Bi-Level Noninvasive Ventilation in Neonatal Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis

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Keywords

Continuous positive airway pressure · Bi-level positive airway pressure · Nasal intermittent positive pressure ventilation · Premature infant · Respiratory distress syndrome · Bronchopulmonary dysplasia · Meta-analysis

Abstract

Background: Bi-level noninvasive ventilation (NIV) has been used in respiratory distress syndrome (RDS) as primary treatment, post-extubation, and to treat apnea. This review summarizes studies on bi-level NIV in premature infants with RDS. Nonsynchronized nasal intermittent positive pressure ventilation (nsNIPPV) and synchronized NIPPV (SNIPPV) use pressure settings $\geq$ those used during mechanical ventilation (MV), and biphasic continuous positive airway pressure (BiPAP) use two nasal continuous positive airway pressure (NCPAP) levels ≤ 4 cm H₂O apart. **Methods:** A systematic review (Medline OVID and Pubmed) and meta-analysis of randomized controlled trials. Primary outcomes were bronchopulmonary dysplasia (BPD) and mortality. Secondary outcomes included NIV failure (intubation) and extubation failure (re-intubation). Data were pooled using a fixed-effects model to calculate the relative risk (RR) with 95% confidence interval (CI) between NIV modes (RevMan v 5.3, Co-

penhagen, Denmark). **Results:** Twenty-four randomized controlled trials that largely did not correct for mean airway pressure (MAP) and used outdated ventilators were included. Compared with NCPAP, both nsNIPPV and SNIPPV resulted in less re-intubation (RR 0.88 with 95% CI (0.80, 0.97) and RR 0.20 (0.10, 0.38), respectively) and BPD (RR 0.69 (0.49, 0.97) and RR 0.51 (0.29, 0.88), respectively). nsNIPPV also resulted in less intubation (RR 0.57 (0.45, 0.73) versus NCPAP, with no difference in mortality. One study showed less intubation in BiPAP versus NCPAP. **Conclusions:** Bi-level NIV versus NCPAP may reduce MV and BPD in premature infants with RDS. Studies comparing equivalent MAP utilizing currently available machines are needed.

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Introduction

Neonatal intensive care units use bi-level noninvasive ventilation (NIV) increasingly to avoid invasive mechanical ventilation (MV) [1–3]. The large heterogeneity of more than 20 years of bi-level NIV studies has resulted in insufficient evidence to make recommendations for indications, choice of modality, and settings [2, 4].

Theoretical advantages of NIV over invasive MV in premature infants with respiratory distress syndrome (RDS) include less bronchopulmonary dysplasia (BPD) [5]. Mechanisms of action of nasal continuous positive airway pressure (NCPAP) include improved oxygenation and ventilation-perfusion matching secondary to increased functional residual capacity (FRC) [6]. Bi-level NIV, that is, NIV with alternating pressure, theoretically adds benefits of increased mean airway pressure (MAP), improved alveolar recruitment, FRC and airway diameter, as well as atelectasis prevention [7, 8]. Controversy exists whether to synchronize pressure peaks with spontaneous breathing [9], and about the reliability [10] of different synchronization methods in bi-level NIV. However, it has been speculated that nonconventional gas-exchange might occur during bi-level NIV [10, 11], potentially limiting the importance of synchronization.

Different Modes and Systems for Bi-Level Noninvasive Ventilation Delivery

Although the terms nasal intermittent positive pressure ventilation (NIPPV) and bi-level positive airway pressure (BiPAP) has been used interchangeably [12], NIPPV is frequently associated with pressure settings equal to or higher than those used during MV (positive inspiratory pressure 14–24, positive end-expiratory pressure 3–6 cm H₂O), $T_{\text{high}}/T_{\text{i}}$ 0.3–0.5 s and rates 10–60/min. “BiPAP” is more commonly used when the infant breathes independently of two CPAP levels that are ≤ 4 cm H₂O apart [13]. T_{high} 0.6–1.0 s and rates of 10–30/min are frequently used. It has been speculated that BiPAP treatment might provide a higher MAP without potential side effects of a high continuous distending pressure [14]. However, it is controversial whether a high continuous distending pressure may cause harm [15]. The NIV system/driver is likely to influence NIV effectiveness [10] including FRC [16], e.g., the CareFusion/Viasys/Vyaire Infant Flow SiPAP that was used in numerous studies of bi-level NIV, was developed to reduce expiratory resistance and airway pressure fluctuations [17].

Despite widespread use [1–3, 18, 19], bi-level NIV is not considered evidence-based treatment. The aim of this review and meta-analysis was to summarize studies in premature infants with RDS to identify the knowledge gaps. The primary research question was “In premature infant with RDS, how does different modes of bi-level NIV influence BPD and mortality, compared to NCPAP?”

Methods

We aimed to identify a broad spectrum of studies, reflecting the heterogeneity of patients with RDS eligible for bi-level NIV including a) Infants who are primarily placed on NIV, and b) Infants who have been intubated and then extubated to NIV.

The systematic review was carried out according to the PRISMA statement [20] and registered in PROSPERO (CRD 42020182190). We searched Medline OVID using search terms including Infant, Newborn OR Infant, Premature AND Non-invasive Ventilation OR bibap.mp OR nippv.mp. A PubMed search included: Infant, Newborn OR Infant, Premature AND Noninvasive Ventilation OR bibap.mp OR nippv.mp NOT child NOT pediatric NOT bronchiolitis NOT PICU NOT high frequency NOT high flow. The last search was performed September 25th 2020.

We searched the reference lists of retrieved studies and performed searches on relevant authors. Randomized controlled trials (RCT) were included, not review papers and commentaries. We only included papers in English, and similar to Ekhuagere et al. [21], we excluded conference abstracts. No limits on publication date were applied.

ALS and PYC independently assessed the quality of the studies using the following criteria: blinding of randomization, blinding of intervention, completeness of follow-up, and blinding of outcome measurement. We assessed risk of bias using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [22]. The quality of the evidence was evaluated by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [23] and GRADEpro Guideline Development Tool Software (McMaster University, developed by Evidence Prime, Inc.). Disagreements were resolved by a 3rd assessor (GS).

For the primary outcomes, BPD and mortality, and secondary outcomes NIV-/extubation failure and MV-/NIV duration, we analyzed trials using risk ratio (RR) with 95% confidence interval for dichotomous outcomes, and mean difference for continuous outcomes. Heterogeneity was assessed using the Q statistic and I^2 [24]. The meta-analyses were performed with the Review Manager software v5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). We used only published data. Thus, outcomes published as median (not mean), for example, duration of MV/NIV, were not included in the meta-analysis. Due to a large heterogeneity of surfactant administration protocols, MV modalities and settings, characteristics of the study population, duration of MV before extubation and weaning criteria from MV, studies where the infants had previously been on MV were excluded from the meta-analysis of the primary outcomes.

Results

The searches retrieved 304 citations. Of these, we included 24 RCTs (PRISMA flow chart and see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/0005514637).

1.1 Duration of mechanical ventilation (hours) as a composite of before and after non-invasive ventilation treatment

1.2 Bronchopulmonary dysplasia

Risk difference nsNIPPV vs NCPAP -0.05 [-0.09, -0.00], number needed to treat (NNT) = 21

1.3 Extubation failure

Risk difference nsNIPPV vs NCPAP -0.06 [-0.11, -0.01], NNT = 19

1.4 Mortality

Risk difference nsNIPPV vs NCPAP -0.02 [-0.05, 0.01]

(Figure continued on next page.)

Fig. 1. nsNIPPV versus NCPAP. nsNIPPV, nonsynchronized nasal intermittent positive pressure ventilation; NCPAP, nasal continuous positive airway pressure.

Included Studies

Studies Comparing Nonsynchronized Nasal Intermittent Positive Pressure Ventilation versus Nasal Continuous Positive Airway Pressure ($N = 15$)

Most studies included very and moderately preterm infants (GA 28–34 weeks) with very low birth weight (<1,500 g) (online suppl. Table 1). Eight studies examined nsNIPPV versus NCPAP as primary treatment [7, 25–31], whereas 5 were in previously intubated infants [32–36], and two a combination of primary and post-extubation NIV-treatment [37, 38].

BPD was lower (47 fewer per 1,000) with similar mortality with nsNIPPV versus NCPAP. There were significantly less primary NIV failure (107 fewer per 1,000) and extubation failure (59 fewer per 1,000) in nsNIPPV versus NCPAP. There was no difference in NIV duration or MV duration (Fig. 1).

In conclusion, nsNIPPV results in less BPD (moderate-quality evidence) and similar mortality (moderate-quality evidence) compared with NCPAP. Primary

NIV- and extubation failure were less in nsNIPPV versus NCPAP (moderate-quality evidence). For the outcomes MV and NIV duration, the heterogeneity of the studies was large ($I^2 > 50\%$), potentially due to different MV modalities and settings, MV weaning criteria, as well as heterogeneity of the patient population. This evidence was downgraded to low quality due to inconsistency.

Studies Comparing Synchronized Nasal Intermittent Positive Pressure Ventilation versus Nasal Continuous Positive Airway Pressure ($N = 5$)

Most studies included very and moderately preterm infants (GA 28–34 weeks) with very low birth weight. Only one examined NIV as primary RDS treatment [39]. The study by Moretti et al. [40] reported MV and NIV days in median (range) and was not included in the meta-analysis for these outcomes. Friedlich et al. [41] reported the length of initial MV, that is, a baseline not an outcome variable. Thus, MV duration as an outcome could not be subject to meta-analysis.

Fig. 2. SNIPPV versus NCPAP. SNIPPV, synchronized intermittent positive pressure ventilation; NCPAP, nasal continuous positive airway pressure.

BPD was lower (159 fewer per 1,000) in SNIPPV versus NCPAP. Mortality could not be assessed. There was less primary NIV (234 fewer per 1,000) (only one study [39]) and extubation failure (321 fewer per 1,000) [8, 40–42] in SNIPPV versus NCPAP (Fig. 2). In conclusion, SNIPPV may prevent primary NIV-and extubation failure compared to NCPAP, and reduce BPD (moderate-quality evidence).

Studies Comparing Biphasic Continuous Positive Airway Pressure versus Nasal Continuous Positive Airway Pressure ($N = 4$)

Most studies included very and moderately preterm infants (GA 28–34 weeks) with very low birth weight. All studies, but one [43] used the Infant flow SiPAP or the Infant flow advance. Only Victor et al. [44] used equivalent MAP in comparison of the two modes. Only Victor et al. [44] reported NIV duration. Thus, this outcome was not included in the meta-analysis.

There was no difference in BPD [12, 43, 45] or mortality [12, 45]. The meta-analysis revealed no difference in

Fig. 3. BiPAP versus NCPAP. NCPAP, nasal continuous positive airway pressure; BiPAP, bi-level positive airway pressure.

extubation failure in BiPAP versus NCPAP. MV duration was not different with BiPAP versus NCPAP (Fig. 3). Zhou et al. [43] used the Fabian DuoPAP and found less primary NIV failure, improved oxygenation and ven-

tilation, and less need for MV and complications when BiPAP was used as primary RDS treatment.

In conclusion, insufficient evidence exists and we cannot conclude whether BiPAP improves RDS treatment

Table 1. GRADE quality of evidence assessment for prespecified outcomes

Outcomes	Certainty assessment		Patients, <i>n</i> (%)				Effect		certainty		
	studies	study design	risk of bias	inconsistency	indirectness	imprecision	Bi-level NIV	CPAP		relative	absolute
<i>Duration of NIV, h</i>											
nsNIPPV	4	RCTs	Serious ^a	Serious	Serious ^b	Serious ^c	148	142		MD 0.25 lower (0.54 lower to 0.03 higher)	Low
SNIPPV	Not assessed										
BiPAP	Not assessed										
<i>Duration of MV, days after NIV failure</i>											
nsNIPPV	2	RCTs	Serious ^a	Serious	Serious ^b	Serious ^c	92	85		MD 8.29 higher (11.19 lower to 27.77 higher)	Low
SNIPPV	Not assessed										
BiPAP	2	RCTs	Serious ^a	Serious	Serious ^b	Serious ^c	315	310		MD 0.04 higher (0.31 lower to 0.39 higher)	Low
<i>BPD</i>											
nsNIPPV	5	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	43/416 (10.3)	63/419 (15.0)	RR 0.69 (0.49–0.97)	47 fewer per 1,000 (from 77 to 5 fewer)	Moderate
SNIPPV	2	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	13/77 (16.9)	23/71 (32.4)	RR 0.51 (0.29–0.88)	159 fewer per 1,000 (from 230 to 39 fewer)	Moderate
BiPAP	3	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	22/132 (16.7)	23/129 (17.8)	RR 0.98 (0.60–1.59)	4 fewer per 1,000 (from 71 fewer to 105 more)	Low
<i>Extubation failure</i>											
nsNIPPV	7	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	328/739 (44.4)	377/761 (49.5)	RR 0.88 (0.80–0.97)	59 fewer per 1,000 (from 99 to 15 fewer)	Moderate
SNIPPV	4	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	9/115 (7.8)	43/107 (40.2)	RR 0.20 (0.10–0.38)	321 fewer per 1,000 (from 362 to 249 fewer)	Moderate
BiPAP	3	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	116/357 (32.5)	117/359 (32.6)	RR 1.00 (0.81–1.23)	0 fewer per 1,000 (from 65 fewer to 75 more)	Low
<i>Mortality</i>											
nsNIPPV	8	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	42/553 (7.6)	57/597 (9.5)	RR 0.76 (0.53–1.10)	23 fewer per 1,000 (from 45 fewer to 10 more)	Moderate
SNIPPV	Not assessed										
BiPAP	2	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	3/87 (3.4)	5/89 (5.6)	RR 0.62 (0.15–2.48)	21 fewer per 1,000 (from 48 fewer to 83 more)	Low
<i>NIV failure</i>											
nsNIPPV	8	RCTs	Serious ^a	Not serious	Serious ^b	Serious ^c	84/577 (14.6)	148/595 (24.9)	RR 0.57 (0.45–0.73)	107 fewer per 1,000 (from 137 to 67 fewer)	Moderate
SNIPPV	1	RCT	Serious ^a	Not serious	Serious ^b	Serious ^c	11/43 (25.6)	20/41 (48.8)	RR 0.52 (0.29–0.95)	234 fewer per 1,000 (from 346 to 24 fewer)	Moderate
BiPAP	Not assessed										

nsNIPPV, nonsynchronized nasal intermittent positive pressure ventilation; SNIPPV, synchronized NIPPV; BiPAP, bi-level positive airway pressure; RCT, randomized controlled trials; RR, risk ratio; MD, mean difference; SD, standard deviation; NIV, noninvasive ventilation; MV, mechanical ventilation; BPD, bronchopulmonary dysplasia. ^a Blinding of the intervention was not possible. ^b Old machines and equipment that are no longer in use. ^c All studies included <2,000 participants.

compared with NCPAP. For the outcome MV duration, the heterogeneity of the studies was large ($I^2 > 50\%$).

Quality of the Evidence

In all the included RCTs, clinicians and investigators were aware of the intervention received by each infant (bi-level NIV or NCPAP). In addition, most studies are dated and used machines that are now largely obsolete. Thus, due to a lack of masking of the interventions and indirectness, we graded the quality of evidence for all outcomes (duration of NIV and MV, BPD, extubation failure, NIV failure, and mortality) as moderate to low (Table 1).

Discussion

NIPPV and BiPAP have been investigated for their potential to augment the benefits of NCPAP in premature infants with RDS. This meta-analysis aimed to distinguish between the individual modalities/modes of bi-level NIV (nonsynchronized NIPPV, synchronized NIPPV, Bi-level CPAP), often used under a single acronym in the literature (e.g., NIV or NIPPV), or included in the same study group, although with significant technical differences. These important differences are explained in our review, which distinguishes the current article from previous reviews and meta-analyses.

The quality of the evidence in the meta-analysis was moderate to low, mainly due to a lack of blinding of intervention and outcome measurement. For some outcomes, there was inconsistency across studies. We found that nsNIPPV versus NCPAP reduced BPD but not mortality and reduced primary NIV- and extubation failure among premature infants with RDS. SNIPPV versus NCPAP reduced BPD, but mortality could not be assessed. SNIPPV versus NCPAP reduced primary NIV- and extubation failure among premature infants with RDS. Most studies used the InfantStar ventilator and a Graseby capsule for synchronization. Insufficient evidence exists regarding BiPAP versus NCPAP.

A limitation of the meta-analysis is that non-English language reports and RCTs presented in conferences were excluded. This may have introduced bias, particularly as RCTs that were only presented as conference abstracts may more likely have demonstrated negative results, that is, no difference between treatment modalities. We did not obtain raw data from the authors of the included studies. The large pragmatic study by Kirpalani et al. [37] included 241 infants that received “mainly

BiPAP” and 215 that received “mainly NIPPV”; the remaining 41 infants had mixed exposures. Different NIV strategies, devices, and settings represented challenges to the inclusion of the study data in the meta-analysis. Strengths of our review include its comprehensiveness and stratification according to different bi-level NIV-modes.

Randomized controlled trials of bi-level NIV are very low to moderate quality, predominantly due to a lack of blinding to the intervention. Although studies have compared NIPPV with BiPAP, there is disagreement whether NIPPV and BiPAP should be viewed as separated entities [10]. Importantly, most studies did not compare the modalities at equal MAP, a variable that has been shown to have important impact on the failure rate of NIV [46].

The included studies span a large time period with varying approaches to surfactant treatment and neonatal care in general. It is uncertain how these data are transferable to modern practice with, for example, increasing use of less invasive surfactant administration/minimally invasive surfactant therapy. Also, the studies that demonstrated a benefit of NIPPV used machines that are now largely obsolete [2, 10, 47]. The Infant flow SiPAP used in most BiPAP studies delivers a pressure ≤ 10 cm H₂O. Its predecessor, the Infant flow advance delivered ≤ 11 cm H₂O. Newer machines and techniques are becoming available and they need scientific evidence, policies, and staff training to be properly utilized. Medin CNO (Medical Innovations GmbH, Puchheim, Germany), Fabian DuoPAP (Acutronic Medical Systems AG, Hirzel, Switzerland), and similar machines are operated through pressure settings, not flow settings like the Infant flow machines. One study using the Fabian DuoPAP was identified, with a hybrid between NIPPV and BiPAP settings used. The latest Fabian DuoPAP model is equipped with a NIV Trigger hot-wire flow sensor.

Inherent to NIV with short bi-nasal prongs or nasal mask is leak from the nose and mouth, which may limit its effectiveness. All included studies used bi-nasal or nasopharyngeal prongs/tubes. Few authors [34, 40, 44] addressed leak and some used a chin strap [7, 12, 28] to achieve the intended pressures. Two studies specifically stated that “No precautions were taken to avoid leakage from the mouth” [34, 40].

Future Research Directions

The significant morbidity and mortality resulting from invasive MV of premature infants with RDS remain an unresolved challenge. NCPAP is beneficial but fails in almost half of (extremely) premature infants in some centers. Other methods for keeping these infants off MV are

thus urgently required. One or more bi-level NIV modes might be an option, and may also prove to be relevant in low-resource settings where MV is not available. As MV is associated with intensive care needs including iv sedation, parenteral nutrition, and hemodynamic support, bi-level NIV may be less costly and might require less staffing compared with MV treatment. More research on health economic aspects of bi-level NIV is needed.

Future studies should compare the NIV modalities at equal MAP in order to discern if it is the phasic pressure changes or the higher MAP that is responsible for the apparent benefit of bi-level NIV. More single-institution studies, preferably during the adoption of new machines and/or policies and procedures, using quality improvement methodology would be useful. We speculate that with regard to nsNIPPV, SNIPPV, and BiPAP, one size does not fit all, that is, subsets of patients may benefit more from one or the other. Quality improvement initiatives may represent a patient-centered approach, including state-of-the-art nursing to optimize pressure transmission, to bi-level NIV.

Conclusion

Based on this updated review, nsNIPPV and SNIPPV might reduce extubation failure and BPD. Newer machines with flow sensors for SNIPPV delivery should be investigated and attention given to the nursing aspects of

providing bi-level NIV including assessing and managing leak. Studies should compare the NIV modalities at equal MAP in order to discern if it is the phasic pressure changes or the higher MAP that is responsible for the apparent benefit of bi-level NIV.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.L.S. drafted the article. A.L.S., P.Y.C., and G.M.S. contributed to the conception and design, collection and assembly of literature, analysis and interpretation of the literature, and critical revision of the article for important intellectual content. All the authors approved the article for submission.

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