Comparison of High Flow Nasal Cannula Therapy to Nasal O_2 as a Treatment for Obstructive Sleep Apnea (OSA) in Infants

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1. ABSTRACT:

This is a prospective, controlled pilot study to test the effectiveness of High Flow Nasal Cannula (HFNC) therapy in infants 12 months or younger when compared to nasal O_2 for treatment of Obstructive Sleep Apnea (OSA).

2. PURPOSE OF STUDY:

To test the effectiveness of High Flow Nasal Cannula (HFNC) therapy in infants as a treatment for obstructive sleep apnea (OSA) and compare with current standard of care, nasal O_2

3. BACKGROUND:

The current standard of care at Cincinnati Children's Hospital (CCHMC) for treating OSA in infants less than 6 months of age is by a continuous flow of oxygen by nasal cannula[1]. This is generally referred to as nasal continuous positive airway pressure or NCPAP. A nasal cannula (NC) is used with oxygen at low flows (1/4 lpm up to 1 lpm) to deliver supplemental oxygen to reduce oxygen desaturations associated with apneic episodes and to provide a positive pressure flow to maintain an open airway. At the CCHMC sleep center, the titration of the lpm flow of oxygen is done during a clinical polysomnograhy (PSG) with continuous monitoring of cardiorespiratory parameters per SOP 031. At Children's Mercy Hospital (CMH) the titration of lpm flow oxygen is done during the clinical polysomnography with continuous monitoring of cardiorespiratory parameters per Oxygen Administration Policy (Attachment 1).

High Flow Nasal Cannula (HFNC) therapy is a non-invasive treatment providing respiratory support. Over the last decade, HFNC has increasingly been used for oxygen delivery in neonatology departments, gradually replacing nasal continuous positive airway pressure (CPAP). Its use in pediatrics departments is more recent. HFNC is designed to administer a heated and humidified mixture of air or oxygen or a mixture of both at a flow higher than the patient's inspiratory flow. There is currently no single, simple definition of high flow. In infants, it usually refers to a flow of >2 l/min and in children it is considered >6 l/min. High flow presents several advantages over conventional 'low-flow' oxygen therapy in terms of humidification, oxygenation, gas exchange, and breathing pattern[2].

Advantages of HFNC include providing a relative humidity of nearly 100% with the gas warmed to between 34°C and 37°C. Some research has shown this to improve mucociliary clearance. Another benefit of humidification is improved inspiratory flow by reducing resistance in the nasal mucosa induced by dry and cold gas. These resistances are thought to make up nearly 50% of the total resistance of the respiratory system. Several studies have shown that a flow higher than the patient's inspiratory flow provides better oxygen delivery than low-flow oxygen therapy or high-concentration oxygenation mask. This observation has been explained as the effect of a high flow on the oropharyngeal dead space, washing out oxygen depleted gas and reducing CO_2 rebreathing. The extrathoracic dead space is proportionally two to three times greater in children than in adults. It may measure up to 3 mL/kg in newborns and becomes similar to the

adult volume only after 6 years of age (0.8 mL/kg). Consequently, the younger a child is, the greater the effect of a high flow on oxygenation and CO2 clearance[3].

Studies contrasting the delivered flow to the generated pressure as measured by pharyngeal pressure are limited and the results showed wide variations in inter- and intra-subject variability. The pressure is determined not only by the flow, but also by the ratio of the prong/nostril fit and whether or not the mouth is closed. One study of infants with viral bronchiolitis suggested that a flow ≥ 7 l/min created positive pharyngeal pressures similar to CPAP. The positive pressures generated by the device prevent pharyngeal collapse, which may be very pronounced in OSA, and HFNC can thereby support the inspiratory effort of patients[3].

Three rare incidents of pneumothorax or pneumomediastinum with use of HFNC have been reported with the cause believed to be from increases in end expiratory lung volume. These incidents occurred on a 2-month old (bronchiolitis), a 22 month- old (post trauma and mechanical ventilation), and a 16 year old (post-anesthesia). Flow rates ranged from 6–20 L/min at the time of the complication. They all had significant hyperinflation at the time of the development of air leak. The risk of generating excessive pulmonary pressures in children with OSA is reduced because the patients are asleep; with shallower tidal breathing and heated humidified air to prevent bronchospasm. This risk will be further minimized in this study since all subjects will be directly monitored for respiratory flow, effort, and gas exchange throughout the intervention [4, 5].

4. STUDY DESIGN:

This is an interventional prospective controlled pilot study to compare to standard of care the effectiveness of HFNC therapy in infants aged 12 months and younger to treat OSA.

The study intervention will occur for approximately 3 to 4 hours immediately prior to a scheduled clinical polysomnography (PSG). Subjects will be prepared for standard clinical PSG and after asleep, the intervention will be titration of room air at different pressure flows delivered by OptiFlow HFNC system. At the end of the research portion of the PSG, the clinical PSG will begin with the standard of care treatment, the nasal O_2 titration for OSA. The results of the clinical PSG will serve as control comparison for the research intervention.

5. DURATION:

For outpatients, the duration of the study for subjects will be about 1 month and involve 2 visits that will be incorporated into a clinical visit and a clinical PSG (polysomnography). For inpatients, the duration of the study for the subject will be 1 night with a clinical PSG (polysomnography).

The duration of the study will be about 12 months with an additional 12 months for analysis.

6. SELECTION & RECRUITMENT OF PARTICIPANTS:

A. Number of participants

We will recruit about 10 subjects.

B. Inclusion/Exclusion criteria

Inclusion

- Infants ≤ 12 months
- Diagnosis of OSA from previous PSG

Exclusion

- Infants who on previous PSG had central apneas > 50% of the AHI (apnea hypopnea index)

D. Recruitment

At Cincinnati Children's Hospital, participants will be recruited from the Pulmonary / Sleep Disorders Clinic and the inpatient pulmonary consults, including the Newborn Intensive Care Unit (NICU). Potential study participants will be identified by study physicians who will notify and request a member of the research team to discuss participation with the family about the research study. Eligibility based in inclusion exclusion criteria will be reviewed before contacting potential study participants Eligible candidates who are interested, willing and give parental permission for their infant to participate will be enrolled. Any recruitment materials used will be submitted to the IRB for approval prior to use.

At Children's Mercy Hospital, participants will be recruited from the Pulmonary and Sleep Disorders Program and the inpatient pulmonary consults, including the Newborn Intensive Care Unit.

E. Vulnerable Populations

Additional efforts will be made to protect this vulnerable population. Parents will be given clear explanations to define the research portion of the scheduled PSG from the clinical portion as the two will be scheduled on the same day. Parents will be given time to have their questions answered and will be informed that they can withdraw their infant at any point in the study.

7. PROCESS OF OBTAINING CONSENT:

We are asking for a waiver of written HIPAA authorization to identify potential subjects by review of medical records for inclusion/exclusion criteria on the inpatient pulmonary consult team and pending clinic visits. Signed HIPAA authorization will be obtained at the time of written informed consent.

The parent will be given the consent for the study and it will be reviewed with the parent by a member of the research team and time given for questions. The parent will sign the consent after all questions are answered and a signed copy of the consent form will be given to the parent to keep. The parent will be informed that this research is voluntary and that they are able to withdraw their infant at any time. No study related procedures will be done prior to consent being signed.

For non-English speaking subjects:

At CCHMC, non-English speaking participants will be consented using a short form consent process as per CCHMC SOP 41-1.8. The approved long consent form will serve as the summary of the research. At CMH, non-English speaking participants will be consented using a short form consent process as per CMH guidelines.

8. STUDY PROCEDURES:

Visits:	Screen visit	PSG Visit
Sign consent	X	
Med record review	X	X
H&P	X	X
Length, weight	X	
3 hr PSG with HFNC titration procedure		X
Capillary blood gas (not done at CMH)		X

Screening visit:
The screening visit will be during a scheduled clinic visit or chart review once patient is identified with the help of the inpatient pulmonary consult team. Medical record review will include review of Inclusion/exclusion criteria from previous PSG, medical history and recent H&P including length and weight. Informed consent will be obtained

PSG Visit:
Approximately 3 to 4 hours prior to a scheduled clinical polysomnography (PSG), subjects will be prepared for the research portion of the PSG. The following parameters will be recorded:

- Electroencephalogram; right and left electro-oculogram; submental, tibial and intercostal electromyogram
- Electrocardiography (ECG)
- Nasal/oral airflow and through nasal pressure and thermal sensors; transcutaneous CO_2 (TCO_2); oxygen saturation by pulse oximeter; oximeter pulse waveform
- Snore sensor
- Video monitoring using an infrared video camera and recorded on a videotape
- Rib cage and abdominal volume changes will be recorded with a computer-assisted respiratory inductance plethysmograph

<u>HFNC Titration procedure</u>
After asleep, the titration procedure will occur in a step like manner with room air delivered by OptiFlow HFNC system. Subjects will be continuously monitored by sleep technicians who are certified respiratory therapists.

Titration will begin with flow of room air at 6 l/min for 30 minutes after returning to sleep. The subject will be observed for apnea-hypopneas, arousals and changes in O_2, CO_2, and flow.

If the patient continues to have obstructive respiratory events and the flow is tolerated based on pre-established criteria listed in the study SOP, then titration will continue.

Room air will be increased by increments of 2 l/min for 30 minutes to a maximum flow of 15 l/min after returning to sleep until the obstructive events have resolved or until not tolerated.

If a subject does not tolerate a titration, they will be dropped and maintained at the last tolerated flow for the remainder of the 3 hour PSG period (from start of 6 l/min titration) or a minimum of 30 minutes after returning to sleep, whichever is longest.

After the completion of the research portion of the PSG, a capillary blood gas will be drawn and the clinical PSG will begin with standard of care O_2 nasal cannula titration. Blood gas will not be drawn at after completion of the research portion at CMH because it is not standard of care and it is not available.

<u>Airvo 2 Humidifier System and OptiFlow Junior Nasal Cannula:</u>
The Airvo 2 (Fisher and Paykel Healthcare, LTD, New Zealand) is a non-invasive ventilation system that delivers high flow warmed and humidified air. It is FDA cleared (510K131895).

The OptiFlow Junior nasal cannula (Fisher and Paykel Healthcare, LTD, New Zealand) has been determined by the FDA to be 510 K exempt under:
Device Cannula, Nasal, Oxygen
Regulation Description Nasal oxygen cannula.

Regulation Number 868.5340
Classification Class I (general controls). The device is exempt from the premarket notification

9. DATA ANALYSIS/METHODS:
A descriptive analysis will be used for demographic data. The comparison of respiratory and sleep parameters between oxygen therapy and HFNC therapy will be done by means, standard deviation and paired two-tailed T test.

Future use
At the close of the study, the data will be anonymized and the code retained in a secure location separate from the data. The data may be used by the PI for future research particularly longitudinal and safety studies.

10. FACILITIES and PERFORMANCE SITES:
This study will be conducted in the CCHMC Sleep Disorders Clinic, CCHMC inpatient units including NICU and in the CCHMC Sleep Center, and CMH Pulmonary and Sleep Disorders Clinic and CMH Sleep Center (including portable bedside polysomnogram studies performed in the hospital)

11. POTENTIAL BENEFITS:
This study does not offer direct benefit but offers the potential future benefit of a new treatment to this very young population that may be safer, more comfortable and effective than the current standard of care.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:

- Noise: the noise level reaches about 80 dB. The decibel level is correlated with the flow and may be higher than that generated by other CPAP systems[3]. According to the CDC, 80 dB is within the safety margin that should not affect hearing [6].
- Nasal trauma: Nasal cannulas may cause irritation and pressure to the ostium, columella and septum [7]. We will evaluate nasal trauma according to the classification proposed by Buettikeral et al [8]. as mild, moderate, and severe as follows:
    - mild injury will be defined as a reddening around the nasal ostium;
    - moderate injury will be defined as bleeding either at the septum or nasal ostium;
    - severe injury will be defined as necrosis either on the septum or nasal ostium.
- Pulmonary air leaks: three episodes of pneumothorax and pneumodiastinum were reported during HFNC use [4]. At both study sites, subjects will be monitored during use of the HFNC by sleep technicians with the PSG monitoring equipment. Sleep technicians are certified respiratory therapists.

13. RISK/BENEFIT ANALYSIS:
This study is minimal risk with the potential of future benefit.

14. DATA SAFETY & MONITORING:

Adverse events will be defined as any illness or injury from the time of enrollment until the last study visit. Reportable events will be defined as any adverse event that is unexpected **and** related to this study **or** an accidental release of PHI. Reportable events will be reported promptly to the IRB per hospital policy. Adverse events that do not meet the criteria of unexpected **and** related as determined by the PI will be will be submitted in table form at the next continuing review.

Adverse Events Defined

1. Unexpected versus Expected Adverse Events
   An *unexpected* adverse event is one that has not been listed previously in the risk section.

2. Relatedness (Attributions)

Attribution	**Description**
Unrelated	The event is unrelated.
Unlikely	The event is unlikely related.
Possibly Related	The event or severity of event is not usually associated, but there is no strong evidence to link the event.
Probably Related	The event or severity of event is such that it can likely be correlated.
Definitely Related	There is a strong correlation.

3. Severity Descriptors

Severity	**Numerical Value**	**Description**
Mild	1	Aware of sign, symptom, or event, but easily tolerated; does not interfere with daily routine
Moderate	2	Discomfort enough to interfere with daily routine and may require some therapeutic intervention
Severe	3	Incapacitating, significantly affects clinical status; requires therapeutic intervention
Life Threatening	4	Life-threatening; immediate intervention required
Death	5	Adverse event causes death.

15. PRIVACY and CONFIDENTIALITY:

Paper records will be kept in secured areas. All subjects enrolled in this study will be identified by a unique study number only. Protected health information other than dates will not be entered into a database. The code linking medical record number to study number will be kept in a secure manner and access restricted to the research team. All computerized records will be kept on a CCHMC and CMH secure network.

The results of this study may be published and presented to the public, and used for educational purposes. No information that could identify a subject will be used in any publication or presentation.

16. COST OF PARTICIPATION: *

The cost for the clinical PSG is not paid for by the research and is the responsibility of the subject and their insurance. There will be no additional charges to the insurance for any of the research procedures because PSG is a single charge independent of time in the sleep center. The capillary blood gas is not a research charge as it is part of the clinical oxygen titration SOP at CCHMC.

17. PAYMENT FOR PARTICIPATION:

Subjects will receive $50.00 as compensation in the form of a reloadable debit card (ClinCard) for completion of the study.

References

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