Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis

Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY

CRD summary
This review concluded that, for every 25 babies born before 32 weeks of gestation and given nasal continuous positive airway pressure (CPAP), instead of intubation, one more survived without bronchopulmonary dysplasia until 36 weeks corrected gestation. The trials recruited women with stable pregnancies, who received antenatal steroids; the conclusion seems reliable, but may not be generalisable to less stable pregnancies.

Authors' objectives
To assess the effectiveness of nasal continuous positive airway pressure (CPAP), from birth, for the prevention of death and bronchopulmonary dysplasia, in very preterm infants.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and abstracts from the Paediatric Academic Society (2000 to 2012) were searched, up to June 2013. Search terms were reported. References of relevant reviews were checked.

Study selection
Randomised controlled trials (RCTs) that compared nasal CPAP with endotracheal intubation, as the primary means of respiratory support, following birth, for babies delivered at earlier than 32 weeks of gestation, were eligible. Trials needed to report deaths or the occurrence of bronchopulmonary dysplasia (defined as the need for oxygen support or mechanical ventilation at 36 weeks of corrected gestation). A range of adverse events, including surfactant administration and the need for mechanical ventilation, were assessed as secondary outcomes.

In the included trials, babies were delivered at between 24 and 29 weeks of gestation. Their mean birth weight by treatment group ranged from 825g to 1,053g. All except one study randomised babies to treatment, after delivery. Thresholds for treatment with surfactant or intubation ranged from 40% to 60% oxygen. Because antenatal consent was required for enrolment, the babies were from more stable pregnancies; this was reflected in the fact that 95% of babies had received antenatal steroids.

More than one reviewer was involved in selecting the trials for inclusion.

Assessment of study quality
The trials were assessed using the Cochrane risk of bias tool. Two reviewers carried out this assessment independently; disagreements were resolved in consultation with a third reviewer.

Data extraction
The data were extracted to calculate relative risks or mean differences, with 95% confidence intervals. As well as the two primary outcomes, relative risks were calculated for a composite outcome of death or bronchopulmonary dysplasia.

Two reviewers independently extracted the data, using a standardised form; disagreements were resolved in consultation with a third reviewer.

Methods of synthesis
Pooled relative risks or weighted mean differences, with 95% confidence intervals, were calculated using a random-effects model. Risk differences were calculated. Heterogeneity was explored and assessed using $\chi^2$ and $I^2$.

The number needed to treat (NNT) was calculated where the pooled estimates of relative risk indicated a statistically significant difference between groups.
Results of the review
Four RCTs, with 2,780 babies, were included in the review. Sample sizes ranged from 208 to 1,316. All trials were at a high risk of bias because blinding of participants and caregivers was not possible, given the nature of the intervention. Other sources of bias were low risk, with appropriate randomisation and allocation concealment, objective criteria for outcome assessment, well-matched groups, and use of intention-to-treat analysis.

There was no difference between the groups, in mortality at 36 weeks corrected gestation (RR 0.88, 95% CI 0.68 to 1.14). There was a trend towards a lower risk of bronchopulmonary dysplasia, with nasal CPAP (RR 0.91, 95% CI 0.82 to 1.01).

The composite outcome of death or bronchopulmonary dysplasia showed a statistically significant benefit with nasal CPAP (RR 0.91, 95% CI 0.84 to 0.99); the number needed to treat to avoid one event was 25.

Statistically significant benefits of nasal CPAP were seen in reduced mechanical ventilation requirements (RR 0.56, 95% CI 0.32 to 0.97, I²=99%) and need for surfactant (RR 0.40, 95% CI 0.23 to 0.70, I²=98%), but with very high levels of heterogeneity. Other outcomes did not show any significant differences between groups.

Authors’ conclusions
For every 25 babies treated with nasal CPAP rather than intubation, one additional infant would survive, without bronchopulmonary dysplasia, to 36 weeks corrected gestation.

CRD commentary
The review addressed a clear question, supported by specific inclusion criteria. The search was reasonably extensive and no restrictions were applied. The authors reported methods designed to reduce reviewer error and bias for all stages of the review. The trials were appraised using an appropriate tool. Trial quality was good, given that blinding was not possible.

The authors’ conclusion accurately reflects the results of the analyses, but relates to a composite outcome; it was not clear whether assessment of this composite was prespecified. The conclusions are likely to be reliable, but benefits for mortality and bronchopulmonary dysplasia did not reach statistical significance, when considered separately. The authors’ concerns about the generalisability of the population due to the need for antenatal consent should be noted.

Implications of the review for practice and research
Practice: The authors did not state any direct implications for practice.
Research: The authors stated that trials should investigate different levels of nasal CPAP and different strategies and thresholds for administering surfactant, in the respiratory support of preterm infants. Long-term follow-up of neurodevelopment was needed, and a waiver or deferral of consent could be considered to avoid selection bias and improve generalisability.

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