

Protocol

HFNC

Physiological Changes with High-Flow Nasal Cannula compared to Nasal CPAP in Extremely Low Birth Weight Infants.

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Sponsor:

None

Objective

To measure changes in physiologic parameters in extremely low birthweight (ELBW) infants on high-flow nasal cannula compared to nasal continuous positive airway pressure (nCPAP).

Background and Significance

Non-invasive ventilation with nCPAP is commonly used in ELBW neonates for post extubation respiratory support and improves the rate of extubation success. (1) Pressure is transmitted from the nCPAP device to distend the upper airways and lungs to promote gas exchange. (2) Nasal masks or short nasal prongs that fit snugly in the nose to provide nCPAP can cause damage to the delicate skin of the bridge of the nose or nasal septum. Although skin damage from nCPAP is usually mild it can lead to serious skin break down and functional and cosmetic side effects. High Flow Nasal Cannula (HFNC) are widely used in Neonatal Intensive Care Units (NICU's) worldwide. HFNC have a simpler, softer interface leading to less nasal trauma and easier patient positioning facilitating mother infant bonding. (3) HFNC leads to significantly less nasal trauma than nCPAP in the first 7 days post extubation especially in ELBW infants. (4) Other benefits of HFNC include reduced infant pain scores and survey's showing it is preferred by both nurses and parents. (5) Recent meta-analysis of HFNC in neonates have concluded "non-inferiority" (6) or "similar rates of efficacy" (7) compared to other methods of non-invasive respiratory support.

There are currently inadequate data on the effects of HFNC in ELBW, or infants <29 weeks gestational age. A recent Cochrane Review (7) included only four small trials studying HFNC as a post-extubation modality including ELBW infants (1, 3, 8, 9). While nCPAP has been shown to be effective as post extubation support in infants with respiratory distress syndrome, it is unclear whether ELBW infants can be successfully transitioned to HFNC once they are stable on nCPAP, due to the small number of ELBW babies in previous studies. Further trials of HFNC in this population, which is the population at highest risk of chronic lung disease and neurodevelopmental impairment,

are required. Furthermore, the starting flow rates currently used for HFNC may vary based on the severity of lung disease, gestational age, and a variety of other factors including clinician preference. (10). A physiological study evaluating lung mechanics and hemodynamics comparing nCPAP to HFNC on 8 liters per minute may be a practical first step to understanding HFNC comparability to nCPAP.

Research Design and Methods

Prospective crossover study (nCPAP to HFNC and back to nCPAP) of 80 stable premature infants born at <29 weeks requiring nCPAP therapy at Sharp Mary Birch Hospital for Women & Newborns (SMBHWN) NICU. The primary endpoint to be used for efficacy evaluation is the percentage of atelectasis as measured by EIT. The non-inferiority margin is set at 3% (0.03). In order to have at least 80 percent power with a one sided alpha of 0.05 at least 40 subjects in each arm would be required. If non-inferiority is established by rejecting that the outcome event rate is worse by 1% or more in the HFNC group, then superiority will be tested at the 3% level. For all superiority testing, the intention to treat analysis will be utilized with a per protocol analysis as a sensitivity analysis. There are no published references using EIT. The study period is up to 8 hours. The enrollment period is estimated at 2-4 years or until the requisite sample size is achieved, whichever is earlier. The pace of enrollment will be influenced by the number of neonates born in the desired gestational age who are utilizing the type of respiratory support under study.

The investigator will ensure that all physicians assisting in the trial are informed at monthly meetings, the respiratory therapists and nurses at the bedside will be educated at weekly meetings (change of shift and sign out rounds).

Inclusion Criteria:

- 23 to 28+6 weeks at birth
- Corrected gestational age less than or equal to 30 weeks

- Over 72 hours of life
- Stable on Nasal CPAP of 5-7cm H₂O
- Hemodynamically stable
- Tolerating routine handling
- Nares size appropriate for Fisher & Paykel Optiflow Jr 2 HFNC size XS or small
- Successfully extubated for 12 hours after administration of surfactant
- Caffeine Citrate at a maintenance dose of 5 to 10 mg /kg
- Transcutaneous monitoring in place
- Stable blood gas (pH \geq 7.25 and PaCO₂ < 60 mmHg torr)

Exclusion Criteria:

- Prior pneumothorax or evidence of pulmonary interstitial emphysema.
- Prior or current pulmonary hemorrhage
- Congenital malformations of the upper airway
- Congenital Diaphragmatic hernia or untreated bowel obstruction
- Poor respiratory drive unresponsive to CPAP therapy.
- Requirement of a nCPAP of >8 cmH₂O or FiO₂ > 0.3 to maintain oxygen saturations between 90-95 percent.
- Receiving positive pressure breaths or SIPAP on prongs
- Conflicting clinical trial
- Clinically unstable per physician discretion

Screening & the Informed Consent Process

Subjects will be identified by reviewing the medical records of neonates in the NICU at SMBHWN, which will require a partial HIPAA waiver and informed consent waiver limited to screening purposes. The parents or guardians of the potential subjects will be approached for consent if: The subject qualifies for the trial after a review of the study inclusion and exclusion criteria, and the subject's physician also agrees to allow participation in the trial. Consent will be obtained by the primary investigator or a delegated

sub-investigator or research associate prior to any research procedures. The mother, or legally authorized representative must sign the informed consent document. Mother (or surrogate mother) must sign a HIPAA authorization providing access to her medical records for collection of maternal data. Either mother or father or legal guardian can sign a HIPAA authorization providing access to the child's medical records for data collection purposes. The subject's legally authorized representatives will be given ample time to read the informed consent, ask questions of the research team, and discuss the study with their family and/or the subject's physician. The informed consent process will be documented in the electronic medical record and copies of the signed and dated consent will be given to the subject's representatives, placed in the subject's physical chart, and stored in a locked cabinet in the offices of the Neonatal Research Institute.

Description of Intervention

Study Period 1

After informed consent is obtained, eligible infants who are stable on nCPAP therapy of 5-7 cm H₂O achieved with a ventilator, an underwater "bubble" system, or a variable-flow device will be enrolled. (Figure 1) All of these methods of providing the therapy are done with FDA approved devices in current use in the NICU. NCPAP treatment can be delivered through short nasal prongs or a nasal mask with sizing per manufacturer's instructions. A data acquisition cart will be placed at the subject's bedside to collect hemodynamic and respiratory parameters measured including: Heart rate (HR), blood pressure (BP), respiratory rate (RR), fraction of inspired oxygen (FiO₂), transcutaneous carbon dioxide (TcCO₂), and peripheral oxygen saturation (SpO₂) via bedside monitoring devices. A neonatal chest belt, sized to the infant's chest circumference (nipple level) using warmed ultrasound gel applied to the belt beforehand, will collect regional lung volume measurements using electrical impedance tomography (EIT). EIT is currently not used for patient care management at SMBHWN. EIT's use for patient care management is purely experimental. EIT, when used solely for physiologic data collection, its use is not subject to 21 CFR 50, 21 CFR 56, or 21 CFR 812. Subject video recording will capture apnea events and the interventions used to resolve them such

as positive pressure ventilation, repositioning, or stimulation. Data will be collected for approximately 15 minutes or less on nCPAP. Data collection via EIT will occur when the subject is in a quiet, sleeping state, and can be accomplished in a convenient time period when care givers or parents are not interacting with the subject.

Study Period 2

Once data has been collected on nCPAP, the infant's respiratory support will be crossed over to a HFNC Optiflow Jr 2 (Fisher & Paykel Healthcare, Auckland, New Zealand) at a flow rate of 8 LPM. (Figure 2) The size of the nasal cannula will be determined according to the manufacturer's instructions in order to maintain a leak at the nares. After 30 minutes of cross over to a HFNC Optiflow Jr, identical data collection will be obtained for 15 minutes or less on HFNC as occurred in Study Period 1.

Study Period 3

After 6 hours on HFNC of 8 LPM, identical data collection will be collected for approximately 15 minutes or less prior to cross back to nCPAP.

Study Period 4

The infant will then be crossed back to the nCPAP device and at the settings previously utilized in Study Period 1. The infant will remain on the nCPAP device and settings. After 30 minutes of crossover to nCPAP, and infant is in a quiet, sleeping state, identical data collection will be obtained for approximately 15 minutes or less. The total duration of the study and data collection will be 8 hours or less. The infant's body position will be similar for each EIT measurement during the study periods. EIT will not be used for any medical decision making during or after the study period of 8 hours. Information for clinical decision making and any patient interventions will be guided by information from the NICU bedside monitors and dictated by the assessment of the clinical team.



Figure 1 Nasal Continuous Positive Airway Pressure with Inca prongs



Figure 2: High Flow Nasal Cannula Optiflow Jr 2

Patient Discontinuation and withdrawal

The participant's parents are free to withdraw the participant from the trial at any time, and this will not have any consequences for the participant's further treatment. Parents will be notified if the subject fails HFNC. The attending physician can withdraw the participant from the trial at any time.

HFNC failure criteria:

Subjects should be returned to nCPAP if at HFNC of 8 LPM:

- there is any hemodynamic instability (bradycardia and hypotension (i.e. mean arterial pressure less than gestational age)
- there is respiratory deterioration i.e. significant sustained increase in oxygen requirement (more than a 0.2 increase in FiO_2) or increase in $\text{PaCO}_2 > 15$ mm Hg and above ordered parameters.
- there is an apneic event requiring positive pressure ventilation.
- Device associated pressure injury stage I/II

Compliance with the Protocol

The clinical investigation will be conducted in compliance with this protocol. Modifications to the protocol will not be implemented before the relevant ethics committee approvals are obtained. Any serious or safety related deviation will be recorded, summarized and monitored. All research study personnel will be adequately trained on the research protocol, trial related duties and functions, and equipment utilized by the research staff. All medical decisions will be made by subject's physician and clinical care team not by the research team.

Enrollment in any concurrent research trials that may involve patients who are eligible for this HFNC study must be approved by the PI for co-enrollment after review of the protocols.

Potential Risks

There should be no more risks for babies in this study than are possible for any ELBW baby needing intensive care. HFNC and nCPAP are commonly used in our NICU. A recent review of all of the studies using HFNC found no significant differences in safety outcomes between HFNC and other methods of respiratory support such as nCPAP. As with all procedures, when the respiratory modality is changed or when the non-adhesive belt is placed around the baby, there is a possibility the infant will have a change in vital signs such as a brief oxygen desaturation. We will make every attempt to minimize this. The EIT that is placed around the chest of the baby could result in skin irritation. Skin assessments will occur and device-associated pressure injuries will be addressed per current SMBHWN NICU unit policy and guidelines of care. If any breakdown or barotrauma from devices would occur they would be treated as clinically indicated by the appropriate team (wound RN etc.)

All of the devices that are being used in this study (nCPAP and High Flow Nasal Cannula) are currently being used in the SMBHWN NICU as part of routine care, and are being used in accordance with their FDA-approved/cleared labeling.

Expected Adverse Events

The population being studied is at increased risk of all complications associated with prematurity and the following adverse events are expected for neonates < 29 weeks gestational age and will be included in data collection:

1. Intraventricular Hemorrhage
2. Periventricular Leukomalacia
3. Sepsis
4. Chronic Lung Disease
5. Necrotizing Enterocolitis
6. Spontaneous Intestinal Perforation
7. Patent Ductus Arteriosus requiring treatment

Potential Benefits

There are no direct benefits to participation in this trial. If the investigators are able to show a physiologic similarity between HFNC and nCPAP, a transition from nCPAP to HFNC may be shown to be possible for this population.

Expense to Subjects

There is no added expense for the subject to be in the study.

Compensation to Subjects

There is no compensation for the subject in the study.

Waiver of Informed Consent and Waiver of HIPAA Authorization for Pre-Screening

Waivers of informed consent and of HIPAA Authorization are requested for pre-screening medical records. The use or disclosure will not adversely affect the rights and welfare of the subjects. This research protocol cannot be conducted without partial waiver because investigators would be unable to identify eligible subjects. This will involve no more than minimal risk to the privacy of subjects. Only research investigators/assistants will access PHI for eligibility and screening purposes.

PHI that will be accessed for screening will be identifiable on research-related forms by a study number. We will take the following precautions to maintain the confidentiality of identifiable subject information. We will also keep subject's identity separate from their data on a Master log and coded. PHI will not be used or disclosed to any other person or entity, except as required by law.

1. Paper-based records will be kept in a secure location and accessible only to persons involved in the study
2. Computer-based files will be available only to persons involved in the study through the use of access privileges and passwords.

3. Prior to accessing any PHI, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable health information
4. Whenever feasible, identifiers will be removed from study-related information
5. PHI will not be disclosed or re-used for other purposes
6. Collect only the minimum necessary subject identifiers.
7. Remove/destroy subject identifiers as soon as they are no longer needed. See the following website for [record retention requirements](#).
8. Limit physical access to any area or computer that contains subject identifiers.
9. Limit electronic access to any computer that contains subject identifiers.
10. Avoid storing subject identifiable data on portable devices (such as laptop computers, digital cameras, portable hard drives including flash drives, USB memory sticks, iPods or similar storage devices) as these devices are particularly susceptible to loss or theft. If there is a necessity to use portable devices for initial collection of subject identifiers, the data files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.
11. Remove necessary subject identifiers from data files, and encrypt data files if stored electronically. Identifiers will be stored in a physically separate and secure location from the data files, and associated with the data files through a key code that is also stored in a separate and secure location.
12. Use only secure modes of transmission of data; subject identifiers submitted over a public network will be encrypted.
13. Review the [Information Security & Privacy website](#) for additional recommendations on how to best secure confidential data.
14. If there is an inadvertent breach of confidentiality of the research data which causes harm or places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm), the Lead Researcher will report this to the IRB through the electronic [Unanticipated Problems](#) reporting process within 5 working days of the researcher becoming aware of the event.

15. Assurance that the privacy of the subject will be maintained by avoiding discussions about the patient within earshot of other patients or non-paripants.

Outcome Measures

Primary Outcome

- **% Unventilated Lung:** The primary endpoint to be used for HFNC efficacy evaluation as compared to nCPAP is the percentage of unventilated lung as measured by EIT. The non-inferiority margin is set at 3% (0.03). If non-inferiority is established by rejecting that the outcome event rate is worse by 1% or more in the HFNC group, then superiority will be tested at the 3% level. For all superiority testing, the intention to treat analysis will be utilized with a per protocol analysis as a sensitivity analysis. Atelectasis will be calculated using the percentage of the lung fields that are not engaged in tidal volume (VT) during the recording with the in-built silent space algorithm. This provides a quantitative value for relative atelectasis and also describes the regional distribution of atelectasis within the chest.

Secondary Outcomes

- **Geometric Center of Ventilation(CoV)** HFNC compared to nCPAP: CoV is a numeric value that describes the geographic point within the thorax that represents the statistical center of VT and is calculated from the EIT VT data and the mathematically determined point of perfect VT homogeneity within the chest based on the patients age and chest shape. It is calculated on a right/left and dependent/non-dependent plane, and described as the percentage point between the extremes of that plane. As the chest is not circular and the lung contents not uniform in shape within the chest, the CoV is referenced to the expected CoV for uniform ventilation within the chest shape. The magnitude of the CoV difference from this ideal provides a simple numeric index for the degree and direction of ventilation inhomogeneity. For example, in the human lung the

ideal non-dependent to dependent CoV is 63%. Thus a value of 55% would indicate greater ventilation in the non-dependent lung.

• **Functional Tomography Images: % of total VT within 8 lung regions, relative change in uncalibrated aeration (end-expiratory lung volume) and tidal volume.** The pattern of VT and atelectasis distribution of HFNC compared to nCPAP periods and will also be displayed using a functional tomogram. The % of total VT within 8 lung regions (4 right lung and 4 left lung) of equal anatomical size. The relative change in uncalibrated aeration (end-expiratory) and tidal volume will be determined from the trough and peak-to-peak height of the time-volume EIT within the 8 regions of interest.

All of the following will be compared between HFNC and nCPAP periods (Time period 1, 2, 3, 4):

- **Oxygenation**, expressed as the $\text{SpO}_2/\text{FiO}_2$ ratio
- **Incidence of Oxygen Desaturation** (defined as a $\text{SpO}_2 < 90\%$).
- **Incidence of Apnea (20 seconds)**
- **Incidence of Bradycardic (HR < 100)**
- **Events Requiring Interventions** (type and number of interventions)
- **The Relationship Between Oxygenation and VT Homogeneity** (ratio of the $\text{SpO}_2/\text{FiO}_2$ to % atelectasis)

Data Collection & Data Analysis

Maternal and Infant demographics will be collected from the mother's and/or infant's electronic medical record. Maternal information is critical to assess how maternal morbidities such as infection, growth restriction could confound the treatment effect. The data regarding clinical interventions during the study period will be collected on an electronic case report form from the electronic medical record. All physiologic data during the study period will be recorded using a real-time data acquisition system which includes

video as well as physiologic data for all monitored infants. Data is collected, processed, and analyzed using Acqknowledge software. Heart rate via Electrocardiogram (ECG), BP, FiO_2 , TcCO_2 , and SpO_2 , are sampled at 200 samples per second (Hz), and the files will be linked to the video to allow for review of temporal relationships. EIT data will be acquired at 48 frames per second using the cross-sectional neonatal chest belt sized to the infant's chest circumference. This belt consisted of 32 integrated AgCl electrodes woven into a non-adherent material which enclosed 0.5 cm of foam padding and flexible printed circuitry to allow unobstructed chest wall movement. Conductance with the skin is achieved using warmed ultrasound gel applied to the belt beforehand. The belt is placed on the infant prior to recording and secured around the chest at nipple level and below the armpit using a Velcro tab. Parameters will be continuously recorded over 15 minutes or less of quiet breathing in the supine position and repeated during each study period to account for the potential of movement artifact and variable ventilation patterns. The EIT files will be analyzed post hoc in IBEX-neo using anatomic finite element models of the human infant chest. Acqknowledge and EIT data will be analyzed to determine stable artifact free periods of tidal ventilation (using video confirmation). From these a total of six 30 s segments will be chosen from each study period to be used for data analysis. The infants will also be maintained in similar positions in both arms. This will be confirmed with continuous video recording. For all measurements, the absolute change in a physiological parameter is of lesser importance in this study than the relative change from a baseline state. Consequently all parameters will be described as the change from the baseline value as well as the absolute value.

As a single center trial we will review the safety outcomes and report all SAEs to the IRB. Adverse outcomes will be reviewed in real time and submitted in progress reports. A DSMB is not needed for lower risk single center studies like this.

Data Security

Each subject will be assigned a study subject ID number. This ID number will also be used on other CRFs and data collection tables or spreadsheets. No other patient identifiers will be used. Only investigators and research personnel who are involved with

the study will access EMRs or physiologic data files. Access to direct identifiers will be limited to research staff who meet all relevant training requirements and are assigned to or support this project, and who must have access to these identifiers. This will be stored on the Sharp NRI network drive on firewall-protected secure servers. Video and physiologic recordings will be viewed and maintained at Sharp HealthCare on a password protected system. Only investigators who are involved with the study will have access. All investigators, statisticians, and staff will have completed the Human Subjects Protection training. Data, such as the final results of the study or de-identified data collected as part of the study, may be shared with co-investigators or Fisher & Paykel Healthcare so that they may better understand breathing patterns of premature babies on HFNC and nCPAP. Fisher & Paykel Healthcare will not use the data for marketing purposes. Following completion of the study, documentation will be stored in secure long term storage per hospital policy.

Publication plan

The study will be registered in ClinicalTrials.Gov prior to the enrollment of the first subject. Attempts will be sought to publish all results, positive, neutral, as well as negative, in a peer-reviewed international journal.

Appendix One: Data Collected

References

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Appendix 1

DATA COLLECTED FROM INFANTS AND MOTHERS

Clinical Data collected from all enrolled mothers:

1. Age
2. Race/Ethnicity
3. Antenatal Steroids (yes/no) (include partial course)
4. Antenatal Magnesium (yes/no)
5. Diabetes (gestational, Type 1 or 2) (yes/no)
6. Chorioamnionitis (yes/no)
7. Hypertension/Pre-eclampsia (yes/no)
8. Rupture of Membranes (hours)
9. Mode of Delivery

Clinical Data collected from all enrolled infants:

10. Gestational Age
11. Multiple gestation (yes/no)
12. Gender
13. Birthweight (grams)
14. APGARS at 1 and 5 minutes
15. Race/Ethnicity

Measured Endpoints and Recorded Outcomes

Primary Outcome

16. % unventilated lung

Secondary Outcomes

17. Geometric centre of ventilation (CoV)
18. % of total VT within 8 lung regions
19. End Expiratory Lung Volume
20. Oxygenation (SpO₂/FiO₂ ratio)
21. Incidence of oxygen desaturation (SpO₂ <90%)
22. Apneic and bradycardic events requiring interventions (type and number of interventions)
23. The relationship between oxygenation and VT homogeneity (ratio of the SpO₂/FiO₂ to % atelectasis)
24. Hemodynamic & Respiratory Parameters during the study period (HR, BP, RR, FiO₂, TcCO₂, SPO₂)

Resuscitation Interventions

25. Maximum inspired oxygen (FiO₂) (percentage)
26. DR Interventions: PPV, CPAP, intubation, chest compressions, medications (Y/N)
27. Intubation (yes/no) (indicate Delivery Room or NICU)
28. Surfactant (yes/no) (Delivery Room or NICU)

Clinical Outcomes

29. SGA (<10%)
30. Venous and/or arterial cord gas (pH+BE)
31. Worst BE on blood gas within 1 hour of life
32. Use of cardiac inotropes (dopamine, dobutamine, epinephrine) (yes/no)
33. Presence of any intraventricular hemorrhage (yes/no)
34. Presence of severe intraventricular hemorrhage (Grade 3 or 4) (yes/no)
35. Presence of PVL, echodense lesions or ventriculomegaly on any US prior to discharge (yes/no)
36. Early onset sepsis (positive blood or CSF culture at \leq 72 HOL) (yes/no)
37. Late onset sepsis (> 72 HOL) (yes/no)
38. Chronic lung disease (receiving supplemental O₂ at 36 weeks (yes/no)
39. Duration of intubated and mechanical ventilation (days)
40. Necrotizing Enterocolitis Bell (Stage \geq 2) (yes/no)
41. Spontaneous Intestinal Perforation
42. Retinopathy stage 3 or greater (yes/no)
43. Patent Ductus Arteriosus requiring treatment (medical and/or ligation) (yes/no)
44. Length of hospitalization (total days)
45. Death (only)