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Protocol #: 17-0827

Project Title: Validation Study of the WatchPAT 200 in the Diagnosis of Obstructive Sleep Apnea in Children 4-12 Years of Age

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I. Hypotheses:

We hypothesize that the WatchPAT™ 200U (Peripheral arterial tonometry recorder; Itamar Medical, Caesarea, Israel), which is a wrist worn, non-invasive, ambulatory sleep recorder device based on peripheral arterial tone (PAT) signal, pulse rate, actigraphy and pulse oximetry will be able to detect obstructive sleep apnea in children 4 to 12 years of age as effectively as an overnight, attended, in-laboratory polysomnogram.

Our Specific Aims:

1. To evaluate the accuracy of the WatchPAT 200 device compared to an in-laboratory polysomnogram (PSG) in detecting obstructive sleep apnea (OSA) through measurement of the peripheral arterial tone apnea hypopnea index (PAHI) in children 4-12 years of age who are referred to the Children's Hospital Colorado (CHCO) sleep lab for a diagnostic PSG due to concerns for possible OSA.
2. To evaluate the diagnostic agreement of the WatchPAT 200 device in detecting between normal sleep and mild ($\geq$ 2 events per hour) versus moderate to severe obstructive sleep apnea (OAHI of $\geq$ 5 events per hour) in children 4-12 years of age compared to an in-laboratory PSG.
3. To evaluate the accuracy of the WatchPAT 200 device in measuring other parameters such as the PAT Respiratory disturbance index (PRDI), oxygen desaturation index (ODI), heart rate and body position compared to an in-laboratory PSG.
4. To evaluate the accuracy of the WatchPAT 200 device in determining sleep architecture compared to an in-laboratory polysomnogram.

II. Background and Significance:

Obstructive sleep apnea is estimated to affect approximately 1% to 5% of children between the ages of 5 to 13 years. [1-4] The morbidity associated with OSA in children is well studied and includes neurobehavioral and cognitive problems, poor school performance, impaired language skills, inattention, hyperactivity and reduced quality of life. [5-10] Other morbidities include insulin resistance, elevated inflammatory markers, systemic hypertension and in severe cases, left or right ventricular failure and cor pulmonale. [11-17] Given these medical consequences, it is very important to screen children and diagnose OSA in a timely manner, especially if there is a high suspicion.

The American Academy of Pediatrics recommend that all children should be screened for snoring. Early identification of OSA is important because of its prevalence in school age children, alleviation of current symptoms once diagnosed and treated, improvement of quality of life, prevention of sequelae, education of parents, and decreased health care utilization.[1] History and physical examination alone has been shown to have poor sensitivity and specificity [18-19]; therefore, objective testing is needed.

The American Academy of Pediatrics (AAP) [1] recommends an overnight, attended, in-laboratory polysomnogram (level 1 sleep study) as the diagnostic test of choice for children with suspected OSA. The polysomnogram measures a number of physiologic functions overnight which includes an EEG, pulse oximetry, oronasal airflow, abdominal and chest wall movements, partial pressure of carbon dioxide (PCO2) and video recording which will help demonstrate the presence or absence of OSA. [20] Specific pediatric measuring and scoring criteria are used. [21]

While the polysomnogram is considered a painless, noninvasive procedure by most adults, it can be challenging and even frightening for some children. [22] Moreover, it is expensive and the studies are time and labor-intensive to record, score, and interpret. Availability is often limited, and wait times can be long in some regions, especially for infants and young children. [23,24,25] The AAP clinical practice guideline also suggests ordering an alternative test (or referral to a sleep specialist or otolaryngologist) when an inpatient polysomnogram is not available, with the rationale that some objective testing is better than none. [1]

For these reasons, healthcare providers and researchers have looked into alternative objective tests in diagnosing OSA in children. However, these alternative tests (i.e. level 3 sleep study, nap test, overnight continuous pulse oximetry, audiotapes and videotapes, etc.) have been found to have a low negative predictive value, indicating that a negative result is not sufficient to exclude OSA, and the tests should not be used in routine practice. [1, 26]

One of these alternative tests is a level 3 sleep study which records a minimum of four channels, including ventilation, oximetry, ECG, or heart rate, and is done at home or outside of the sleep laboratory, unattended. [27] This test has been used in some adults; however, it does not usually record sleep, is not routinely utilized in children, and is not the standard of care in this age group. Therefore, a continued search for alternative testing is needed.

A viable alternative to the polysomnogram is the WatchPAT 200. This is an FDA approved wrist worn ambulatory sleep study device in patients $\geq$ 12 years of age that uses peripheral arterial tonometry in conjunction with pulse oximetry and actigraphy to assess respiratory disturbances. [28] It has 6 channels which includes the following: 1. Peripheral arterial tone (PAT) which measures the arterial volume changes, reflecting sympathetic nervous system activation caused by respiratory disturbances during sleep; 2. Oximetry; 3. Actigraphy, which measures body movement during sleep; 4. Heart rate; 5. Body position, which can measure supine, prone or side sleeping positions and 6. Snoring intensity. Clinical parameters measured include: 1. PAT apnea-hypopnea index (PAHI), 2. PAT respiratory disturbance index (PRDI), 3. PAT sleep staging identification (PSTAGES) and optional snoring level and body position discrete states from an external integrated snoring and body position (SBP) sensor. [28]

The technology is based on the pathophysiologic mechanism of obstruction-induced transient elevations of sympathetic tone which have been associated with arousals from sleep. [29-35] The device then indirectly detects apnea and hypopnea via selectively measuring peripheral arterial volume changes mediated by alpha-adrenergic receptors in smooth muscle via a finger mounted plethysmograph. This information is collected together with data from the pulse oximeter and heart rate, which is further analyzed using a predeveloped automated algorithm. [36]

It requires minimal cleaning, preparation and handling before or after patient use. Fully automated reports are also generated within minutes; thereby helping increase workflow efficiency and hopefully diagnose and treat patients in a more timely manner. Furthermore, it has the advantage of eliminating interscorer variability. This technology has the potential to be an accurate and safe alternative in diagnosing OSA in the younger age group, where the disease is known to be prevalent.

III. Preliminary Studies/Progress Report:

There have been validation studies which were mostly performed in adult patients. Weimin et al. studied 28 adults with suspected OSA who underwent an inpatient polysomnogram while wearing a WatchPAT 200. The study showed comparable accuracy in detecting OSA based on AHI (mean PSG score for events/hour was 23 ± 21.55 compared to a mean score of 25.00 ± 19.09 for the WatchPAT, r=0.92, P<0.001). It also provided a reasonably accurate estimation of sleep and wakefullness (agreement was 89±6%). [37] In another validation research using the WatchPAT200, Gan et al studied 20 patients with suspected OSA who also had simultaneous PSG and WatchPAT200 concurrently at the sleep lab. The study showed the WatchPAT being 100% sensitive when compared to PSG for detecting mild OSA and concluded that it is a good screening test for the undiagnosed general population. They study showed 100% specificity when compared to PSG for severe OSA suggesting that it is a good diagnostic test for people with a high suspicion of OSA.[38]

A meta-analysis by Yalamanchali et al. on 14 studies assessing the correlation of sleep indexes between PAT devices and PSG in adults (aged >18 years). The researchers found high overall correlation of the RDI and AHI (r=0.889 [95% CI, 0.862-0.911]; P<.001). Studies comparing the RDI between PAT and PSG had a combined correlation of 0.879 (95% CI, 0.849-0.904; P <.001); those comparing the AHI, 0.893 (0.857-0.920; P <.001); and those comparing the ODI, 0.942 (0.894-0.969; P < .001). [36]

Hedner et al. specifically studied the agreement in determining sleep architecture between the WatchPAT 100 and an in laboratory polysomnogram. The overall agreement in detecting light/deep and REM sleep were 88.6% + 5.9% and 88.7% + 5.5% respectively. OSA severity did not affect the sensitivity and specificity of the algorithm. The Cohen K coefficient for detecting all sleep stages: sleep from wake, REM from NREM sleep and deep from light sleep were 0.48, 0.55, 0.59 and 0.46, respectively. They concluded that analysis of signals from the PAT recorder can detect sleep stages with moderate agreement to more standard techniqes in normal subjects and OSA patients.[39]

There are a few studies looking into the utility of the WatchPAT in the younger population. A pilot study by Serra et al was performed to evaluate the efficiency of the WatchPAT in determining pediatric sleep disordered breathing (PSDB) in 28 children (5-12 years) presenting with symptoms of SDB but with a negative nocturnal pulse oximetry test. The study showed that in these children, the WatchPAT was able to detect sleep disordered breathing in 10/28 (35.7%) using a cut off of PAT Respiratory Disturbance Index (PRDI) of 5 in patients who tested negative during a nocturnal oximetry test. When the threshold for SDB was changed to a PAHI of >1, the number of positive patients for PSDB increased to 17/28 (60.7%). [40] A study by Su et al. examined 50 children aged 3-11 years with symptoms of snoring and assessed the sensitivity and specificity in the diagnosis of OSA using a PAT portable sleep monitor and compared it to an in-lab polysomnogram as the reference standard. The study found that in the 6-11 year old age group, 14 cases were diagnosed with OSA by the PAT and polysomnogram; however, in the 3-5 year age group, only six children were diagnosed with OSA and there was a significant difference between the PAT and PSG (p<0.05). [41] More validation studies in this age group is needed.

IV. Research Methods

A. Outcome Measure(s):

Primary outcome: Peripheral arterial tone apnea-hypopnea index (PAHI) and severity index
Secondary outcomes: Peripheral arterial tone respiratory disturbance index (PRDI), Oxygen desaturation index (ODI), Sleep staging and sleep time, Oxygen saturation, Heart rate, Body Position

B. Description of Population to be Enrolled:

Inclusion Criteria:

1. Age 4 through 12 years of age.
2. Referral to the CHCO Sleep Lab due to concerns for OSA and presenting with symptoms such as snoring, witnessed apneas, daytime sleepiness, mouth breathing, etc.
3. Informed consent obtained.

Exclusion Criteria:

1. Medical conditions that can affect the tonometer reading such as peripheral vascular disease, cyanotic heart disease, systemic hypertension and sickle cell crisis.
2. Medical conditions that can potentially limit tolerance of the WatchPAT 200 device such as autism spectrum disorder, Trisomy 21 and neurodevelopmental disorders.
3. History of neuromuscular or craniofacial malformation
4. History of current supplemental oxygen use
5. History of current vasoactive, cardiac or seizure medication use
6. Inability or unwillingness to provide informed consent

C. Study Design and Research Methods

This is an investigator-initiated pilot study that evaluates the efficacy of the WatchPAT 200 device in the diagnosis of pediatric OSA. Subjects will be identified through the Children's Hospital Colorado Sleep Clinic and will have already been referred for a clinically indicated sleep study. After IRB approval is obtained, subjects will be recruited through the sleep lab by the research team who fit the inclusion and exclusion criteria. Subjects who appear via chart review to be a good fit will be approached prior to their sleep study to inform them of the research protocol and gauge interest in participation.

For all subjects, the sleep study will be scheduled and equipment set up in a fashion routine to therapeutic sleep studies. The standard of care will not be altered or changed due to participation in the study or not.

Subjects who decide to participate in the research protocol will undergo their normal PSG setup in the sleep lab. Additionally, they will wear the WatchPAT 200 device on their wrist to validate both the PSG and WatchPAT 200 at the same time. The WatchPAT 200 will be placed on the subject's wrist by a registered sleep technician or member of the study team that is familiar with the device. The consenting process will also take place by designated research sleep technicians or members of the study team.

Data to be collected from all subjects include results of baseline/diagnostic polysomnogram (PSG) and sleep parameter indices (apnea-hypopnea index, etc.). Upon completion of the sleep study, the clinically indicated study will be scored by a physician as normal. The PSG will then be scored again by a single-point dedicated sleep technician research scorer to ensure consistent scoring methods between subjects and clinical sleep study scorers. The data collected by the WatchPAT 200device will be scored through the WatchPAT 200 software installed on a local encrypted and password-protected computer. Additional information that may be collected includes medical history, medications, and basic demographic information.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

The use of the WatchPAT 200 device has very low risk to the subject. This is a closed system that is worn on the wrist and finger that is not invasive to the patient. The device includes connections the EKG leads and other standard markers that are included in a clinical polysomnogram but are

optional and can be removed from the device between subjects. There is a slight risk of irritation of wearing the device as patients will most likely not be used to wearing someone on their wrists during their habitual sleep episodes.

E. Potential Scientific Problems:

There are no potential scientific problems at this time.

F. Data Analysis Plan:

Statistical Analysis plan

Data collected for a participant will be excluded from the analysis if any of the following: 1) WatchPAT 200 sleep time of less than 4 hours, 2) Lab test sleep time of less than 4 hours, 3) poor quality Lab test, consisting of a substantial portion of the Lab test not assessable, as determined by research staff occurred and 4) all WatchPAT 200 channel information not available from the study. The primary goal of the study is to validate and compare two sleep study modalities: 1) WatchPAT 200 and 2) Lab Testing sleep apnea.

Summary statistics of basic demographics on the study population will be calculated. Wilcoxon signed rank test will compare median outcomes of interest (Total AHI, OAHI,etc) between WatchPAT 200 and PSG Lab testing. Spearman's correlation coefficient will be used to measure correlation between WatchPAT 200 and Lab testing. Bland Altman plots will graphically assess modality correlation. Sensitivity and specificity with 95% confidence intervals of WatchPAT 200 will be calculated for three cutoffs of the outcomes (<2, <5, and <10 events/hour) using the PSG lab study as the gold standard. Finally, test agreement on apnea categories will be assessed using Cohen's Kappa statistics fixing OSA diagnosis as dichotomized as none or mild (OAHI <2 events/hour) versus moderate or severe (OAHI ≥ 5 events/hour) disease. Other analyses may be conducted on specific strata of participants, based on either patient age or BMI percentile.

Power and Sample Size

Power and sample size were calculated for the primary aim of the study using Power Analysis & Sample Size Software, PASS 15.0 (NCSS, LLC. Kaysville, Utah, USA). The primary aim is to assess whether the PatWatch device agrees with PSG laboratory studies in its ability to detect OSA. For the power analysis OSA diagnosis was dichotomized as non or mild (AHI<4.5) versus moderate or severe (AHI ≥ 4.5) disease.

From previous clinical sleep study experience, (from personal review of PSG's performed at the Main Campus of Children's Hospital Colorado in the month of February 2017), investigators anticipate roughly 11 PSG sleep studies per month with about 2 patients diagnosed with OSA.

In a test for agreement between two raters using the Kappa statistic, a sample size of 120 participants achieves 80% power to detect a true Kappa value of 0.95 in a test of H0: Kappa ≤ κ0 vs. H1: Kappa > κ0 when there are 2 categories with frequencies equal to 0.82 and 0.18. This power calculation is based on a significance level of alpha = 0.05.

Investigators also wished to determine whether the difference of proportions of individuals detected to have OSA between testing modalities was no larger than 5%.

A sample size of 147 participants achieves 80 % power at a significance level of 0.05 using a one-sided non-inferiority test of correlated proportions when the standard proportion is 0.18, the maximum allowable difference between these proportions that still results in non-inferiority (the range of non-inferiority) is 0.05 or 5%, and assuming the actual difference of the proportions is 0.0.

With 17 months enrollment and an enrollment rate of 80%, investigators anticipate enrolling 150 participants to ensure power >80% for each hypothesis test described above.

G. Summarize Knowledge to be Gained:

We hope to gain the knowledge that the WatchPAT 200 device will be able to detect OSA in children 4-12 years of age with comparable accuracy with an in-laboratory PSG.

H. References:

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