

Randomized Controlled Trial of Nonsynchronized Nasal Intermittent Positive Pressure Ventilation versus Nasal CPAP after Extubation of VLBW Infants

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Keywords

Noninvasive ventilation · Nasal intermittent positive pressure ventilation, nonsynchronized · Preterm infants · Nasal continuous positive airway pressure · Respiratory distress syndrome

Abstract

Background and Objectives: Nasal continuous positive airway pressure (NCPAP) is a useful method of respiratory support after extubation. However, some infants fail despite CPAP use and require reintubation. Some evidence suggests that synchronized nasal intermittent positive pressure ventilation (NIPPV) may decrease extubation failure in preterm infants. Nonsynchronized NIPPV (NS-NIPPV) is being widely used in preterm infants without conclusive evidence of its

benefits and side effects. Our aim was to evaluate whether NS-NIPPV decreases extubation failure compared with NCPAP in ventilated very low birth weight infants (VLBWI) with respiratory distress syndrome (RDS). **Methods:** Randomized controlled trial of ventilated VLBWI being extubated for the first time. Before extubation, infants were randomized to receive NCPAP or NS-NIPPV. Primary outcome was the need for reintubation within 72 h. **Results:** 220 infants were included. The mean \pm SD birth weight was $1,027 \pm 256$ g and gestational age 27.8 ± 1.9 weeks. Demographic and clinical characteristics were similar in both groups. Extubation failure was 32.4% for NCPAP versus 32.1% for NS-NIPPV, $p = 0.98$. The frequency of deaths, bronchopulmonary dys-

Clinical Trial Registration: study registered at ClinicalTrials.gov NCT01778829.

plasia, intraventricular hemorrhage, air leaks, necrotizing enterocolitis and duration of respiratory support did not differ between groups. **Conclusions:** In this population of VLBWI, NS-NIPPV did not decrease extubation failure after RDS compared with NCPAP.

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Introduction

Invasive mechanical ventilation use has been associated with adverse outcomes such as bronchopulmonary dysplasia (BPD) and neurodevelopment impairment [1, 2]. This has led to the consensus to reduce its use. Nasal continuous positive airway pressure (NCPAP) is useful in the management of preterm infants with respiratory distress syndrome (RDS) and apnea [3–5] and has been successfully used after extubation in infants recovering from RDS [6–8]. However, some infants fail extubation despite CPAP use and require reintubation, ranging from 25 to 50% in different patient series [7, 8].

Noninvasive ventilation has been successfully used in children and adults with respiratory failure reducing the risk of extubation failure [9, 10]. Similarly, there is some evidence that synchronized nasal intermittent positive pressure ventilation (S-NIPPV) may decrease extubation failure in preterm infants recovering from RDS [11–13]. However, most of the successful studies were done using the Infant-Star[®] ventilator with Graseby[®] abdominal sensor, to detect and synchronize ventilator breaths with patient effort. Although the studies did not involve a large number of patients, a meta-analysis from these studies showed a significant reduction of the need of reintubation with S-NIPPV use [14]. However, this ventilator is not currently available, and other methods of synchronization, such as the nasal flow sensor used by Moretti et al. [15, 16], with the Giulia ventilator have not FDA approval and are not available in our region to provide noninvasive ventilation in preterm infants.

Other studies have evaluated the use of nonsynchronized NIPPV (NS-NIPPV) for respiratory support in preterm infants [17–19]. Some studies compared it with CPAP, showing a decrease in the rate of apneas and atelectasis [19], but the overall impact in decreasing extubation failure is modest according to a meta-analysis [14]. These studies included a small number of patients, and used different equipment and strategies, so it is difficult to reach firm conclusions, thus limiting the strength of the evidence [14]. Nonetheless, NS-NIPPV is being wide-

ly used in preterm infants without clear evidence of its benefits and possible adverse effects [20].

We designed this study to evaluate the hypothesis that NS-NIPPV may significantly decrease extubation failure in ventilated preterm infants with RDS compared with NCPAP.

Subjects and Methods

This was a multicenter, randomized, controlled, open trial, which enrolled ventilated very low birth weight infants (VLBWI) recovering from RDS and ready to be extubated for the first time. Infants with birth weights ranging from 400 to 1,500 g and gestational age ≤ 34 weeks were included. Infants born between December 2011 and 2014 and admitted to 9 NICUs of the NEOCOSUR Neonatal Network were eligible. The study was approved by the Ethics Committee of the Faculty of Medicine of the Catholic University of Chile, Approval 10-035, and by each hospital Ethics Committee. A written informed consent from the parents was required. The presence of major congenital anomalies, respiratory or hemodynamic instability, necrotizing enterocolitis, prolonged ventilation (>14 days) or lack of parental consent were considered exclusion criteria.

Study Protocol

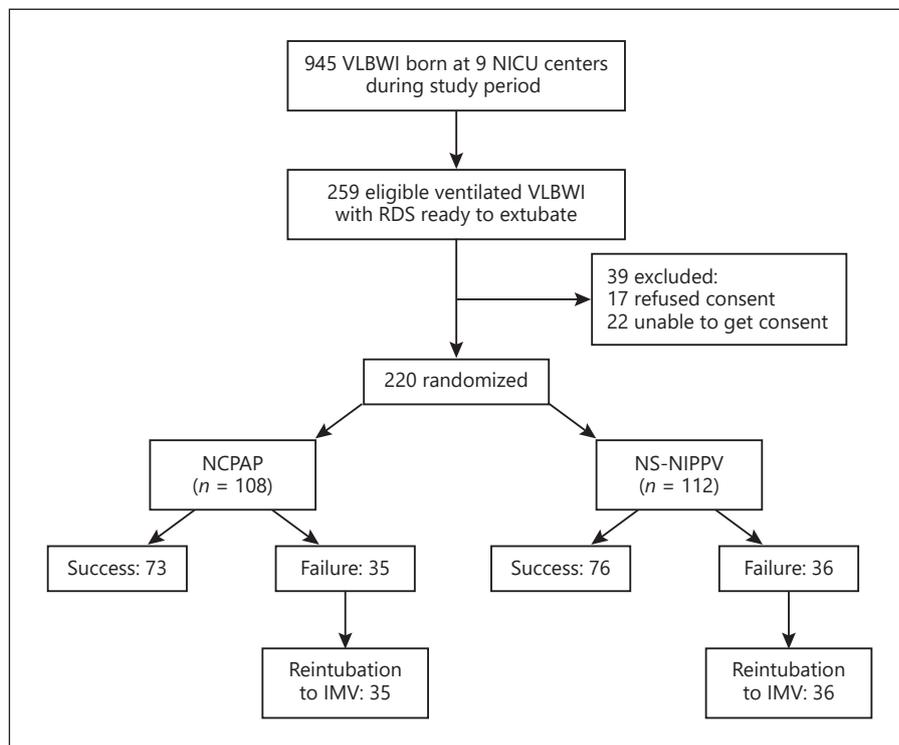
Infants were enrolled while receiving mechanical ventilation. The timing of extubation was determined when the infant met the following ventilatory parameters: $\text{FiO}_2 \leq 0.5$, $\text{PIP} \leq 18$ cm H_2O , $\text{RR} \leq 20$, to maintain a $\text{pH} \geq 7.25$, oxygen saturation $\geq 88\%$ and a $\text{PaCO}_2 \leq 65$ mm Hg. All infants were started on methylxanthines (either aminophylline or caffeine) prior to extubation. NCPAP was provided using neonatal ventilators or Bubble NCPAP system (Fisher & Pykel[®], New Zealand). NS-NIPPV was provided by time-cycled pressure-limited ventilators in a nonsynchronized invasive mechanical ventilation mode. Appropriate size short binasal prongs (Silmag[®], Argentina) were used for both modes.

Enrolled infants were randomized prior to extubation based on 2 birth weight strata (400–999 g and 1,000–1,500 g) into 2 groups: NCPAP or NS-NIPPV using sequentially sealed opaque envelopes from a computer-generated randomization list. This allocation sequence was generated centrally by an independent statistician, and sealed envelopes were sent to each center. Caregivers were not blinded to the assigned group.

NCPAP was set at 5–6 cm H_2O in the CPAP group using a gas flow of 5 L/min. In the NS-NIPPV group, the following parameters were set: a PIP of 12–15 cm H_2O (for infants $<1,000$ g) and 14–18 cm H_2O (for infants of 1,000–1,500 g), PEEP of 5–6 cm H_2O , air flow of 8 L/min, peak pressure duration time of 0.45–0.6 s and ventilator rate of 20 breaths/min. These parameters were adjusted according to careful clinical evaluation in order to obtain good chest excursion. If needed PIP could be increased up to 20 cm H_2O , ventilator rate could be increased up to 30 breaths/min if a patient presented apnea or hypoventilation. On the contrary, ventilator rate was reduced if PaCO_2 was <40 . Inspired oxygen was adjusted to maintain oxygen saturation between 88 and 94%.

Randomized infants remained in the assigned group during the intervention period of at least 72 h. All infants were monitored including oxygen saturation, ECG and respiratory rate. Arterial

Fig. 1. CONSORT diagram of patient group allocation and main outcome. NS-NIPPV, nonsynchronized nasal intermittent positive pressure ventilation; NCPAP, nasal continuous positive airway pressure; IMV, invasive mechanical ventilation; RDS, respiratory distress syndrome; VLBWI, very low birth weight infants.



blood gases were obtained within 2 h after extubation and at least every 24 h during the study period. An open orogastric tube was kept in all patients.

Clinical data including the use of pre- and postnatal steroids, surfactant, blood gases, oxygen saturation and respiratory support were collected. Total duration of mechanical ventilation and oxygen supplementation were documented from birth until discharge or death. A supplemental oxygen or ventilation day was defined as a daily requirement of $\text{FiO}_2 > 0.21$ or ventilation > 12 h, respectively. All infants were followed until they reached 36 weeks corrected postmenstrual age, discharge or death.

The primary outcome was defined as the need for reintubation within 72 h of extubation, according to the presence of at least 1 of 3 failure criteria: (1) hypercapnia in 2 consecutive blood gases with $\text{PaCO}_2 > 65$ mm Hg and $\text{pH} < 7.25$; (2) the requirement for $\text{FiO}_2 > 0.60$ in order to obtain oxygen saturation $\geq 88\%$; (3) repeated episodes of significant apnea (2 or more episodes apnea per hour associated with bradycardia $< 100 \times \text{min}$) or desaturation $< 80\%$ in a 4-h period); (4) presence of 2 or more severe apnea and bradycardia episodes that required bag and mask ventilation for recovery.

After the 72-h postextubation intervention period, further respiratory management was determined by the clinical team. Clinical and nursing care and monitoring were done according to the center's routine protocols.

Secondary outcome variables were considered: the occurrence of death within the 72-h postextubation period or at any time after randomization. Respiratory outcomes included total duration of mechanical ventilation, length of oxygen supplementation, BPD defined by oxygen requirement for ≥ 28 days and moderate to severe BPD defined as the persistence of oxygen requirement at 36 weeks postmenstrual age. The combined outcome of death or BPD

was also assessed. The occurrence of other morbidities including intraventricular hemorrhage, pneumothorax, necrotizing enterocolitis and retinopathy of prematurity was documented.

Sample Size and Statistical Analyses

Based on data from the Neocor Network, where approximately 35% of ventilated VLBWI presented extubation failure and previous published studies [11–13], we estimated the enrollment of 210 neonates (105 per group) to detect a reduction in extubation failure from 35 to 18% at an α of 0.05 with a power of 80%. Statistical analyses were based on an intention-to-treat model according to the assigned group. Continuous variables were compared using Student's *t* test or the Mann-Whitney rank sum test as appropriate. Categorical variables were compared using the χ^2 test. A *p* value ≤ 0.05 was considered significant.

An interim analysis by an independent team was done at half of the recruited sample size to determine the possible early termination because of safety if the rate of adverse events increased or early efficacy if the primary end point was better in one of the groups at a more stringent level of significance.

Results

During the study period 945 VLBWI were born at the participant study centers, 259 of them presented with RDS requiring intubation and mechanical ventilation, therefore were eligible and screened for enrollment. Thirty-nine were excluded due to lack of parental consent: in

Table 1. Patient characteristics at study entry

	NCPAP (n = 108)	NS-NIPPV (n = 112)	p value
Birth weight, g	1,019±245	1,034±270	ns
Gestational age, weeks	27.9±1.9	27.8±2	ns
Sex female, %	47.2	43.8	ns
Median 1-min Apgar score (range)	5 (1–9)	5 (0–9)	ns
Median 5-min Apgar score (range)	8 (1–10)	8 (1–10)	ns
Antenatal steroids, %	94	91	ns
Surfactant use, %	92	96	ns
Age at extubation, h	50.3±64.3	54.4±64.9	ns

NCPAP, nasal continuous positive airway pressure; NS-NIPPV, nonsynchronized nasal intermittent positive pressure ventilation.

22 we were unable to get consent on time, and 17 parents refused to give permission. A total of 220 infants were included (Fig. 1). Their mean ± SD birth weight was 1,027 ± 256 g with a gestational age of 27.8 ± 1.9 weeks. As seen in Table 1, demographic and clinical characteristics were very similar in both groups at randomization.

There was no difference in extubation failure rate between the 2 groups: 32.4% for NCPAP versus 32.1% for NS-NIPPV. When the analysis was performed by birth weight stratification (Fig. 2), although we did not find significant differences between the groups, we observed that infants within the NS-NIPPV group behave differently: the extubation failure in infants <1,000 g was significantly higher (44.6%) compared to those >1,000 g of the same group (19.6%), $p < 0.01$. This difference was smaller in the CPAP group.

Secondary Outcomes. As shown in Table 2, respiratory outcomes were not different between the groups including BPD, air leaks, duration of oxygen and respiratory support. We did not observe differences in the rate of death and in any of the other morbidities evaluated including: BPD, intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis and gastrointestinal perforations (Table 3).

Discussion

We compared 2 current strategies for noninvasive ventilation after extubation from an RDS in VLBWI. Importantly, this study was confined to the first episode of

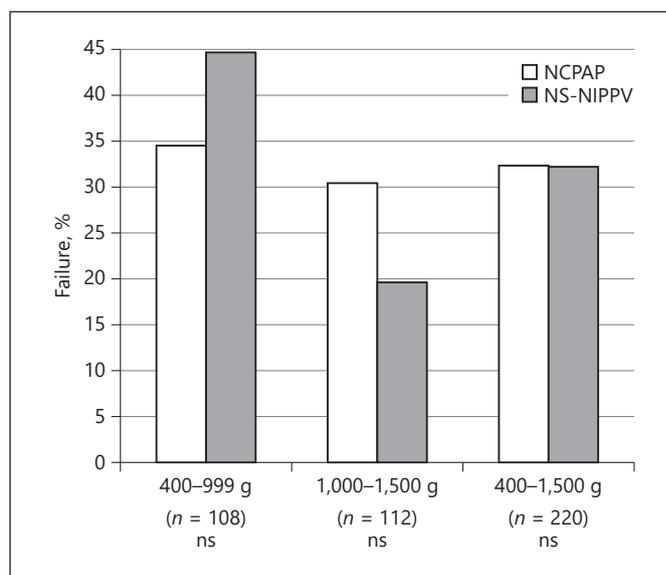


Fig. 2. Extubation failure rate by birth weight strata and treatment group. NS-NIPPV, nonsynchronized nasal intermittent positive pressure ventilation; NCPAP, nasal continuous positive airway pressure.

extubation, the potentially most important time to reduce baro-volutrauma. In this population, we found that NS-NIPPV did not decrease extubation failure compared with NCPAP. We also found no significant difference in rates of other complications. These findings lead us to re-evaluate the current widespread use of NS-NIPPV.

Several trials supporting NIPPV [11–13] show a reduction of respiratory failure and risk of reintubation after ventilation in infants with RDS. However, a recent meta-analysis shows that most of the effect is driven by studies evaluating S-NIPPV [14]. In their subgroup analysis, which included only studies evaluating NS-NIPPV versus NCPAP, they show that although NS-NIPPV reduced extubation failure, the effect is modest and the evidence is graded as low. The results of the studies included in that meta-analysis may differ from our own for several reasons. Most of them were single-center and enrolled larger infants, who have a lower risk of failure. In most of the trials, the number of included infants was low and the impact in reduction of failure was not significant; thus, the results reached significance only when the data from all studies were pooled together.

In a large randomized controlled trial, Kirpalani et al. [21] evaluated NIPPV vs. NCPAP in more than 1,000 extremely low birth weight infants, their main outcome measure was the rate of death or BPD. They consider different strategies of NIPPV including a ventilator or bi-

Table 2. Respiratory outcomes

	NCPAP (n = 108)	NS-NIPPV (n = 112)	p value
Extubation failure, %	32.4	32.1	ns
BPD, %	52.9	53.2	ns
BPD at 36 weeks PMA, %	25.9	25.8	ns
Air leak, %	2.7	1.8	ns
Oxygen (mean ± SD), days	41±40.4	40.5±36.2	ns
Median (range)	31 (1–178)	35 (1–123)	ns
Ventilation (mean ± SD), days	11±17.7	12.2±17.8	ns
Median (range)	4 (1–180)	5 (1–123)	ns

NCPAP, nasal continuous positive airway pressure; NS-NIPPV, nonsynchronized nasal intermittent positive pressure ventilation; BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

level NIPPV and allowed synchronization or not. They concluded that the rate of survival to 36 weeks postmenstrual age without BPD did not differ significantly with NIPPV as compared with NCPAP. They also did not find significant differences in the rate of reintubation between NIPPV (59.5%) and NCPAP (61.8%), $p = 0.52$. In a more recent post hoc subanalysis of this study, Millar et al. [22] did not find differences in the combined outcome death or BPD and in the extubation failure rate comparing NIPPV using a ventilator versus bilevel NIPPV.

In the present study, we found that NS-NIPPV did not decrease extubation failure after RDS compared with NCPAP. Interestingly, when we conducted the analysis considering birth weight strata, we observed that infants <1,000 g in the NS-NIPPV group showed a significantly higher extubation failure when compared with infants >1,000 g of the same group (Fig. 2). We did not observe this marked difference in the CPAP group. We do not have a clear explanation for this lack of effectiveness of NS-IPPV observed in infants <1,000 g. A reasonable speculation about this absence of effect is the lack of synchronization. Chang et al. [23] demonstrated that asynchrony during NS-IPPV cycles delivered late in spontaneous inspiration or during exhalation disrupted the infant's spontaneous breathing pattern. These elicited active expiratory efforts against the ventilator cycle, delaying spontaneous exhalation, and consequently delayed the onset of the next inspiration. It is possible, that smaller infants are more vulnerable to suffer these changes and a decrease in their lung volume when this active expiratory effort and asynchrony happen, due to their collapsing

Table 3. Secondary outcomes

	NCPAP (n = 108)	NS-NIPPV (n = 112)	p value
Death, %	10.2	8.9	ns
Death or BPD at 36 weeks, %	35.2	34.8	ns
IVH all grades, %	32.4	32.1	ns
IVH III–IV, %	12.1	10.7	ns
GI perforation, %	3.7	1.8	ns
NEC, %	12.9	12.5	ns
ROP, %	17.5	20.5	ns
Nasal trauma, %	3.7	4.5	ns

NCPAP, nasal continuous positive airway pressure; NS-NIPPV, nonsynchronized nasal intermittent positive pressure ventilation; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; GI, gastrointestinal; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

chest wall and poor diaphragmatic strength. In another study, Owen et al. [24] investigated the effects of NS-NIPPV on ventilation measured by plethysmography. They found that NIPPV pressure peaks only resulted in a small increase in tidal volumes when it coincides with the onset of spontaneous inspiration. On the other side, when peak pressures occurred during expiration or apnea, transmission of the pressure to the chest was uncommon and did not result in chest expansion. In a synchronized mode, ventilator breaths are delivered just after the infant's respiratory effort initiation, when the glottis is open [12] allowing better pressure transmission to the lungs. Thoracoabdominal asynchrony is common in extreme preterm infants, and synchronization can improve chest wall stability and reduce asynchrony [25–27].

It has been reported that infants become adapted with NS-NIPPV [28] when they match their spontaneous respiratory rates to the ventilator rhythm; this has been described with rates >40 cycles/min. We did not use rates higher than 30 cycles/min, and peak pressures were not increased above 20 cm H₂O. These were the criteria set for all centers because we were concerned about potential adverse effects of higher pressures. Similar settings were used in most of the other reported studies evaluating NIPPV.

In terms of respiratory outcomes, including the prevalence of BPD, duration of respiratory support and oxygen therapy, there were no significant differences between the 2 groups.

There have been concerns that NS-NIPPV may result in an increased risk of air leaks and gastrointestinal

perforations [8, 29]. In this study, we did not observe differences in the rate of these complications between the groups. Our trial showed no significant benefit of NIPPV compared with NCPAP with respect to other adverse events including death, intraventricular hemorrhage and retinopathy of prematurity. However, this study is underpowered to evaluate these secondary outcomes.

Another consideration is the resources required to implement these therapies: in order to provide NIPPV a precious mechanical ventilator and a circuit are required, while NCPAP can be delivered using a simpler and less expensive system like the bubble NCPAP. This should be especially considered in centers with limited resources.

Conclusion

In this population of VLBWI, NS-NIPPV did not decrease extubation failure after RDS compared with NCPAP and may be less effective in infants <1,000 g. No other clinically important outcomes differed significantly between groups. Synchronization may be important in delivering effective NIPPV. This should be studied in future clinical trials.

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Statement of Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine of the Catholic University of Chile, Approval 10-035, and by each hospital Ethics Committee. A written informed consent from the parents was required.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Alberto S. Estay and Alvaro González conceptualized and designed the study and its data collection instruments, supervised data collection, carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Alberto S. Estay was the principal investigator, and Alvaro González coordinated Chilean centers and acted as alternate principal investigator. Gonzalo L. Mariani contributed to study design, coordinated and supervised data collection of Argentinean centers and critically reviewed the manuscript. Claudio A. Alvarez, Beatriz Milet, Daniel Agost, Claudia P. Avila, Liliana Roldan, Daniel A. Abdala, Rodolfo Keller and María F. Galletti coordinated the individual centers, collected data, and reviewed and revised the manuscript. All authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

Appendix 1

The following group of persons contributed to the study at each of the listed centers as collaborators; they contributed with data collection and provided clinical care for study patients. The following members from the Neocosur Neonatal Network are nonauthor contributors to this study:

Argentina

Instituto Universitario del Hospital Italiano de Buenos Aires: Carlos Fustiñana[†], Mónica Ballardó, Silvia Fernández, María Paola Carrascal.

Hospital Fernández, Buenos Aires: Jorge Tavosnaska, Gladys Saa, Debora Sabatelli.

Hospital Luis Carlos Lagomaggiore, Mendoza: Mónica Rinaldi, Gabriela Torres.

Hospital Español de Mendoza, Mendoza: Horacio Roge, Martín Guida, Damian Pretz.

Hospital Universitario Austral, Buenos Aires: Gabriel Musante, Leila Acha.

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Hospital Clínico Universidad Católica de Chile, Santiago: Jorge Fabres, José L. Tapia, Javier Kattan, Mónica Avaca, Mariela Quezada, Solange Rojas.

Hospital Dr. Gustavo Fricke, Viña del Mar: Jane Standen, Mari-sol Escobar, Daniela Sandino.

Hospital San José, Santiago: Agustina González, Paula Ponce.

Hospital Dr. Sotero del Río, Santiago: Marcela Díaz, Patricia Mena, Claudia Toro.

References

- 1 Tapia JL, Agost D, Alegría A, Standen J, Escobar M, Grandi C, et al. Bronchopulmonary dysplasia: Incidence, risk factors and resource utilization in a very low birth weight infant. *J Pediatr (Rio J)*. 2006;82:15–20.
- 2 Walsh MC, Morris BH, Wrage LA, Vohr BR, Poole WK, Tyson JE, et al.; National Institutes of Child Health and Human Development Neonatal Research Network. Extremely low birth-weight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr*. 2005 Jun;146(6):798–804.

- 3 Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *N Engl J Med*. 1971 Jun;284(24):1333-40.
- 4 De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health*. 2001 Apr;37(2):161-7.
- 5 Tapia JL, Urzua S, Bancalari A, Meritano J, Torres G, Fabres J, et al. Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants. *J Pediatr*. 2012 Jul;161(1):75-80.e1.
- 6 Higgins RD, Richter SE, Davis JM. Nasal continuous positive airway pressure facilitates extubation of very low birth weight neonates. *Pediatrics*. 1991 Nov;88(5):999-1003.
- 7 Davis P, Jankov R, Doyle L, Henschke P. Randomised, controlled trial of nasal continuous positive airway pressure in the extubation of infants weighing 600 to 1250 g. *Arch Dis Child Fetal Neonatal Ed*. 1998 Jul;79(1):F54-7.
- 8 Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev*. 2003;(2):CD000143.
- 9 Fortenberry JD, Del Toro J, Jefferson LS, Evey L, Haase D. Management of pediatric acute hypoxemic respiratory insufficiency with bilevel positive pressure (BiPAP) nasal mask ventilation. *Chest*. 1995 Oct;108(4):1059-64.
- 10 Keenan SP, Kernerman PD, Cook DJ, Martin CM, McCormack D, Sibbald WJ. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. *Crit Care Med*. 1997 Oct;25(10):1685-92.
- 11 Friedlich P, Lecart C, Posen R, Ramicone E, Chan L, Ramanathan R. A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. *J Perinatol*. 1999 Sep;19(6 Pt 1):413-8.
- 12 Barrington KJ, Bull D, Finer NN. Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. *Pediatrics*. 2001 Apr;107(4):638-41.
- 13 Khalaf MN, Brodsky N, Hurley J, Bhandari V. A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. *Pediatrics*. 2001 Jul;108(1):13-7.
- 14 Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev*. 2017 Feb;2(2):CD003212.
- 15 Moretti C, Giannini L, Fassi C, Gizzi C, Papoff P, Colarizi P. Nasal flow-synchronized intermittent positive pressure ventilation to facilitate weaning in very low-birthweight infants: unmasked randomized controlled trial. *Pediatr Int*. 2008 Feb;50(1):85-91.
- 16 Salvo V, Lista G, Lupo E, Ricotti A, Zimmermann LJ, Gavilanes AW, et al. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT. *Pediatrics*. 2015 Mar;135(3):444-51.
- 17 Lin CH, Wang ST, Lin YJ, Yeh TF. Efficacy of nasal intermittent positive pressure ventilation in treating apnea of prematurity. *Pediatr Pulmonol*. 1998 Nov;26(5):349-53.
- 18 Ryan CA, Finer NN, Peters KL. Nasal intermittent positive-pressure ventilation offers no advantages over nasal continuous positive airway pressure in apnea of prematurity. *Am J Dis Child*. 1989 Oct;143(10):1196-8.
- 19 Kahramaner Z, Erdemir A, Turkoglu E, Cosar H, Sutcuoglu S, Ozer EA. Unsynchronized nasal intermittent positive pressure versus nasal continuous positive airway pressure in preterm infants after extubation. *J Matern Fetal Neonatal Med*. 2014 Jun;27(9):926-9.
- 20 Bancalari E, Claire N. The evidence for non-invasive ventilation in the preterm infant. *Arch Dis Child Fetal Neonatal Ed*. 2013 Mar;98(2):F98-102.
- 21 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 Aug;369(7):611-20.
- 22 Millar D, Lemyre B, Kirpalani H, Chiu A, Yoder BA, Roberts RS. A comparison of bilevel and ventilator-delivered non-invasive respiratory support. *Arch Dis Child Fetal Neonatal Ed*. 2016 Jan;101(1):F21-5.
- 23 Chang HY, Claire N, D'ugard C, Torres J, Nwajee P, Bancalari E. Effects of synchronization during nasal ventilation in clinically stable preterm infants. *Pediatr Res*. 2011 Jan;69(1):84-9.
- 24 Owen LS, Morley CJ, Dawson JA, Davis PG. Effects of non-synchronised nasal intermittent positive pressure ventilation on spontaneous breathing in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2011 Nov;96(6):F422-8.
- 25 Ali N, Claire N, Alegria X, D'Ugard C, Organero R, Bancalari E. Effects of non-invasive pressure support ventilation (NI-PSV) on ventilation and respiratory effort in very low birth weight infants. *Pediatr Pulmonol*. 2007 Aug;42(8):704-10.
- 26 Kiciman NM, Andréasson B, Bernstein G, Mannino FL, Rich W, Henderson C, et al. Thoracoabdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. *Pediatr Pulmonol*. 1998 Mar;25(3):175-81.
- 27 Huang L, Mendler MR, Waitz M, Schmid M, Hassan MA, Hummler HD. Effects of synchronization during noninvasive intermittent mandatory ventilation in preterm infants with respiratory distress syndrome immediately after extubation. *Neonatology*. 2015;108(2):108-14.
- 28 Moretti C, Marzetti G, Agostino R, Panero A, Picece-Bucci S, Mendicini M, et al. Prolonged intermittent positive pressure ventilation by nasal prongs in intractable apnea of prematurity. *Acta Paediatr Scand*. 1981 Mar;70(2):211-6.
- 29 Garland JS, Nelson DB, Rice T, Neu J. Increased risk of gastrointestinal perforations in neonates mechanically ventilated with either face mask or nasal prongs. *Pediatrics*. 1985 Sep;76(3):406-10.