPAP titration study is the current standard of care for those diagnosed with OSAS and for whom treatment with CPAP is prescribed. Following CPAP titration the subject will return to clinic, a standard practice to initiate CPAP therapy. At that visit, device data from the treatment period will be downloaded including therapy usage hours, average 90th pressure percentile and average CPAP pressure. The PSQ, PedsQL and ESS will be re-administered, per current clinical practice. He or she will also complete a CPAP Follow-Up Questionnaire (CFQ) to score the comfort and side-effects of treatment. Questions similar to those found in the CFQ are typically reviewed with the patient during the regular clinic visit, however, for the purposes of the study, we will standardize those questions. The subject will then be randomized in a double blind fashion to either traditional fixed pressure CPAP at the pressure determined by in-hospital titration or APAP. This treatment will continue for 4 weeks, after which time the subject will return to clinic (standard follow-up after initiating CPAP therapy), where the PSQ, PedsQL, ESS and CFQ will be re-administered and data from the device will be downloaded. Treatment will continue for another 4 weeks on the alternative setting with the same device and same mask interface. The subject will present for follow-up sleep clinic appointment at the end of the second randomization period, at which time he or she will complete another PSQ, PedsQL, ESS and CFQ. Information from the device will be downloaded, and the study will end. This final clinic visit will occur approximately 1 month sooner than the typical follow-up appointment, but in all, the patient will not have additional visits beyond the standard clinical practice.

A. Drugs, Devices and Biologics:

The Respironics REMstar Auto device will be used during this study period to deliver both APAP and fixed CPAP. It currently has FDA approval for treatment of patients weighing >30 kg with OSAS. As a comparison, one of the most common devices used to deliver fixed CPAP to CCHMC patients at home (REMstar Pro C-flex+) also carries the same >30 kg indication, however, the device is frequently used off label to treat smaller children in routine clinical practice. The device will be dispensed in Pulmonary

Sleep Disorders clinic at the appropriate study visit. A log will be kept documenting the serial number and information on patient use. The equipment will be kept in locked areas when not in use.

B. Studies Using Surveys or Questionnaires:

The Pediatric Sleep Questionnaire (PSQ) was developed by researchers at the University of Michigan and has been used extensively in both research and clinical applications to determine the presence of sleep related breathing disorders and associated symptoms in children. Validity and reliability of the PSQ was demonstrated in a study conducted by Chervin, et al. which was published in 2000[7]. It was also validated in a pilot study conducted here at CCHMC[8]. The Pediatric Quality of Life Inventory 4.0 (PedsQL) is an instrument designed to measure health-related quality of life in children and adolescents aged 2-18. It was shown to be a valid and reliable means of measuring quality of life for use in clinical trials, research, clinical practice, school health settings, and community populations according to conclusions of a study published in 2001[9]. The Epworth Sleepiness Scale (ESS) is an 8 item questionnaire determined to be a valid and reliable means of measuring daytime sleepiness in adult patients[10]. The ESS has been modified for use in pediatric patients, however, the modified version has not yet been validated. Current clinical practice at CCHMC is to administer the original ESS to all pediatric sleep patients. The CPAP Follow-Up Questionnaire was developed for use in this study. The items included in this questionnaire are typically reviewed with patients in sleep clinic regarding side-effects, patient comfort, problems encountered with CPAP use and adherence to treatment. It has not been validated, but is merely a means of collecting the above information.

9. DATA ANALYSIS/METHODS:

For each patient, 90th APAP pressure percentile, average CPAP pressure delivered and therapy usage hours will be downloaded from the APAP device and recorded in a central database which will be stored on secure CCHMC servers. Questionnaire responses and CPAP titration values for each patient will be stored in like manner. Based on the study's outcome variables we anticipate requiring enrollment of 45 patients to power the study adequately, and to have enough subjects of each race, gender and pre-and post-adolescent ages. For analysis of the primary outcome of APAP run-in period vs. CPAP titration pressure, statistical analysis of the data will be completed using the standard 2 tailed paired t-test or Wilcoxon Signed-Rank test. To determine the effect of treatment on adherence and quality of life outcomes as well as any carry over effect in the crossover portion of the study, an appropriate mixed effects model including period, sequence, and subject effects will be employed[11].

10. FACILITIES and PERFORMANCE SITES:

All research activities will take place at CCHMC facilities including the CCHMC Pulmonary Sleep Center (sleep lab), pulmonary sleep clinic on Main campus, and pulmonary sleep clinic on Liberty Campus.

11. POTENTIAL BENEFITS:

Potential benefits to the patient enrolled in the study include the ability to receive prompt treatment for sleep disordered breathing once his or her diagnostic sleep study is read, instead of awaiting results from a subsequent CPAP titration study, as is the current practice. Subjects would benefit from the ability to use a machine that is potentially more comfortable than fixed CPAP, with potential for better

adherence to therapy, translating to improved resolution of symptoms and improved quality of life. Future patients may derive similar benefits from these study findings.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:

There are no identifiable risks to the patient receiving the treatment being studied, above those risks conveyed with conventional therapy. There are no known risks to pregnant patients. All research procedures including the clinic visits and questionnaires are included in current clinical practice, with the exception of a 15 item questionnaire (CFQ) that will be given to study participants in the final 3 clinic visits. There is a risk of unintentional disclosure of patient health information (PHI). All patient identifiers will be removed at the time of data entry into a secure database. Adverse events, including unanticipated problems and disclosure of PHI will be conveyed to the CCHMC IRB and to the Pharmacy and Therapeutics Committee consistent with the requirements of each of these organizations.

13. RISK/BENEFIT ANALYSIS:

This is a minimal risk study with a potential benefit to participants and to future patients.

14. DATA SAFETY AND MONITORING:

To protect the confidentiality of study subjects, all information will be entered into a secure database that is password protected. Subjects will be assigned study subject identifiers for data downloaded from the CPAP/APAP device, questionnaire responses and CPAP titration study results. The database will be maintained by study nurses and respiratory therapists. Data will be published in aggregate format only, without the possibility of identifying individual participants. This study will not include a DSMB. The data safety monitoring plan includes a review of adverse events by the PI at regular bi-weekly research team meetings. Adverse events that meet the criteria of reportable events will be reported to the IRB per hospital policy. All other adverse events will be reported to the IRB in table form at the time of IRB review. The study will be stopped for review if any study related adverse event results in hospitalization of the subject.

15. PRIVACY AND CONFIDENTIALITY:

We will take all precautions to protect the privacy of our subjects and their families by respecting their requests regarding contact preferences. We will protect confidentiality by protecting patient's PHI. Subjects will be given a study ID that does not include any personal identifiers. All PHI will be removed and the study ID will be used in databases and all study records. The ID code and the research records will be maintained in a secured location and/or in password protected databases. CCHMC's IRB will have the right to inspect and review all records.

16. COST OF PARTICIPATION:

All of the clinic visits and sleep studies (initial diagnostic and CPAP titration) will be done for clinical indications and do not deviate from the standard of care. They will therefore be billed to the patient's insurance company in the usual manner. The REMstar Auto devices will be provided by Respironics for use in the study without charge.

17. PAYMENT FOR PARTICIPATION:

No reimbursement will be provided to the study participants.

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