Nasal high frequency oscillation ventilation versus nCPAP to reduce post-extubation pCO_2 in very low birth weight infants: a randomized controlled trial

Objectives

To investigate whether nasal high frequency oscillation ventilation (nHFOV) immediately after extubation reduces the $paCO_2$ in comparison with nasal continuous positive airway pressure (nCPAP) at 72 hours after extubation in very low birth weight infants (VLBWs).

Protocol/Methods

1. **Trial design**

   Randomized controlled clinical trial of nHFOV versus nCPAP immediately after extubation.

2. **Participants**

   Eligibility criteria

   - Gestational age <32+0 weeks
   - Birth weight <1500 g
   - Received mechanical ventilation via an endotracheal tube for ≥120 h
   - Caffeine treatment according to unit guidelines
   - Arrival at the preset extubation criteria:
     - Time-cycled, pressure-controlled ventilation:
       PIP ≤22 cm H_2O, PEEP ≤6 cm H_2O,
       F_iO_2 25-40% to maintain SpO_2 at 90-94%.
       $paCO_2$ <65 mmHg with pH >7.2
     - Volume guarantee ventilation:
       Working P_{peak} ≤22 cm H_2O, PEEP ≤6 cm H_2O
       F_iO_2 25-40% to maintain SpO_2 at 90-94%.
       $paCO_2$ <65 mmHg with pH >7.2
     - High frequency oscillation ventilation: set P_{mean} ≤12 cm H_2O, Amplitude ≤30 cm H_2O
       F_iO_2 25-40% to maintain SpO_2 at 90-94%.
       $paCO_2$ <65 mmHg with pH >7.2
   - Decision of the attending clinician to extubate

   Exclusion criteria

   - Major congenital malformation requiring surgery (e.g. esophageal atresia, diaphragmatic hernia, abdominal wall defect)
   - Duct-dependent congenital heart disease
   - Neuromuscular disease
   - Participation in another RCT
   - Death before reaching the eligibility criteria
   - Hydrocortisone treatment at the time of enrolment
   - Chronological age >28 days

3. **Study settings**

Two universitarian tertiary neonatal intensive care units in Berlin.

4. **Intervention**

Application of nHFOV or nCPAP immediately after extubation from endotracheal HFOV or from conventional ventilation.

- Equipment:
  - Devices used for endotracheal ventilation, nHFOV and nCPAP: Leoni Plus (Heinen und Löwenstein, Germany) or VN 500 (Dräger, Germany)
  - Interfaces: Endotracheal tubes (Vygon, France; Portex, Smiths Medical, UK) for endotracheal ventilation. Binasal prongs (Fisher & Paykel, New Zealand) for nHFOV and nCPAP.
  - Humidifier: MR 850 AGU (Fisher & Paykel, New Zealand)
- Primary intervention:
  - Extubation by withdrawing the endotracheal tube without sustained inflation
  - nHFOV group: immediately after extubation, apply nHFOV via binasal prongs.
    Set frequency at 10 Hz, I:E ratio 33:66, Amplitude 20 cm H_2O, Pm 8 cm H_2O, flow automatic (7 l/min).
    Set F_iO_2 to maintain SpO_2 at 90-94%.
  - nCPAP group: immediately after extubation, apply nCPAP via binasal prongs.
    Set CPAP level at 8 cm H_2O, flow 7 l/min.
    Set F_iO_2 to maintain SpO_2 at 90-94%.
- Weaning of non-invasive respiratory support:
  - The weaning process is left to the discretion of the attending physician.
  - Once the infant is considered stable on nHFOV, intermittent or permanent weaning to nCPAP is allowed.
  - Once the infant is considered stable on nCPAP, intermittent or permanent weaning to high flow nasal cannula is allowed.
- Increasing non-invasive respiratory support:
  - Increasing non-invasive respiratory support is left to the discretion of the attending physician. The following settings are allowed in the nHFOV- and nCPAP-group, respectively.
  - nHFOV group:
    - Maximum amplitude 30 cm H_2O, minimum frequency 9 Hz.
    - Maximum set P_{mean} 8 cm H_2O.
  - nCPAP group:
    - Maximum CPAP level 8 cm H_2O, maximum flow 8 l/min.
- Definition of treatment failure (infant meets at least one criterion):
  - Sustained pCO_2 >80 mmHg and pH <7.20 confirmed by arterial or capillary blood gas analysis in spite of optimized non-invasive respiratory support with maximum settings as defined above.
  - F_iO_2 >0.6 to maintain SpO_2 at 90-94% in spite of optimized non-invasive respiratory support with maximum settings as defined above.
- Reintubation:
  - Study patients may be intubated at any time due to clinical considerations (with or without reaching a criterion of "treatment failure", as defined above).
- "Rescue-nHFOV" for infants in the nCPAP-group who "fail" nCPAP (defined as reaching a criterion of "treatment failure", as defined above), but do not need immediate reintubation:
  - Trial of nHFOV via binasal prongs.
  - Choice of nHFOV settings are at the discretion of the attending clinician.
- "Rescue treatment" for infants in the nHFOV-group who "fail" nHFOV (defined as reaching a criterion of "treatment failure", as defined above), but do not need immediate reintubation:

    - Choice of non-invasive respiratory support for the "rescue treatment" (e.g. nIPPV, nHFOV) and ventilator settings are at the discretion of the attending clinician.
- Planned data collection to document the respiratory support provided in the nCPAP- and the nHFOV-group:
    - Blood gas result before extubation (pH, paO_2, $paCO_2$ and BE).
    - Ventilator settings before extubation (mode and F_iO_2 in all patients; set P_{mean} during HFO; PIP and PEEP during time-cycled, pressure-controlled ventilation; working P_{peak} and PEEP during volume guarantee ventilation).
    - Documentation of non-invasive respiratory support, including settings of nHFOV and/or nCPAP every 24h during the first 3 days after extubation and at 7 days after extubation (mode, set mean nHFOV pressure, frequency, amplitude; CPAP level; flow, F_iO_2), and after switch to "rescue treatment" or "rescue-nHFOV", if applicable.

5. Outcomes

- Primary outcome:
    - $paCO_2$ at 72 h (timeframe: 64 h to 80 h) after extubation
- Secondary outcomes:
    - pH, paO_2, $paCO_2$, BE at 2 h (timeframe: within first 6 h) after extubation
    - pH, paO_2, BE at 72 h (timeframe: 64 h to 80 h) after extubation
    - Successful extubation (defined as spontaneous breathing in the assigned treatment group for ≥72h without being reintubated or reaching the criterion of "treatment failure", as defined above)
    - Treatment failure (defined as reaching the criterion of "treatment failure", as defined above, within the first 7 days after extubation)
    - Reintubation within the first 7 days after extubation
    - Adverse effects observed after extubation: documented episodes of airway obstruction due to highly viscous secretions, IVH III°-IV° (Papile), surgical NEC, pneumothorax, pulmonary interstitial emphysema, mild BPD (Jobe), PDA requiring surgical closure, ROP requiring laser treatment and/or injection of bevacizumab, PVL
    - Respiratory support: total duration of mechanical ventilation, total duration of supplemental oxygen, number of infants discharged with home oxygen
- Additional secondary outcomes for those infants who received "rescue treatment":
    - pH, paO_2, $paCO_2$, BE at 2 h (timeframe: within first 6 h) after switch to "rescue" therapy
    - Successful rescue (defined as spontaneous breathing for ≥72h after starting "rescue" therapy, without reaching the criterion of "treatment failure", as defined above)
- Follow-up study:
    - Lung function testing at 52 weeks' corrected gestational age.

6. Sample size

Assuming a variability of the $paCO_2$ as previously reported for difficult-to-wean preterm infants in our unit (Czernik C, *J Matern Fetal Neonatal Med* 2012) and a reintubation rate of 21% within 72 h after extubation, we calculated a sample size of 28 patients in each study arm to detect a difference in the $paCO_2$ of 7 mmHg between the study groups, using a two-sided significance of 0.05 and a power of 0.8.

7. **Interim analyses and stopping guidelines**
   An independent statistician performs an interim-analysis on the primary and secondary endpoints once 50% of the patients are randomized and outcome data is available.

8. **Randomization: sequence generation**
   Sequence generation by an independent statistician and a study nurse.

9. **Randomization: type**
   Block randomization using at least two different block sizes, stratification by center.

10. **Randomization: allocation concealment mechanism**
    Sequentially numbered opaque sealed envelopes. Patients are randomized immediately before extubation.

11. **Registration of the trial**
    clinicaltrials.gov

Document dated 03-13-2012
Document translated 01-15-2015