Weaning of nasal Continuous Positive Airway Pressure in infants born with a gestational age under 32 weeks – a randomized controlled multicenter trial

Background

Despite several advances in the care of the premature infant respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) are still the leading cause of neonatal morbidity and mortality (1-11). Among infants born before 32 weeks of gestation 80% develop RDS (9). RDS is due to a deficiency of alveolar surfactant and structural immaturity of the lung. If left untreated, death can occur from respiratory failure and progressive hypoxia (10). Nasal continuous positive airway pressure (CPAP) and the INSURE procedure (Intubation-Surfactant-Extubation) are widely accepted methods used in the care of preterm infants with RDS (10;12-18). CPAP apply a constant distending pressure level above atmospheric during inhalation and exhalation and supports the spontaneously breathing premature infants. This prevents alveolar atelectasis thereby maintaining the functional residual capacity of the lungs and gas exchange which reduce apneas, work of breathing and lung injury (14;19). Up to now the research concerning CPAP therapy has focused on the indications for the use of CPAP, the risk of potential complications and the optimal technique of CPAP delivery (16;20-24). So despite nearly 40 years of experience with CPAP therapy the best strategy for withdrawal of CPAP remains unknown. Current CPAP weaning is based on the individual evaluation of the medical staff and can be described as an “ad hoc” approach to CPAP weaning (25). This approach may prolong the duration of CPAP which increases the risk of possible complications and prolongs the stay in the Neonatal Intensive Care Unit (NICU). A review was performed in 2011 (26) to determine the risks and benefits of different strategies used for the withdrawal of CPAP in preterm infants. Randomized controlled trials and some non-randomized trials were considered. Three eligible studies were included. The conclusion was that infants who have their CPAP pressure weaned to a predefined level and then stop CPAP therapy completely have less total time on CPAP and shorter durations of oxygen therapy and hospital stay compared with those that have CPAP removed for a predetermined number of hours each day. Furthermore research concerning ventilation therapy gives rise to suspect that the cycle of recruitment and atelectasis may lead to damage of the lungs, and hence more BPD (27).
The aim of this study is to investigate two different strategies for the withdrawal of CPAP in preterm infants born before 32 weeks of gestation. In a randomized controlled trial the strategy with weaning CPAP pressure to a predefined level and then stop the CPAP therapy completely will be compared to a strategy called sudden wean where the infant is taken off the CPAP therapy and stays without CPAP unless certain specific failure criteria are met. Both strategies will primarily be compared considering the infant’s weight at a gestational age of 40 completed weeks; secondary outcomes will be the weight gain during CPAP therapy, the duration of oxygen therapy and length of stay in the NICU.

In the future it is essential that weaning of CPAP in preterm infants is guided by evidence. Therefore this study is of great clinical relevance. It is important that the CPAP therapy is not prolonged since risks, primarily nasal septum necrosis, are linked to the duration of the therapy (28-32). The relationship between the mother and child may be influenced for example the handling of the infant and breastfeeding. Furthermore, CPAP therapy requires constant observation involving both equipment and specially trained personal which are expensive.

**Method**

**Study design**
A randomized controlled multicenter trial.

**Study population**
All live born infants born before 32 weeks of gestation and admitted to the NICU’s at Aarhus University Hospital, Aalborg University Hospital and the Regional Hospitals of Randers, Viborg, Herning and Vendsyssel, between 1st September 2012 and 31th August 2014.
Inclusion criteria

- Gestational age (GA) < 32 weeks at birth
- Current GA > 28+6 weeks
- CPAP for > 24 hours
- CPAP pressure < 8 cmH2O
- Oxygen requirement < 30% and not increasing
- Respiratory rate < 70 per min.
- Less than 3 episodes of oxygen saturation < 70% or a heart rate < 70 beat per min in the preceding 24 hours
- Tolerates time off CPAP during cares (max. 15 minutes)

Exclusion criteria

- Congenital malformations of the heart (except PDA/ASD/PFO*), lung and gastrointestinal tract
- Surgical procedures performed on the gastrointestinal tract
- Known or suspected to have congenital neuromuscular disease
- Known or suspected syndrome

*PDA: patent ductus arteriosus, ADS: atrial septal defect, PFO: patent foramen ovale

Randomization

At the randomization process eligible infants are stratified according to gestational age (24 to 27 weeks or 28 to 31 weeks) and site of admission. The infants are then randomized into two groups:

1) The pressure weaning group
2) The sudden wean group

The randomization and stratification on gestational age and site of admission is via an online web-based server. The program is designed with alternating block size of 2-4-6 in random. Twins are randomized to the same treatment. The attending physician or nurse register the infant on the online web-based server and it is determined in which arm the infant is treated. Infants excluded
from the study are registered along with the cause for exclusion.

**The pressure weaning group**

The reduction of the CPAP pressure begins at the morning ward round and the pressure is reduced in steps with 1 cmH2O maximum once a day. Each time the pressure is to be reduced the infant needs to be evaluated according to the inclusion criteria and only if these are still met, will the pressure be reduced. In case the reduction in pressure fails by the criteria mentioned below and the child meets the failure criteria the infant either stays on the same pressure or the pressure is increased, whichever is deemed appropriate by the medical staff. The infant is then treated with the “new” CPAP pressure for the remaining of the day before another attempt of pressure weaning is undertaken. When a CPAP pressure at 4 cmH2O is reached the infant is treated with this pressure for 24 hours and then the CPAP is discontinued. Infants are considered successfully weaned if they are off CPAP for three days.

**The sudden wean group**

The CPAP is taken off at the morning ward round. If the discontinuation of the CPAP fails, according to the failure criteria, CPAP is recommenced and continued at least 24 hours. Then a new evaluation takes place and if the infant again meets the inclusion criteria another attempt of sudden weans can be undertaken. Infants are considered successfully weaned if they are off CPAP for three days.

**Failure criteria**

Minimum one of the following criteria needs to be met:

- Respiratory rate > 70 per minute
- Difficult breathing with retractions
- Increased oxygen requirement by more than 10% (e.g. from 25% to 35%)
- More than 3 episodes of oxygen saturation < 70% or a heart rate < 70 beat per min in the preceding 24 hours
- Major apnea or bradycardia requiring resuscitation
- Transcutaneous CO2 > 2.0 kPa from starting point (if measured)
Primary endpoint

- The weight difference measured at a GA of 40 weeks (+/- 3 days)

Secondary endpoints

- Difference in weight gain during CPAP weaning
- Duration of CPAP therapy
- Duration of oxygen therapy
- Duration of hospital admission
- Occurrence of BPD defined as need for oxygen therapy (> 21%) at a gestational age of 36 weeks or treatment with oxygen > 21% for at least 28 days (a day of treatment with oxygen > 21% means that the infant received oxygen > 21% for more than 12 hours that day)
- Anxiety in parents
- Depression in parents
- Exterior distortion of the nose

Occurrence of serious, but rare complications to CPAP therapy for example pneumothorax, air embolism, nasal septum necrosis, chronic distortion of the nasal flares and snub nose are registered but not considered endpoints. A picture will be taken of all children at PMA of 40 weeks to evaluate the degree of exterior distortion of the nose.

Statistics

All primary analyses will be analyzed as intention to treat. In addition several per protocol analyses will be performed. The weight gain will be assessed as a continuous variable and the analyses based on linear regression.

The size of the study population is determined based on a power calculation in STATA (statistical software) with the following assumptions:

We want to demonstrate a difference in weight gain of 5 g/kg/day between the two intervention groups. We assume an average weight of 2500 g when the CPAP therapy is successfully weaned and a standard deviation of 200 g, both of which are based on experience from the NICU. With these assumptions we compare an average 2550 g (95% PI (prediction interval): 2158-2942) with
2480 g (95% PI: 2088-2872). To achieve a power of 80% by this comparison, 129 infants must be included in each intervention group.

Based on experiences from comparable studies in our unit we assume a participation rate of 85% and the size of the study population must be 300 infants.

**Science Ethical Review**

The study does not pose an increased risk or disadvantaged for the infant. No additional blood tests or examinations will be performed. Blood tests are only taken as part of the usual observation and treatment of the preterm infant.

The parents can at any time withdraw their informed consent with no impact on the treatment or follow up of the infant.

This study will contribute to determining the best approach to CPAP weaning with maximal benefits of treatment for the infant and point out the best way to potentially reduce the number of complications to the CPAP therapy and costs and inconvenience to the parents.

**Time frame**

1/12 2011 – 29/2 2012: Study preparations, application for permission from the Ethics Committee

1/3 2012 – 31/8 2012: Pilot study

1/9 2012 – 31/12 2016: Inclusion of the patients and data collection

1/1 2017 – 22/12 2017: Data analysis and scientific writing

**Organizational affiliation**

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Research Unit and Department of Pediatrics, Aarhus University Hospital.

The study involves all pediatric departments in the Central and North Denmark Region and all necessary equipment and support are available.

Reference List


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