Nasal Ventilation is Not Superior to Nasal CPAP in Extreme Preterm Infants

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CONTEXT
There has been special interest in the use of noninvasive ventilation for preterm infants as a strategy to minimize or avoid intubation and invasive ventilation aiming to decrease the incidence of bronchopulmonary dysplasia (BPD).

Nasal continuous positive airway pressure (NCPAP) is used in many centers as an initial respiratory support for preterm infants with respiratory distress syndrome (RDS), and contributed to a lower incidence of BPD at some centers. However, some infants fail NCPAP and require invasive ventilation.
Nasal intermittent positive pressure ventilation (NIPPV) is a newer noninvasive ventilation method that has been used in neonates. Its use improves tidal and minute volumes and decreases the inspiratory effort required by neonates compared with NCPAP.\[1\]

There is evidence that NIPPV compared with NCPAP reduces extubation failures and rates of apnea in preterm infants.\[2,3\]

**Study question**

Is NIPPV compared with NCPAP, would reduce BPD in extremely preterm infants.

**MATERIALS AND METHODS**

Randomized multicenter trial in 34 tertiary care neonatal intensive care units in 10 countries.

**Population**

**Inclusion**

- Extreme low birth weight infants (1,009 infants) gestational age, <30 weeks and birth weight < 1,000 g.
- Candidates for noninvasive respiratory support, shortly after birth or as post-extubation support in first 28 days of life.

**Exclusion**

- Infants expected to die.
- Infants with congenital abnormalities including any airway abnormality and neuromuscular disorder.
- Infants required surgery.

**Intervention**

- Infants to receive NIPPV or CPAP as initial support shortly after birth (birth 7 days) or as post-extubation support during the first 28 days of life.
- NIPPV (includes any technique that combines nasal CPAP with an intermittent increase in applied pressure) no devices were specified. Infants assigned to nasal CPAP were not allowed to receive nasal IPPV; however, those assigned to nasal IPPV and stable for 7 days after extubation could be shifted to nasal CPAP.
- If infant condition could not be maintained with the assigned method of noninvasive respiratory support were reintubated, and the originally assigned intervention was resumed after extubation.
- Reintubation when more than one episode of apnea requiring bag mask ventilation or more than six episodes of apnea requiring stimulation in a 6-h period).

**Randomization and allocation**

- Enrolment and treatment assignments were performed with the use of a secure study website after verification of eligibility and consent status.

- Assignments (in a 1:1 ratio) were based on a prespecified randomized sequence (with a random block size of 2 or 4), and was stratified by center, birth weight (<750 or 750-999 g) and status prior intubation (the duration and timing of intubation).
- The non-intubated stratum comprised infants deemed eligible within the first 7 days of life whose cumulative duration of intubation was 24 h or less, and the prior intubation stratum consisted of babies exposed to more than 24 h of intubation and ventilatory support who were extubated and given noninvasive support within the first 28 days of life.
- For all infants in the prior-intubation stratum randomization was performed at the time of the first decision to use noninvasive support.

**Outcomes**

**Primary outcome**

The primary outcome was a composite of death or survival with BPD at 36 weeks of postmenstrual age.

**RESULTS**

A total of 1,009 infants were enrolled between May 7, 2007 and June 29, 2011. The baseline characteristics of enrolled infants with the exception of sex were similar, the proportion of male infants was higher in the NIPPV group n = 265 (52.6%) compared with n = 232 (46.1%) in the NCPAP group, but there was no interaction of gender with the primary outcome of death or BPD (adjusted odds ratio (OR) 1.09; 95% CI 0.83-1.43; P = 0.56) [Table 1].

Of the 497 infants who received NIPPV, 191 (38.4%) died or survived with BPD as compared with 180 of 490 (36.7%) infants assigned to NCPAP (P = 0.56). There were no differences in rates of reintubation between the two groups (59.5% NIPPV vs 61.8% NCPAP). There were no differences in rates of complication such air leaks, nasal trauma, the duration of respiratory support, and the time to full feedings and necrotizing enterocolitis between the two groups.

**CONCLUSION**

There was no significant difference in either death or survival with BPD at 36 weeks after noninvasive respiratory support with nasal ventilation as compared with nasal CPAP. The rates of other neonatal complications were not significantly different between groups.

**COMMENTARY**

A meta-analysis involving three randomized controlled trials (RCTs) (n = 360) have previously demonstrated...
the benefit of NIPPV in preterm infants with RDS, with a significant reduction in the need for intubation and invasive mechanical ventilation within the first 72 h of life. This is the largest international study to date compared two current strategies for noninvasive respiratory support its showed an unexpected result that nasal intermittent positive-pressure ventilation does not improve BPD and the risk for reintubation. NCPAP has become the standard of care as initial respiratory support for preterm infants with RDS in many centers, its simple and widely used, but NCPAP failure is exciting. BPD is a complex disease and the need for mechanical ventilation especially early in life, is a significant risk factor for its development. This new finding put the clinicians on the dilemma of deciding on neonatal ventilation options aiming to prevent lung damage in extreme preterm infants.

Abstracted from
Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS. NIPPV Study Group. A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med 2013;369:611–20.

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### Table 1: Primary outcome for infants assigned to receive either NIPPV or NCPAP

| Outcome |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Nasal IPPV, no./total (%) | Nasal CPAP, no./total (%) | Odds ratio | Odds ratio adjusted for strata (95% CI) | P value | Odds ratio adjusted for strata and baseline covariates (95% CI) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Primary outcome: Death at<36 weeks or BPD | 191/497 (38.4) | 180/490 (36.7) | 1.07 | 1.09 | 0.56 | 1.05 |
| Components of primary outcome | | | | | | |
| Death at<36 week of postmenstrual age | 34/504 (6.7) | 41/503 (8.2) | 0.82 | 0.81 | 0.39 | 0.77 |
| Survival with BPD | 157/463 (33.9) | 139/449 (31.0) | 1.14 | 1.17 | 0.32 | 1.14 |
| Death at<36 week of postmenstrual age or BPD according to older NIH criteria | 197/504 (39.1) | 193/503 (38.4) | 1.03 | 1.03 | 0.82 | 1.00 |