A COMPARISON OF METHODS OF DISCONTINUING NASAL CPAP IN PREMATURE INFANTS <30 WEEKS GESTATION – A FEASIBILITY STUDY

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A COMPARISON OF METHODS OF DISCONTINUING NASAL CPAP IN PREMATURE INFANTS <30 WEEKS GESTATION – A FEASIBILITY STUDY

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Introduction: Nasal continuous positive airway pressure (NCPAP) mode of respiratory support is now widely used to support premature infants, especially those who are less than 30 weeks of gestation.[1-2] Recently, three large studies have shown that NCPAP therapy initiated in the delivery room is equally effective as prophylactic surfactant in the treatment of respiratory distress syndrome (RDS).[3-5] Additionally, volutrauma and atelectrauma have been implicated in the development of Bronchopulmonary dysplasia (BPD).[6] Therefore, premature infants are being preferentially treated with NCPAP rather than mechanical ventilation. However, while there is significant body of literature justifying the use of NCPAP, very little is known about how long to continue CPAP and more importantly how and when to wean off NCPAP. There are three published trials, one of which showed, that infants are likely to tolerate being taken of NCPAP after gradual reduction in pressure with some increase in oxygen need.[7] The second trial showed, that weaning from NCPAP to supplemental oxygen via high flow nasal cannula (HFNC) did not decrease duration of NCPAP therapy but, increased the duration of oxygen use.[8] Another recent trial showed, that discontinuation of NCPAP, rather than cycling NCPAP, results in faster weaning off CPAP. In clinical practice, CPAP is either discontinued regardless of the pressure or, the pressure is gradual reduced before discontinuing CPAP based on individual physician preferences. However, a clinical trial comparing discontinuation of NCPAP with and without weaning the CPAP pressure has not been published. Therefore, this is a feasibility study comparing two strategies of discontinuing NCPAP.

Study question:

Among infants <30 weeks gestational age on NCPAP, does discontinuing CPAP after gradual reduction in CPAP pressure leads to successful weaning off CPAP when compared to discontinuing CPAP without weaning pressure.

P: Premature infants <30 weeks gestation requiring NCPAP therapy for respiratory support who are ready to wean NCPAP

I: Wean NCPAP pressure gradually before discontinuing NCPAP

C: Discontinue NCPAP without weaning pressure

O: Number of total days on NCPAP after wean started or discontinuation, failure to wean off NCPAP, time to failure, need for intubation

T: 28 days after randomization

Study Population:

- **Inclusion criteria:**
  - All infants < 30 weeks by dates, on NCPAP therapy, on caffeine 10mg/kg daily
  - Meet CPAP stability criteria for ≥ 12hours
    - CPAP 6 cm H2O
    - FiO2 </=0.25 and stable (to maintain sats 85-95%)
    - Respiratory rate consistently less than 60
    - Mild to no subcostal/intercostal retractions
    - No Apnea or bradycardia event that requires bag mask ventilation
    - Less than 3 apnea/brady/desat episodes in any 1 hour period for previous 6 hours.
    - Tolerated time off CPAP during routine CPAP care (~15 min)

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- **Exclusion criteria:**
    - Major congenital anomalies including congenital heart disease
    - Anomalies that prevent discontinuation of NCPAP
    - Undergoing current evaluation for and/or treatment of sepsis

Allocation Plan: Blinding is not possible due to technological constraints. Subjects will be randomized using permuted blocks using 4-6-6 scheme. Assignment will be sequentially numbered and placed in opaque envelopes. Consent will be obtained in first 48hrs of life in potentially eligible patients. Subjects will be randomized once the subject meets eligibility (CPAP stability) criteria.

Interventions:

1. **Discontinue NCPAP after weaning pressures**: After randomization, CPAP pressure will be weaned by 1 every 24hours as long as the subjects continue to meet stability criteria after each wean, until CPAP of 4. If after decrease in CPAP pressure, the subject meets CPAP failure criteria (described below) pressure will be increased back to the previous level and after stabilization for 24 hours weaning process will be started again. Once the subject meets stability criteria on CPAP of 4, NCPAP will be stopped and subject will be placed on nasal cannula (NC) according to unit guidelines (max 1L flow, 30% FiO2). Subjects will be considered to have failed CPAP discontinuation if they meet any one of the CPAP failure criteria after routine suctioning and prone positioning:
    - Respiratory rate >75 consistently
    - Respiratory distress defined as moderate-severe retractions, grunting, nasal flaring that persists for >30 min
    - FiO2 >30% for 6 hours* (to keep oxygen saturations 85-95%)
    - Apnea or bradycardia that requires bag mask ventilation
    - >2 apnea/bradycardia episodes in 1 hour period

    Subjects will be restarted on CPAP of 6 and will be allowed to recover for 1 week. After 1 week, the weaning procedure will start again if the subject meets CPAP stability criteria.

2. **Discontinue NCPAP without weaning pressures:** After randomization, once the subject meets stability criteria, NCPAP will be stopped and subject will be placed on nasal cannula (NC) according to unit guidelines (max 1L flow, 30% FiO2). Subjects will be considered to have failed CPAP discontinuation if they meet any one of the CPAP failure criteria as described before. Subjects will be restarted on CPAP of 6 and will be allowed to recover for 1 week. After 1 week, the weaning procedure will start again if the subject meets CPAP stability criteria.

End of study: Each patient will be followed for 28 days from randomization OR failure of CPAP wean x 2 attempts. Should patient need further escalation of care from CPAP, will be eligible to enter NIPPV study.

Outcomes: Primary outcome of interest is the number of days on NCPAP or mechanical ventilation from randomization until discharge (1 day= 0-24h). Secondary outcomes to be analyzed will be duration of endotracheal ventilation, failure to wean off NCPAP, rate of BPD, rate of NEC, time to full PO ad lib feeds, length of hospital stay, rate of air leak disorders.

Sample size calculation: This type of intervention has not been reported in literature as a result we have no prior data to help us determine the sample size. Therefore, this study will carried out in two phases. During the initial phase, the study will be carried out for 1 year. The data from the first phase will be used estimate the sample size for the subsequent definitive trial. The initial goal for enrollment is 50 patients.

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 NCPAP before enrollment
- Duration of mechanical ventilation
- Co morbidities such as NEC, Sepsis episodes, IVH, treatment of PDA

Outcome indicators to be collected

- Total days on NCPAP since enrollment
- Total days on endotracheal ventilation since enrollment
- Time to wean off NCPAP
- Number of attempts
- Total days until full PO feeds
- Length of hospital stay

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, CPAP duration and mechanical ventilation before weaning off NCPAP. Difference between times to wean off NCPAP will be assessed using survival analysis (Kaplan-Meier methods for unadjusted and/or Cox proportional hazards analyses for adjusted (multivariable) outcomes).

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