A COMPARISON OF NON-INVASIVE VENTILATION METHODS USED TO PREVENT ENDOTRACHEAL INTUBATION DUE TO APNEA IN VERY LOW BIRTH WEIGHT INFANTS

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Introduction:

Apnea of prematurity is an almost universal problem in the very low birth weight (VLBW) infant population. Apnea refers to a pause in breathing for greater than 20 seconds. It can affect more than 50% of preterm infants.[1-3] Apnea of prematurity can be controlled through the use of caffeine, a central nervous system stimulant; however, some patient's apneic events cannot be managed on caffeine alone and if severe enough, may require endotracheal intubation and invasive mechanical ventilation.[4] Multiple complications are associated with this procedure including airway trauma that may result in subglottic stenosis and tracheal stenosis as well as the increased risk of hospital-acquired pneumonia.[5] In addition, a prolonged duration of mechanical ventilation in the VLBW population has been associated with an increased risk of death or survival with neurologic impairment.[6]

Non-invasive ventilation is another tool used in an attempt to reduce apneic events in preterm infants. When applying different modes of non-invasive ventilation for apnea prevention, small studies have shown that nasal intermittent positive pressure ventilation (NIPPV) is more effective in reducing apneic evens when compared to nasal continuous positive airway pressure (NCPAP). [5,7] A larger, more recent trial primarily revealed that there is no significant difference in bronchopulmonary dysplasia (BPD) outcomes when comparing the use of NIPPV and NCPAP in VLBW infants. However, this study did not specifically address the need for reintubation due to apnea between the two groups.[6]

This proposed study is to determine whether NIPPV reduces the need for endotracheal intubation in very low birth weight infants who fail NCPAP secondary to apnea.

Study question:

Among infants <30 weeks gestational age, does NIPPV reduce the need for endotracheal intubation in very low birth weight infants with persistent apnea despite NCPAP?

P: Preterm infants <30 weeks gestational age requiring non-invasive ventilation for whom intubation is being considered secondary to apnea

I: NIPPV as rescue method for apnea prevention

C: Continued NCPAP as alternative method for apnea prevention

O: Frequency and duration of required endotracheal intubations between both groups over 28 day time period

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Study Population:

- **Inclusion criteria:**
  - Infants born at < 30 weeks gestational age who develop clinically significant apnea while on NCPAP ≥ 6cm H_2O or whose team is considering intubation due to apnea
    - Consider clinically significant apnea as 1 or more events treated with bag-mask ventilation or 3 episodes of apnea requiring stimulation within 1 hour
  - Infants on maximum caffeine therapy (10mg/kg/day)

- **Exclusion criteria:**
  - Major congenital anomalies including congenital heart disease

Allocation Plan: Blinding is not possible due to technological constraints. Subjects will be randomized, once the subject meets eligibility criteria.

Interventions:

NCPAP as mode for apnea prevention: After randomization, with recurrence of apneic events, infants on NCPAP will have changes made in NCPAP settings per the team's discretion in attempt to prevent future apneic events.

If apneic events persist despite NCPAP adjustments, clinicians may intubate based on clinical judgment.

NIPPV as rescue mode for apnea prevention: After randomization, with recurrence of apneic events, infants will be placed on NIPPV with settings and adjustments per the team's discretion.

If apneic events persist despite NIPPV placement and setting adjustments, clinicians may intubate based on clinical judgment.

- When an infant in either arm is deemed stable by the team for de-escalation of care, the method in which this is performed is per the team's discretion for both groups.

  All infants randomized to the NIPPV arm will remain in the NIPPV arm until the end of the study; meaning, if an infant has been weaned from NIPPV to CPAP but again develops apnea within the study period, NIPPV will continue to be a rescue mode for apneic events prior to endotracheal intubation.

End of study:

- Each patient will be followed for 28 days from randomization OR until his/her second required intubation within the 28-day time period.
- If an infant requires intubation while on either arm of the study and later tolerates extubation still within the 28-day study period, the infant will remain in his/her assigned arm of the study.
- If an infant develops hemodynamic instability at the time of proposed study intervention and immediate intubation is warranted, then the non-invasive trial can be deferred. However, for those infants that have been randomized, any intubation during the study period will still be included in primary outcome analysis.
- If infants in either group are deemed stable for wean off of NIPPV or CPAP, those patients may be eligible to enter the CPAP weaning study.

Outcomes: The primary outcome of interest is whether there is a difference in the need for endotracheal intubation due to apnea between the NIPPV and NCPAP groups during the 28-day duration of the study.
Secondary outcomes to be analyzed will be the number of apneic events that occur after intervention, rates of BPD, air leaks, and necrotizing enterocolitis (NEC), weight gain at 36 weeks corrected gestational age, length of hospital stay, and death.

Sample size calculation: The first phase will be a pilot study – the study will run for one year or until 50 patients have been enrolled. The data from this initial phase will be used to estimate the sample size for the subsequent definitive trial.

Data analysis:
Baseline characteristics to be collected:

- Gestational age
- Birth weight
- Prenatal steroids
- Surfactant use
- Corrected gestational age at enrollment
- Weight at enrollment
- Duration of mechanical ventilation
- Co-morbidities such as NEC, sepsis episodes, IVH, treatment of PDA

Outcome indicators to be collected

- Number of intubations during enrollment
- Duration of intubations during enrollment
- Number of apneic events after intervention
- Rates of BPD, NEC and air leak disorders
- Weight gain at 36 weeks corrected gestational age
- Length of hospital stay
- Death

Statistical analysis plan: Data will be analyzed using t-test for continuous variable and chi-square for categorical assuming parametric criteria can be satisfied. Data will be reported as unadjusted and adjusted for gestational age, birth weight, prenatal steroids administrations, surfactant administration, and duration of mechanical ventilation by performing multivariate analysis generalized linear models.

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