High-flow Nasal Cannulae in Very Preterm Infants after Extubation

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CONTEXT

Non-invasive respiratory support had been increasingly becoming popular among neonatologists as the preferred mode of ventilating preterm neonates in an attempt to try to reduce the incidence of bronchopulmonary dysplasia. Among those, the use of high flow nasal cannulae (HFNC) is gaining high preference as alternative to nasal continuous positive airway pressure (NCPAP) post-extubation for very preterm neonates (gestational age, <32 weeks).

Several studies had shown that HFNC as a mode of non-invasive respiratory support is well-tolerated by these preterm neonates with less incidence of the local trauma that are often associated with the bi-prong NCPAP. However, data on the efficacy or safety of such cannulae in this population are lacking.

MATERIALS AND METHODS

Study design

This is a multicenter, randomized, non-inferiority trial which was conducted in three Australian neonatal ICUs at the Royal Women's Hospital, Melbourne; Women's and Children's Hospital, Adelaide; and the Royal Brisbane and Women's Hospital, Brisbane from May 31, 2010 to July 3, 2012. Non-inferiority was determined by calculating the absolute difference in the risk of the primary outcome; the margin of non-inferiority was 20% points.

Outcome

The primary outcome was treatment failure within 7 days (168 h) after extubation and is declared if the infant met one or more of the following four criteria for failure within 7 days after extubation:

- A fraction of inspired oxygen of 0.2 or more above the baseline value before extubation that was required to maintain a peripheral oxygen saturation of 88-92%
- A pH of <7.2 and a partial pressure of carbon dioxide of more than 60 mm Hg on an arterial or free-flowing capillary blood gas sample
- More than one apneic episode requiring intermittent positive pressure ventilation within a 24-h period or six or more apneic episodes requiring stimulation within 6 consecutive hours
- An urgent need for re-intubation and mechanical ventilation, as determined by the treating physician.

Pre-specified secondary outcomes included reintubation during the primary-outcome period, death before hospital discharge, a requirement for supplemental oxygen at a gestational age of 36 weeks, pneumothorax after trial entry, total days of any respiratory support after trial entry, duration of oxygen supplementation after trial entry and length of hospital admission.

Population

Eligible patients

- Infants born at a gestational age of <32 weeks
- Infants who are receiving mechanical ventilation through an endotracheal tube and were scheduled to undergo extubation for the 1st time to non-invasive respiratory support.

Excluded patients

- Infants with gestational age more than 36 weeks at the time of extubation
- Neonates who were participating in a concurrent study that prohibited inclusion
- Babies with known major congenital anomaly that might affect breathing
- Or if maximal intensive care was not being provided.

Randomization and allocation

A computer-generated block-randomization sequence with random block sizes was used. All infants were stratified according to gestational age (<26 weeks vs. ≥26 weeks) and study center. Infants who were part of multiple births underwent individual randomization.

Consecutively numbered, sealed and opaque envelopes were opened by the clinicians immediately before extubation to determine the study-group assignment.

In the case of an unplanned extubation in an infant for whom consent had already been obtained, randomization occurred if the treating physician decided to provide non-invasive respiratory support. If the infant required resuscitation and immediate reintubation, randomization did not occur and the infant remained eligible for inclusion with the next planned extubation.

Intervention

Infants received oral or intravenous caffeine (either a loading dose of 20 mg/kg of body weight or a maintenance dose of 5-10 mg/kg) 24 h before extubation.

Decision to extubate an infant is made before randomization and the infants receive their assigned treatment immediately after extubation.

Infants in the nasal cannulae group were treated with the Optiflow device, which included the MR850 humidifier and binasal infant cannulae (Fisher and Paykel Healthcare). Infants were fitted with prongs that maintained a leak at the nose, with the aim of occluding approximately half the nares. The device includes a pressure relief valve that limits circuit pressure to 45 cm of water.

The starting flow rate was based on the size of the prongs used, with 5 L/min for "premature" or "neonatal" prongs or 6 L/min for "infant," "intermediate infant," or "pediatric" prongs. Flow rates were altered at the physician's discretion in a stepwise fashion, with mandated limits between 2 L/min and the maximum recommended for the prong size: 6 L/min for "premature" and "neonatal" prongs, 7 L/min for "infant" or "intermediate infant" prongs and 8 L/min for "pediatric" prongs.

Infants in the continuous positive airway pressure (CPAP) group were started on a pressure of 7 cm of water with either binasal midline prongs (Fisher and Paykel Healthcare) or subnasal prongs (Hudson RCI), depending on the practice in the individual unit. NCPAP was generated with the use of a mechanical ventilator or an underwater "bubble" system. Pressures were altered at the physician's discretion, within limits of 5-8 cm of water during the first 7 days after extubation. Non-synchronized nasal intermittent positive-pressure ventilation can be used at the time of extubation or at any later time during the admission, with a maximum inflating pressure of 25 cm of water and a maximum rate of 40 inflations/min.

Infants who failed in the HFNC group were treated with NCPAP (7 cm of water), with the same pressure limits as those used in the CPAP group. If the CPAP treatment failed under the maximal pressure during the first 7 days after extubation, infants were reintubated. Infants in the CPAP group were not permitted to receive treatment with HFNC at any time during their admission.

All analyses were performed on an intention-to-treat basis and infants remained in their assigned group for all outcomes.

RESULTS

A total of 303 infants underwent randomization (152 to the nasal cannulae group and 151 to the CPAP group) during the study period. The demographic and clinical characteristics of the mothers and infants in the two groups were similar.

The use of HFNC was found to be non-inferior to the use of NCPAP as previously defined, with treatment failure occurring in 52 of 152 infants (34.2%) in the nasal cannulae group and 39 of 151 infants (25.8%) in the CPAP group (risk difference, 8.4% points; 95% CI: 1.9-18.7).

The most common reason for treatment failure in the two study-groups was apnea with no significant between-group difference in the reason for failure. Failure was most likely to occur during the 1st day after extubation in the two groups.

Of the 52 infants in whom treatment with HFNC failed during the first 7 days after extubation, 25 (48%) were successfully treated with NCPAP or non-synchronized nasal intermittent positive-pressure ventilation without re-intubation. Thus, only 17.8% of infants in the nasal cannulae group were re-intubated, as compared with 25.2% of those in the CPAP group ($P = 0.12$).

There were no significant between-group differences in rates of other secondary outcomes or in rates of death or other serious adverse events. The pneumothorax rate after trial entry was low in the two study-groups. In the nasal cannulae group, infants had a significantly lower incidence of nasal trauma than those in the CPAP group (39.5% vs. 54.3%, $P = 0.01$) and fewer infants required a change in therapy because of nasal trauma ($P = 0.001$).

CONCLUSION

Although the result for the primary outcome was close to the margin of non-inferiority, the efficacy of HFNC was similar to that of CPAP as respiratory support for very preterm infants after extubation. However since the trial was underpowered to show non-inferiority in infants with a gestational age of <26 weeks, the use of HFNC as first-line respiratory support after extubation in this extremely preterm group requires caution.

COMMENTARY

A very interesting study that is the largest of published trials to date addressing the same clinical question. The use of HFNC in the preterm population is feasible, practical and results in less trauma of treated infants. Having said that, I would have preferred the study to be designed as superiority rather than non-inferiority trial hence the complex statistics that are involved in power calculations of non-inferiority studies. Although the heterogeneity in CPAP methods utilized in different reflects real practice, it would have been better to standardized prongs type, and method of CPAP delivery in the control arm to allow a stable comparison to the intervention as some of the differences or treatment could have results form utilizing an inferior form of CPAP as shown in previous studies. It is also important to note that infants treated with CPAP have a 25% more chance to succeed as compared to HFNC group.

The current evidence still doesn't support a complete replacement of conventional CPAP with HFNC. We do believe that both options of non-invasive support should be available to neonatologists until more data especially for the very small preterm infants are available.

Abstracted from

Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, *et al.* High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med 2013;369:1425-33.

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