Efficacy of noninvasive respiratory support modes for primary respiratory support in preterm neonates with respiratory distress syndrome: Systematic review and network meta-analysis

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Abstract

Objectives: To compare the efficacy of different noninvasive respiratory support (NRS) modes for primary respiratory support of preterm infants with respiratory distress syndrome (RDS).

Design: Systematic review and network meta-analysis using the Bayesian random-effects approach. MEDLINE, EMBASE, and CENTRAL were searched.

Interventions: High flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), bilevel CPAP (BiPAP), noninvasive positive pressure ventilation (NIPPV).

Main Outcome Measures: Requirement of invasive mechanical ventilation (MV), any treatment failure.

Results: A total of 35 studies including 4078 neonates were included. NIPPV was more effective in decreasing the requirement of MV than CPAP (risk ratios [95% credible interval]: 0.60 [0.44, 0.77]) and HFNC [0.66 (0.43, 0.97)]. Surface under the cumulative ranking curve (SUCRA) for NIPPV, BiPAP, HFNC, and CPAP were 0.95, 0.59, 0.32, and 0.13. For the outcome of treatment failure, both NIPPV and BiPAP were more efficacious compared to CPAP and HFNC (0.56 [0.44, 0.71] [NIPPV vs CPAP], 0.69 [0.51, 0.93] [BiPAP vs CPAP], 0.42 [0.30, 0.63] [NIPPV vs HFNC], 0.53 [0.35, 0.81] [BiPAP vs HFNC]). The SUCRA for NIPPV, BiPAP, CPAP, and HFNC were 0.96, 0.70, 0.32, and 0.01. NIPPV was associated with a reduced risk of air leak compared to BiPAP and CPAP (0.36 [0.16, 0.73]; 0.54 [0.30, 0.87], respectively). NIPPV resulted in lesser incidence of bronchopulmonary dysplasia or mortality when compared to CPAP (0.74 [0.52, 0.98]). Nasal injury was lesser with HFNC compared to CPAP (0.15 [0.01, 0.60]).

Conclusions: Most effective primary mode of NRS in preterm neonates with RDS was NIPPV.

KEYWORDS

Bilevel CPAP, CPAP, heated humidified high flow cannula, noninvasive positive pressure ventilation, no invasive ventilation, RDS

1 | INTRODUCTION

The introduction of surfactant had a major impact on improving the outcomes of preterm neonates with respiratory distress syndrome (RDS).¹ There was a major shift in the practice of surfactant therapy in the last decade with studies showing better outcomes with early selective rescue treatment when compared to the previously practiced prophylactic administration.² Stabilising neonates with RDS on a noninvasive respiratory support (NRS) such as continuous positive airway pressure (CPAP) and then instituting surfactant therapy in selective neonates who have an increased oxygen requirement has become the standard practice.³ Newer modalities of NRS strategies that have come into practice in neonatal medicine in the past two decades, include heated and humidified high flow cannula (HFNC), noninvasive positive pressure ventilation (NIPPV), bilevel CPAP (BiPAP) as well as nasal high-frequency oscillation ventilation (nHFOV).^{4,5}

Several systematic reviews compared different NRS strategies in pair-wise meta-analysis, however, only one network meta-analysis (NMA) evaluated different NRS strategies in preterm neonates with RDS.⁶⁻¹⁰ The NMA by Isamaya et al¹⁰ also included different modalities of surfactant instillation (Less Invasive Surfactant Administration [LISA], Intubate Surfactant and Rapid Extubation [INSURE] and mechanical ventilation [MV] following surfactant) along with CPAP and NIPPV.¹⁰

In this systematic review, we critically review the different modes of NRS and compare their effects in an NMA.

2 | METHODS

The efficacy and safety of four NRS modalities used as primary respiratory support in preterm neonates with RDS were compared: HFNC, CPAP, BiPAP, and NIPPV. The systematic review protocol was registered with PROSPERO (CRD42020177474).¹¹ The reporting of this review is consistent with the PRISMA for network meta-analyses guidelines.¹²

2.1 | Types of studies

Only randomized controlled trials (RCTs) that have compared the four different NRS treatments (HFNC, CPAP, BiPAP, and NIPPV) were included. Studies published as peer-reviewed abstract form as

well as non-English language studies were included in the final synthesis. Neonates with gestational age less than 37 weeks with a primary diagnosis of RDS and who were started on a non-invasive ventilation (NIV) support within the first 24 hours of life. Neonates who had received surfactant via standard practice (INSURE or LISA) before randomization were included. Trials that had evaluated any of the two NRS modalities as a single intervention (for example NIPPV and BiPAP both assessed as a single intervention) were excluded.

2.2 | Outcomes

The primary outcomes were: (a) requirement of invasive MV within the first 7 days of randomization; (b) treatment failure, defined as requirement of an additional form of respiratory support for various reasons such as respiratory acidosis, hypoxemia, or severe apnea within the first 7 days of randomization. The secondary outcomes included incidence of mortality (neonatal and before discharge), incidence of bronchopulmonary dysplasia (BPD) defined as oxygen requirement at 36 weeks of postmenstrual age, incidence of mortality or BPD, incidence of air leak, incidence of severe intra-ventricular haemorrhage defined as grade more than 2,¹³ incidence of necrotising enterocolitis (NEC) stage ≥ 2 ,¹⁴ incidence of patent ductus arteriosus requiring medical therapy or surgical intervention, incidence of severe retinopathy of prematurity defined as those requiring laser therapy and or intra-vitreous antivascular endothelial growth factor and/or stage ≥ 3 as per International committee for the classification of retinopathy of prematurity¹⁵ and incidence of nasal injury.

2.3 | Search methods for identification of studies

Three electronic databases were searched, namely MEDLINE via Pubmed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception till 29th March 2020. The search strategy that was used is provided in the E-Table S1.

2.4 | Selection of studies

Two authors (VVR and PBH) independently reviewed the abstracts of the search results. Full texts of the eligible articles were extracted by

the two review authors for further evaluation. In case of any conflicts, a third author's (KM) opinion was sought.

2.5 | Assessment of risk of bias in included studies

The Cochrane risk of bias tool version 1 was used to assess the risk of bias of the included studies by two review authors independently (VVR and KM).¹⁶ The risk of bias was evaluated based on the following five domains—selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Any disagreement between the reviewers was resolved by discussion or consultation with the third author (PBH).

2.6 | Data synthesis

The characteristics of the included studies were tabulated and reviewed to exclude those studies that might result in intransitivity. NMA was done by the Bayesian approach using a random-effects model with Markov chain Monte Carlo simulation with vague priors (GEMTC, BUGSnet) using the R-software (Version-R 3.6.2).^{17,18} Generalized linear models with four chains, burn-in of 50 000 iterations followed by 100 000 iterations with 10 000 adaptations were used.¹⁸ The geometry of the networks was assessed using network plots with the size of the nodes being proportional to the number of subjects included in the intervention and the thickness of the arms connecting the different intervention nodes corresponding to the number of studies included in the comparison. Model convergence was assessed using Gelman-Rubin plots as well as by analyzing the trace and density plots.¹⁹ Inconsistency was assessed by node-splitting.²⁰ Pair-wise meta-analysis evaluating the direct evidence for the different NIV modalities was also done and heterogeneity was assessed using I^2 statistic and Cochran Q test. The results of the NMA were expressed as risk ratios (RR) with 95% credible intervals (CrIs) in league matrix tables and forest plots. The league matrix tables display the RR of the outcome parameter for the intervention in the row vs that in the column in the lower triangle and vice versa in the upper triangle. The comparison of direct and indirect evidence using node-splitting are expressed as odds ratios with 95% CrIs. Surface under the cumulative ranking curve (SUCRA) was used to rank interventions for all the outcomes. SUCRA is an index with values from 0 (least effective intervention) to 1 (best intervention).²¹ SUCRA should always be interpreted with 95% CrIs as well as the quality of the evidence. The confidence in the final estimates for all the outcomes was assessed using the GRADE approach as recommended by the GRADE working group.²²

2.7 | Meta-regression and sensitivity analysis

The following sensitivity analyses were done—

- Excluding trials with high risk of bias
- Excluding trials that had enrolled neonates who had already received surfactant prior to randomization
- Assessing the interventions NIPPV and BiPAP based on synchronization—synchronized NIPPV (S-NIPPV), nonsynchronized NIPPV (NS-NIPPV), synchronized BiPAP (S-BiPAP) and nonsynchronized BiPAP (NS-BiPAP)

Meta-regression was done using age as the covariate. The results of the meta-regression were illustrated with regression plots. The network estimates (expressed as RR [95% CrI]) for different gestational ages were depicted using forest plots.

3 | RESULTS

The electronic database search revealed a total of 9032 studies. After screening for suitability, 35 studies were included in the final synthesis.²³⁻⁵⁷ The PRISMA flow diagram is depicted in Figure 1. Thirty-three studies (3994 neonates) and thirty-two studies (3867 neonates) were analyzed for the primary outcomes of treatment failure and requirement of MV, respectively. The mean gestational age of the neonates was 31 weeks (E-Figure S1). Five studies had enrolled neonates who had already received surfactant before randomization. The time cuts-offs for treatment failure and MV were within the first 72 hours after randomization for most of the included studies. The NRS settings (initial and maximum) used in the included studies is given in E-Table S2. The characteristics of the included studies are given in Table 1. Some of the studies that were excluded for varying reasons are given in Table 2.⁵⁸⁻⁸⁹

3.1 | Risk of bias assessment of included studies

Overall, 13 studies^{25,28,30,32,33,37,40-44,51,57} were regarded as having a low risk of bias, the remaining studies were found to have variable degrees of risk of bias. Fourteen studies had high risk of bias^{27,34-36,38,45,47-50,52,54-56} with issues in randomisation and/or allocation concealment. Eight studies^{23,24,26,29,31,39,46,53} had unclear bias as methodology was not described very well. The risk of bias of the included studies is depicted in E-Figure S2.

3.2 | Primary outcomes

3.2.1 | Requirement of MV

A total of 32 studies enrolling 3867 neonates with 699 events in the network was analyzed (Figure 2 and Table 3). Inconsistency assessed by node-splitting for all the outcomes is illustrated in E-Figures S3 and S4. In comparison with HFNC, only NIPPV showed a statistically significant reduction in the requirement of MV (0.66 [0.43, 0.97]) (Figure 3). Also, NIPPV was more effective in decreasing the risk of MV intubation when

FIGURE 1 Search results and selection of studies (PRISMA flow diagram)

compared to CPAP (0.60 [0.44, 0.77]). The league matrix is given in Table 3. SUCRA for NIPPV, BiPAP, HFNC, and CPAP were 0.95, 0.59, 0.32, and 0.13, respectively, making NIPPV the best initial mode of NRS and CPAP the least effective (Figure 4). Meta-regression with gestational age as covariate showed a trend of improving efficacy of HFNC in reducing the risk for MV with increasing gestational age when compared to NIPPV, BiPAP, and CPAP (E-Figure S5). The pairwise comparison of different NRS interventions evaluating the direct evidence for the primary outcomes is illustrated as forest plots in Figure 5A,B.

3.2.2 | Treatment failure

A total of 33 studies enrolling 3994 neonates with 678 events in the network were analysed (Figure 2 and Table 3). Both NIPPV and BiPAP were associated with lesser risk of treatment failure when compared to HFNC (0.42 [0.30, 0.63] and 0.53 [0.35, 0.81], respectively) and CPAP (0.56 [0.44, 0.71] and 0.69 [0.51, 0.93], respectively) (Figure 3 and Table 4). The SUCRA for NIPPV, BiPAP, CPAP,

and HFNC were 0.96, 0.70, 0.32, and 0.01, respectively (Figure 4). Meta-regression showed a trend similar to the outcome of MV (E-Figure S6).

3.3 | Secondary outcomes

The geometry and other characteristics of the networks for the different secondary outcomes are displayed in Figure 2 and E-Figure S7 and Table 3, respectively. The network assessing the outcomes mortality and NEC were inconsistent as assessed by node-splitting. The SUCRA plots for the secondary outcomes are given in the Figure 4 and E-Figure S8.

3.4 | Air leak

NIPPV was associated with lesser incidence of air leak when compared to both CPAP (0.54 [0.30, 0.87]) and BiPAP (0.36 [0.16, 0.73]) (Figure 3 and Table 4).

TABLE 1 Characteristics of the included studies

Author	Gestational age (wk)/birth weight for inclusion, g	Mean gestational age (wk)/birth weight of included neonates, (g)	1. Age at randomization (h) 2. Surfactant received before randomization (yes/no) 3. Age at INSURE/LISA (early <2 h; late >2 h)			Interventions with n	Time cut off for treatment failure	Time cut off for reintubation	Other comments
HFNC vs CPAP									
Nair ²³	27-34 wk	32 wk	<6 h No			HFNC (5-6 L/min; n = 33) Bubble CPAP (5-6 cm H2O; n = 34)	Not mentioned	Not mentioned	...
Iranpour ²⁴	30-35 wk	Not available	<24 h No			HFNC (1-4 L/min) CPAP (6 cm H2O) (n = 70)	Not mentioned	Not mentioned	...
Yoder ²⁵	>28 wk >1000 g	33 wk 2100 g	<24 h Yes Not mentioned			HFNC (3-8 L/min; n = 58) CPAP (5-8 cm H2O; n = 67)	72 h	72 h	Different devices for CPAP/HFNC delivery
Kadivar ²⁶	28-34 wk	31 wk 1600 g	<48 h Yes Not mentioned			HFNC (2-4 L/min; n = 27) Ventilator CPAP (5-8 cm H2O; n = 27)	72 h	72 h	Only neonates who had received INSURE enrolled
Roberts ²⁷	28-36 wk	32 wk 1700 g	<24 h No			HFNC (6-8 L/min; n = 278) Bubble/variable flow CPAP (6-8 cm H2O; n = 286)	72 h	72 h	HFNC failure infants were eligible for CPAP
Shin ²⁸	30-34 wk	32 wk 2000 g	<24 h No			HFNC (3-7 L/min; n = 42) Variable flow CPAP (4-7 cm H2O; n = 43)	72 h	7 d	Treatment failure eligible for other NIV modes
Murki ²⁹	≥28 wk ≥1000 g	32 wk 1600 g	<6 h No			HFNC (5-7 L/min; n = 133) Bubble CPAP (5-7 cm H2O; n = 139)	72 h	72 h	HFNC failure eligible for CPAP
Shokouhi ³⁰	28-36 wk	32 wk	<24 h Yes Not mentioned			HFNC (2-8 L/min; n = 30) CPAP (4-8 cm H2O; n = 30)	Not mentioned	Not mentioned	Infants who received INSURE were randomized
Sharma ³¹	26-34 wk	32 wk 1800 g	<6 h No			HFNC (n=50) CPAP (n=50)	72 h	72 h	HFNC and CPAP settings not mentioned
Demirel ³²	≤32 wk	31 wk 1500 g	Immediately after birth No			HFNC (6-8 L/min, n = 53) Ventilator CPAP (6-7 cm H2O; n = 30)	Not mentioned	Not mentioned	Prophylactic respiratory support used in all infants

(Continues)

TABLE 1 (Continued)

Author	Gestational age (wk)/birth weight for inclusion, g	Mean gestational age (wk)/birth weight of included neonates, (g)	1. Age at randomization (h) 2. Surfactant received before randomization (yes/no) 3. Age at INSURE/LISA (early <2 h; late >2 h)	Interventions with n	Time cut off for		Other comments
					treatment failure	reintubation	
CPAP vs BiPAP Lista ³³	28-34 wk	30 wk 1400 g	1 h	Variable flow CPAP (6 cm H ₂ O; n = 20)	Not mentioned	Not mentioned	Maximum PEEP for CPAP and maximum P high/P low for BiPAP not mentioned
			No	BiPAP (P high = 8 cm H ₂ O, P low = 4.5 cm H ₂ O; n = 20)			
Kong ³⁴	30-35 wk	33 wk 2000 g	<6 h	Ventilator CPAP (4-6 cm H ₂ O; n = 33)	72 h	72 h	BiPAP other parameters—Ti: 0.35-0.5 s, rate: 20-30 bpm
			No	BiPAP (P high = 12-15 cm H ₂ O, P low = 4-6 cm H ₂ O; n = 34)			
Wood ³⁵	28-32 wk	30 wk 1300 g	<6 h	Variable flow CPAP (n = 60)	72 h	72 h	Settings for the two interventions not mentioned
			No	BiPAP (n = 60)			
Gao ³⁶	<35 wk	32 wk 1600 g	<12 h	Ventilator CPAP (5 cm H ₂ O; n = 39)	Not mentioned	Not mentioned	BiPAP other parameters—Ti: 0.5 s, rate: 30 bpm
			Yes Not mentioned	BiPAP (P high = 8 cm H ₂ O, P low = 5 cm H ₂ O; n = 35)			Upper limit of pressures used not mentioned Neonates who underwent INSURE were randomized
Aguilar ³⁷	27-32 wk	31 wk 1300 g	At NICU admission	Variable flow CPAP (6-8 cm H ₂ O; n = 109)	120 h	120 h	BiPAP other parameters—Ti: 2-3 s, rate: 10-15 bpm)
			No	BiPAP (P high = 8 cm H ₂ O, P low = 6 cm H ₂ O; n = 111)			
Zhou ³⁸	≥37 wk <1500 g	31 wk 1300 g	≤12 h	Ventilator CPAP (3-8 cm H ₂ O, n = 40)	Not mentioned	Not mentioned	BiPAP other parameters—Ti: 0.5 s, rate: 30-40 bpm
			No	BiPAP (P high = 8-15 cm H ₂ O, P low = 5-8 cm H ₂ O, n = 45)			

TABLE 1 (Continued)

Author	Gestational age (wk)/birth weight for inclusion, g	Mean gestational age (wk)/birth weight of included neonates, (g)	1. Age at randomization (h) 2. Surfactant received before randomization (yes/no) 3. Age at INSURE/LISA (early <2 h; late >2 h)			Interventions with n	Time cut off for treatment failure	Time cut off for reintubation	Other comments
Sadeghnia ³⁹	No gestational age cut off <1500 g	28 wk 1100 g	At NICU admission No			Bubble CPAP (6-8 cm H ₂ O; n=35) BiPAP (P high =6-8 cm H ₂ O, P low =4 cm H ₂ O; n = 35)	Not mentioned	Not mentioned	BiPAP other parameters—Ti: 0.5-0.7 s, rate: 30 bpm
Lee ⁴⁰	30-35 wk	33 wk 2000 g	<24 h No			Variable flow CPAP (4-7 cm H ₂ O, n = 46) BiPAP (P high = 7-10 cm H ₂ O, P low = 4-7 cm H ₂ O, n = 47)	Not mentioned	Not mentioned	BiPAP other parameters—Ti: 0.35 s, rate: 20-40 bpm Infants failing CPAP were eligible for BiPAP
CPAP vs NIPPV									
Biscegia ⁴¹	24-37 wk		Not mentioned			Ventilator CPAP (4-6 cm H ₂ O; n = 46) NIPPV (PIP = 14-20 cm H ₂ O, PEEP = 4-6 cm H ₂ O; n = 42)	Not mentioned	Not mentioned	NIPPV other parameters—rate: 40 bpm
Kugelman ⁴²	24-35 wk	31 wk 1550 g	<1 h No			Ventilator CPAP (6-7 cm H ₂ O, n = 41) NIPPV (PIP = 14-22 cm H ₂ O, PEEP = 6-7 cm H ₂ O; n = 43)	No time cut off	No time cut off	NIPPV other parameters—rate: 12-30 bpm; Ti: 0.3 s
Sai Sunil Kishore ⁴³	28-34 wk	31 wk 1250 g	<6 h No			CPAP (5-7 cm H ₂ O; n = 39) NIPPV (PIP = 15-26 cm H ₂ O, PEEP = 5-6 cm H ₂ O, n = 37)	48 h	48 h	CPAP device not specified Other NIPPV parameters—rate: 50-60 bpm, Ti: 0.3-0.35 s
Meneses ⁴⁴	26-34 wk	30 wk 1100 g	Immediately after birth No			Bubble CPAP (5-6 cm H ₂ O; n = 100) NIPPV (PIP = 15-20 cm H ₂ O, PEEP = 4-6 cm H ₂ O; n = 100)	72 h	72 h	NIPPV other parameters—Ti: 0.4-0.5 L/min; rate: 20-30 bpm
Fu ⁴⁵	30-34 wk	32 wk 1500 g	<1 h No			Ventilator CPAP (5-10 cm H ₂ O; n = 50) NIPPV (PIP = 15-25 cm H ₂ O, PEEP = 5-10 cm H ₂ O)	Not mentioned	Not mentioned	NIPPV other parameters—Ti: 0.3-0.45 L/min; rate: 20-60 bpm

(Continues)

TABLE 1 (Continued)

Author	Gestational age (wk)/birth weight for inclusion, g	Mean gestational age (wk)/birth weight of included neonates, (g)	1. Age at randomization (h) 2. Surfactant received before randomization (yes/no) 3. Age at INSURE/LISA (early <2 h; late >2 h)	Interventions with n	Time cut off for		Other comments
					treatment failure	reintubation	
Sasi ⁴⁶	28-36 wk	...	<1 h No	NPPV (n=37) NCPAP (n=41)	48 h	48 h	CPAP device not mentioned NIPPV settings not mentioned
Armanian ⁴⁷	≤34 wk ≤1500 g	30 wk 1200 g	At NICU admission No	Bubble CPAP (5-6 cm H2O; n = 54) NIPPV (PIP = 16-20 cm H2O, PEEP = 5-6 cm H2O; n = 44)	48 h	48 h	NIPPV other parameters—rate: 40-50 bpm
Shi ⁴⁸	<37 wk	34 wk 2400 g	At NICU admission Yes Not mentioned	Bubble CPAP (4-6 cm H2O; n = 91) NIPPV (PIP = 15-20 cm H2O, PEEP = 4-6 cm H2O; n = 91)	Not mentioned	Not mentioned	1. The mean age of recruitment was approximately 20 h with predominantly out-born infants and majority had received surfactant before randomization 2. NIPPV other parameters— rate: 10-20 bpm
Salama ⁴⁹	28-34 wk	31 wk 1500 g	At NICU admission No	Bubble CPAP (6 cm H2O; n = 30) NIPPV (PIP = 5-12 cm H2O, PEEP = 4-6 cm H2O; n = 30)	Not mentioned	Not mentioned	1. <29 wk gestation infants received prophylactic surfactant 2. NIPPV other parameters— Ti: 0.3-0.5, rate: 15-18 bpm
Chen ⁵⁰	28-36 wk	32 wk 1800 g	At NICU admission No	Ventilator CPAP (4-6 cm H2O; n = 143) NIPPV (PIP = 15-25 cm H2O, PEEP = 4-6 cm H2O; n = 143)	Not mentioned	Not mentioned	1. Only twins were randomized 2. NIPPV other parameters— rate: 10-30 bpm
Oncel ⁵¹	26-32 wk	29 wk 1200 g	<1 h No Not mentioned	Ventilator CPAP (5-6 cm H2O; n = 100) NIPPV (PIP = 15-20 cm H2O, PEEP = 5-6 cm H2O; n = 100)	72 h	72 h	1. NIPPV other parameters—rate: 20-30 bpm
Dursun ⁵²	24-32 wk	29 wk 1300 g	At NICU admission No	Ventilator CPAP (6-8 cm H2O; n = 42) NIPPV (PIP = 16-20 cm H2O, PEEP = 6-8 cm H2O; n = 42)	72 h	72 h	NIPPV other parameters—Ti: 0.40 s, rate: 20-30 bpm

TABLE 1 (Continued)

Author	Gestational age (wk)/birth weight for inclusion, g	Mean gestational age (wk)/birth weight of included neonates, (g)	1. Age at randomization (h) 2. Surfactant received before randomization (yes/no) 3. Age at INSURE/LISA (early <2 h; late >2 h)			Interventions with n	Time cut off for treatment failure	Time cut off for reintubation	Other comments
Garehbaghi ⁵³	28-32 wk	30 wk 1300 g	At NICU admission No			Bubble CPAP (5-6 cm H ₂ O; n = 31) NIPPV (PIP = 18-20 cm H ₂ O, PEEP = 5-6 cm H ₂ O; n = 30)	72 h	72 h	1. NIPPV other parameters—Ti: 0.35-0.40 s, rate: 30-40 bpm
Skariah ⁵⁴	28-36 wk	32 wk 1400 g	<6 h No			Ventilator CPAP (3-5 cm H ₂ O, n = 41) NIPPV (PIP = 11-18 cm H ₂ O, PEEP = 3-5 cm H ₂ O, n = 37)	48 h	48 h	1. - NIPPV other parameters—Ti: 0.36-0.40 s, rate: 18-30 bpm
HFNC vs NIPPV									
Kugelman ⁵⁵	<35 wk >1000 g	33 wk 1800 g	At NICU admission No			HFNC (1-5 L/min; n = 38) NIPPV (PIP = 14-22 cm H ₂ O, PEEP = 6 cm H ₂ O; n = 38)	72 h	72 h	1. NIPPV other parameters—Ti: 0.30 s, rate: 12-30 bpm
Zhu ⁵⁶	28-32 wk 1000-1500 g	30 wk 1300 g	<6 h No			HFNC (5 L/min; n = 43) NIPPV (PIP = 18 cm H ₂ O, PEEP = 6 cm H ₂ O; n = 46)	72 h	72 h	1. NIPPV other parameters— rate: 40 bpm
BiPAP vs NIPPV									
Salvo ⁵⁷	<32 wk <1500 g	29 wk 1100 g	At NICU admission No			NIPPV (PIP = 15-25 cm H ₂ O, PEEP = 4-7 cm H ₂ O; n = 62) BiPAP (P high = 8-10 cm H ₂ O, P low = 4-7 cm H ₂ O; n = 62)	Not mentioned	Not mentioned	1. NIPPV other parameters—Ti: 0.30-0.40 s, rate: 40-60 bpm 2. BiPAP other parameters— Ti: 1 s, rate: 15-20 bpm

Abbreviations: BiPAP, bilevel CPAP; bmp, beats per minute; CPAP, continuous positive airway pressure; HFNC, humidified high flow cannula; INSURE, Intubate Surfactant and Rapid Extubation; NIPPV, noninvasive positive pressure ventilation; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.

TABLE 2 Excluded studies with reasons

Author	Comparison	Reason for exclusion
Friedlich ⁵⁸	NIPPV vs CPAP	Postextubation trial
Barrington ⁵⁹	NIPPV vs CPAP	Postextubation trial
Khalaf ⁶⁰	NIPPV vs CPAP	Postextubation trial
Campbell ⁶¹	CPAP vs HFNC	Postextubation trial
Bhandari ⁶²	NIPPV vs mechanical ventilation	Early extubation to NIPPV was compared with continued invasive mechanical ventilation
Moretti ⁶³	NIPPV vs CPAP	Postextubation trial
Khorana ⁶⁴	NIPPV vs CPAP	Postextubation trial
Gao ⁶⁵	NIPPV vs CPAP	Postextubation trial
Ramanathan ⁶⁶	NIPPV vs CPAP	Both BiPAP and NIPPV were evaluated as one single intervention
O'Brien ⁶⁷	CPAP vs BiPAP	Postextubation trial
Collins ⁶⁸	CPAP vs HFNC	Postextubation trial
Kirpalani ⁶⁹	NIPPV vs CPAP	Both BiPAP and NIPPV were evaluated as one single intervention (Labelled as NIPPV)
Manley ⁷⁰	CPAP vs HFNC	Postextubation trial
Kahramaner ⁷¹	NIPPV vs CPAP	Postextubation trial
Gharehbaghi ⁷²	CPAP vs HFNC	Postextubation trial
Liu ⁷³	CPAP vs HFNC	Postextubation trial
Chen ⁷⁴	CPAP vs HFNC	Postextubation trial
Millar ⁷⁵	NIPPV vs CPAP	Nonrandomized comparison of a subgroup of neonates of a randomized controlled trial
Jasani ⁷⁶	NIPPV vs CPAP	Postextubation trial
Silveira ⁷⁷	NIPPV vs CPAP	Postextubation trial
Hegde ⁷⁸	CPAP vs HFNC	Nonrandomized study
Komatsu ⁷⁹	NIPPV vs CPAP	Postextubation trial
Lavizzari ⁸⁰	CPAP vs HFNC	Neonates in CPAP arm received BiPAP as rescue therapy
Victor ⁸¹	CPAP vs BiPAP	Postextubation trial
Soonsawad ⁸²	CPAP vs HFNC	Postextubation trial
Kang ⁸³	CPAP vs HFNC	Postextubation trial
Esmailnia ⁸⁴	NIPPV vs CPAP	Postextubation trial
Elkhwad ⁸⁵	CPAP vs HFNC	Postextubation trial
Ribeiro ⁸⁶	NIPPV vs CPAP	Postextubation trial
Salvo ⁸⁷	NIPPV vs BiPAP vs CPAP	Nonrandomized study
Bourque ⁸⁸	NIPPV vs CPAP	Secondary cohort study of a randomized controlled trial data
Ding ⁸⁹	NIPPV vs CPAP	Postextubation trial

Abbreviations: BiPAP, bilevel CPAP; bmp, beats per minute; CPAP, continuous positive airway pressure; HFNC, humidified high flow cannula; NIPPV, noninvasive positive pressure ventilation.

3.4.1 | Mortality

NIPPV decreased the risk of mortality when compared to CPAP (0.60 [0.37, 0.89]) and BiPAP (0.48 [0.22, 0.95]) (Figure 3 and Table 4).

3.4.2 | Mortality or BPD

NIPPV was associated with a decreased risk of the combined outcome of BPD or mortality when compared to CPAP (0.74 [0.52, 0.98]) (Figure 3 and Table 4).

(A) Mechanical Ventilation

(B) Treatment Failure

(C) Air leak

(D) BPD

(E) Mortality

(F) BPD or Mortality

FIGURE 2 Geometry of the network for the outcomes—(A) mechanical ventilation, (B) treatment failure, (C) air leak, (D) BPD, (E) mortality, (F) BPD or mortality. The size of the nodes is proportional to the number of subjects with the intervention and the thickness of the limbs are proportional to the number of studies comparing the two interventions. BPD, bronchopulmonary dysplasia [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Network characteristics

Comparison	Number of studies	Number of subjects	Number of outcomes	Event rate (%)
Primary outcome—requirement of mechanical ventilation				
BIPAP vs CPAP	8	769	137	17.8
CPAP vs HFNC	9	1419	172	12.1
CPAP vs NIPPV	13	1514	358	23.6
HFNC vs NIPPV	2	165	32	19.4
Primary outcome—treatment failure				
BIPAP vs CPAP	8	769	139	18.1
CPAP vs HFNC	10	1504	237	15.8
CPAP vs NIPPV	13	1508	306	19.2
HFNC vs NIPPV	1	89	8	9.0
BiPAP vs NIPPV	1	124	18	14.5
Secondary outcome—air leak				
BIPAP vs CPAP	8	769	32	4.2
CPAP vs HFNC	8	1334	29	2.2
CPAP vs NIPPV	11	1326	51	3.8
HFNC vs NIPPV	2	165	8	4.8
BiPAP vs NIPPV	1	122	6	4.9
Secondary outcome—mortality				
BIPAP vs CPAP	8	769	31	4.0
CPAP vs HFNC	7	1237	10	0.8
CPAP vs NIPPV	9	1134	99	8.7
HFNC vs NIPPV	1	76	0	0
Secondary outcome—CLD				
BIPAP vs CPAP	8	758	38	5.0
CPAP vs HFNC	7	1230	42	3.4
CPAP vs NIPPV	6	855	82	9.6
HFNC vs NIPPV	2	165	10	6.1
BiPAP vs NIPPV	1	122	14	11.4
Secondary outcome—CLD or mortality				
BIPAP vs CPAP	8	769	69	9.0
CPAP vs HFNC	7	1235	51	4.1
CPAP vs NIPPV	6	906	174	19.2
HFNC vs NIPPV	1	76	3	3.9
BiPAP vs NIPPV	1	124	16	12.9
Secondary outcome—NEC stage II or more				
BIPAP vs CPAP	5	538	16	3.0
CPAP vs HFNC	3	921	4	0.4
CPAP vs NIPPV	5	648	32	4.9
HFNC vs NIPPV	1	89	4	4.5
Secondary outcome—severe IVH				
BIPAP vs CPAP	4	423	15	3.6
CPAP vs HFNC	3	921	6	0.6
CPAP vs NIPPV	3	436	23	5.3
HFNC vs NIPPV	1	89	5	5.6
BiPAP vs NIPPV	1	122	4	3.2
Secondary outcome—PDA requiring treatment				
BIPAP vs CPAP	1	220	17	13.2
CPAP vs HFNC	3	921	47	5.1
CPAP vs NIPPV	2	400	107	26.1
BiPAP vs NIPPV	1	122	32	26.2

TABLE 3 (Continued)

Comparison	Number of studies	Number of subjects	Number of outcomes	Event rate (%)
Secondary outcome—severe ROP				
BiPAP vs CPAP	2	253	1	0.4
CPAP vs HFNC	2	836	14	1.7
CPAP vs NIPPV	3	419	28	6.7
BiPAP vs NIPPV	1	122	5	4.1
Secondary outcome—nasal trauma				
CPAP vs HFNC	8	1326	152	11.5
CPAP vs NIPPV	2	136	24	17.6
HFNC vs NIPPV	1	91	9	9.9

Abbreviations: BiPAP, bilevel CPAP; bpm, beats per minute; CPAP, continuous positive airway pressure; HFNC, humidified high flow cannula; NIPPV, noninvasive positive pressure ventilation.

3.4.3 | Nasal trauma

HFNC resulted in reduced incidence of nasal injury when compared to CPAP (RR: 0.15 [0.01, 0.60]) (E-Figure S9 and Table 4).

outcome MV. The results were unchanged for other outcomes (E-Figures S10 and S11).

3.5 | Sensitivity analysis

3.5.1 | Excluding studies with high risk of bias

When studies with high risk of bias were excluded, there was no difference in efficacy between any of the NRS modalities for the

3.5.2 | Excluding studies which had enrolled neonates who had already received surfactant

The results were unchanged after excluding trials that had enrolled neonate who had already received surfactant before randomization (E-Figures S10 and S11).

FIGURE 3 Forest plots depicting the RR (95% CrI) for different NRS modalities with HFNC as a common comparator for the outcomes—(A) mechanical ventilation, (B) treatment failure, (C) air leak, (D) BPD, (E) mortality, (F) BPD or mortality. BPD, bronchopulmonary dysplasia; CrI, credible interval; HFNC, humidified high flow cannula; NRS, noninvasive respiratory support; RR, risk ratios

FIGURE 4 SUCRA plots for the outcomes—(A) mechanical ventilation, (B) treatment failure, (C) air Leak, (D) BPD, (E) mortality, (F) BPD or mortality. BPD, bronchopulmonary dysplasia; SUCRA, surface under the cumulative ranking curve

TABLE 4 League tables comparing the different NIV modalities for all the outcomes

Treatment failure; risk ratio (95% credible intervals)			
BiPAP	1.44 (1.07, 1.93)	1.90 (1.24, 2.81)	0.81 (0.56, 1.15)
0.69 (0.51, 0.93)	CPAP	1.32 (0.97, 1.72)	0.56 (0.44, 0.71)
0.53 (0.35, 0.81)	0.75 (0.58, 1.03)	HFNC	0.42 (0.30, 0.63)
1.23 (0.87, 1.76)	1.78 (1.40, 2.26)	2.34 (1.59, 3.33)	NIPPV
Requirement of mechanical ventilation; risk ratio (95% credible intervals)			
BiPAP	1.29 (0.88, 1.89)	1.18 (0.70, 1.97)	0.77 (0.47, 1.21)
0.78 (0.53, 1.15)	CPAP	0.92 (0.64, 1.28)	0.60 (0.44, 0.77)
0.85 (0.51, 1.44)	1.09 (0.77, 1.58)	HFNC	0.65 (0.43, 0.96)
1.30 (0.83, 2.12)	1.68 (1.30, 2.25)	1.54 (1.04, 2.31)	NIPPV
Air leak; risk ratio (95% credible intervals)			
BiPAP	0.66 (0.36, 1.21)	0.41 (0.15, 1.00)	0.36 (0.16, 0.73)
1.50 (0.83, 2.78)	CPAP	0.63 (0.28, 1.20)	0.54 (0.30, 0.87)
2.41 (0.99, 6.67)	1.596 (0.83, 3.58)	HFNC	0.86 (0.40, 1.93)
2.80 (1.37, 6.26)	1.86 (1.14, 3.30)	1.16 (0.52, 2.50)	NIPPV
CLD; risk ratio (95% credible intervals)			
BiPAP	0.95 (0.60, 1.52)	0.90 (0.42, 1.86)	0.72 (0.40, 1.19)
1.05 (0.66, 1.67)	CPAP	0.94 (0.51, 1.68)	0.75 (0.48, 1.09)
1.11 (0.54, 2.39)	1.06 (0.59, 1.96)	HFNC	0.80 (0.40, 1.52)
1.39 (0.84, 2.47)	1.33 (0.91, 2.06)	1.25 (0.66, 2.47)	NIPPV
Mortality; risk ratio (95% credible intervals)			
BiPAP	0.80 (0.44, 1.44)	0.37 (0.10, 1.25)	0.48 (0.22, 0.95)
1.24 (0.69, 2.26)	CPAP	0.47 (0.15, 1.33)	0.60 (0.37, 0.89)
2.68 (0.80, 9.55)	2.14 (0.75, 6.59)	HFNC	1.26 (0.42, 4.11)
2.07 (1.05, 4.56)	1.67 (1.12, 2.73)	0.79 (0.24, 2.37)	NIPPV
Mortality or CLD; risk ratio (95% credible intervals)			
BiPAP	1.05 (0.73, 1.52)	1.02 (0.51, 1.93)	0.78 (0.49, 1.17)
0.95 (0.66, 1.38)	CPAP	0.97 (0.53, 1.68)	0.74 (0.52, 0.98)
0.98 (0.52, 1.97)	1.03 (0.60, 1.88)	HFNC	0.76 (0.41, 1.42)
1.29 (0.86, 2.05)	1.36 (1.03, 1.92)	1.32 (0.70, 2.46)	NIPPV
Severe IVH; risk ratio (95% credible intervals)			
BiPAP	0.87 (0.37, 2.07)	0.58 (0.11, 2.39)	0.50 (0.16, 1.35)
1.14 (0.48, 2.68)	CPAP	0.66 (0.15, 2.21)	0.57 (0.23, 1.25)
1.73 (0.42, 9.05)	1.50 (0.45, 6.52)	HFNC	0.86 (0.23, 3.62)
1.99 (0.74, 6.04)	1.74 (0.80, 4.37)	1.16 (0.28, 4.31)	NIPPV
NEC stage II or more; risk ratio (95% credible intervals)			
BiPAP	1.62 (0.51, 4.58)	1.83 (0.29, 10.22)	0.81 (0.18, 2.98)
0.62 (0.22, 1.96)	CPAP	1.13 (0.29, 4.71)	0.50 (0.20, 1.10)
0.55 (0.10, 3.42)	0.89 (0.21, 3.50)	HFNC	0.44 (0.10, 1.80)
1.23 (0.33, 5.62)	2.00 (0.91, 4.88)	2.28 (0.56, 10.42)	NIPPV
PDA requiring treatment; risk ratio (95% credible intervals)			
BiPAP	1.01 (0.49, 1.90)	1.19 (0.44, 3.24)	0.92 (0.48, 1.74)
0.99 (0.52, 2.03)	CPAP	1.18 (0.59, 2.57)	0.91 (0.55, 1.62)
0.84 (0.31, 2.24)	0.84 (0.39, 1.70)	HFNC	0.77 (0.31, 1.88)
1.08 (0.57, 2.08)	1.10 (0.62, 1.82)	1.29 (0.53, 3.24)	NIPPV
Severe ROP; risk ratio (95% credible intervals)			
BiPAP	0.67 (0.19, 2.10)	0.38 (0.05, 2.02)	0.62 (0.18, 1.87)
1.49 (0.47, 5.25)	CPAP	0.56 (0.12, 2.04)	0.93 (0.40, 2.07)
2.65 (0.50, 21.15)	1.77 (0.49, 8.41)	HFNC	1.64 (0.36, 9.33)
1.60 (0.54, 5.66)	1.08 (0.48, 2.51)	0.61 (0.11, 2.77)	NIPPV

(Continues)

TABLE 4 (Continued)

Nasal trauma; risk ratio (95% credible intervals)		
CPAP	0.15 (0.01, 0.60)	0.17 (0.00, 2.13)
6.75 (1.67, 72.94)	HFNC	1.13 (0.06, 24.87)
5.84 (0.47, 178.5)	0.88 (0.04, 17.06)	NIPPV

Note: The RR (95% credible interval) for the intervention in the row vs the intervention in the column is given in the lower triangle and vice versa in the upper triangle.

Abbreviations: BiPAP, bilevel CPAP; bmp, beats per minute; CPAP, continuous positive airway pressure; HFNC, humidified high flow cannula; NIPPV, noninvasive positive pressure ventilation; RR, risk ratio.

3.5.3 | Assessing NIPPV and BiPAP based on synchronization

NS-BiPAP, S-NIPPV, and NS-NIPPV decreased the risk of MV when compared to CPAP (RR [95% CrI]: 0.51 [0.29, 0.85]; 0.54 [0.32, 0.90]; 0.61 [0.43, 0.83], respectively). There were no statistically significant differences in the efficacies between NS-BiPAP, S-BiPAP, NS-NIPPV, and S-NIPPV for preventing MV. The best intervention in descending order to decrease the risk of MV as indicated by SUCRA was as follows—NS-BiPAP, S-NIPPV, NS-NIPPV, S-BiPAP, HFNC, and CPAP. The network plot, the forest plot and the SUCRA plot are given in E-Figure S12 and the network estimates for the various NRS companions are shown in league matrix table in E-Table S3.

NS-BiPAP, S-NIPPV, and NS-NIPPV had decreased incidence of treatment failure when compared to CPAP as well as HFNC. There were no statistically significant differences between NS-BiPAP, S-BiPAP, NS-NIPPV, and S-NIPPV for preventing treatment failure. SUCRA values indicated that S-NIPPV was the best NRS modality followed by NS-BiPAP, NS-NIPPV, S-BiPAP, CPAP, and HFNC in descending order to prevent treatment failure. The network plot, the forest plot, and the SUCRA plot are given in E-Figure S13 and the network estimates for the various NRS companions are shown in the league matrix table in E-Table S3 (Figure 5).

3.6 | Quality of evidence

The overall confidence in the NMA effect estimate for the primary outcomes of treatment failure and requirement of MV was moderate for HFNC vs CPAP; CPAP vs NIPPV; HFNC vs NIPPV comparisons and low to very low for other comparisons. The quality of evidence was very low to moderate for all other secondary outcomes for the different comparisons. The quality of evidence for all the comparisons across outcomes is given in Table 5.

4 | DISCUSSION

This NMA included data of 35 studies (4078 neonates) to evaluate the efficacy of different NRS modalities as primary support for RDS.

Clear differences between NRS modes were found. NIPPV reduced the risk of MV when compared to both CPAP and HFNC. Also, both NIPPV and BiPAP were associated with lesser treatment failure in comparison to CPAP and HFNC. Ranking probabilities indicate that NIPPV might be the most appropriate primary modality of NRS in preterm neonates with RDS.

The findings of this NMA are similar to Lemyre et al's⁹ with NIPPV being superior to CPAP in preventing treatment failure as well as MV.⁹ The relative risk reduction for both the primary outcomes was much larger than that reported by Lemyre et al⁹ with narrower CrIs. Reasons for this could be that this NMA had included more recently published studies and also that the modalities BiPAP and NIPPV were evaluated as separate interventions. Also, this was an NMA where apart from the direct synthesis, the indirect evidence also contributed toward the overall effect estimate. It is evident from the included studies that the peak inspiratory pressure and hence the mean airway pressure (MAP) that was delivered with NIPPV was much higher than the positive end-expiratory pressure generated with CPAP.⁴¹⁻⁵⁴ This might be one of the reasons for NIPPV being more effective than CPAP. The fact that the incidence of air leak, as well as that of the combined outcome of BPD or mortality, was much lesser with NIPPV when compared to CPAP might suggest that the use of a relatively higher MAP with NIPPV is not deleterious.

The results of this NMA were similar to those by Fleeman et al⁸ and Hong et al⁷ with HFNC being equally efficacious as CPAP as a primary mode of respiratory support in neonates with RDS.^{7,8} It should be noted that most of the studies that had compared HFNC with CPAP had enrolled neonates of gestational ages of more than 28 weeks. Hence, these findings are not generalizable to the more immature neonates. The meta-regression also showed a trend of HFNC being less efficacious at lesser gestational ages compared to other NRS modalities. However, the results were imprecise making it difficult to draw reasonable conclusions.

Both NIPPV and BiPAP were equally efficacious in preventing treatment failure and MV. Most of the evidence that contributed to this comparison was indirect and there was only a single RCT that had compared these two interventions.⁵⁷ Millar et al⁷⁵ in their a priori planned nonrandomized comparison of neonates randomized to the NIPPV arm of the NIPPV trial (a large RCT comparing NIPPV/ BiPAP vs CPAP as primary as well as postextubation respiratory support) had reported similar findings with no differences in the

CPAP vs NIPPV

CPAP vs BiPAP

HFNC vs CPAP

HFNC vs NIPPV

FIGURE 5 Pair-wise meta-analysis comparing different NIV modalities for the primary outcomes—(A) mechanical ventilation, (B) treatment failure

TABLE 5 Quality of evidence/GRADE

	Indirect evidence	Direct evidence	Network meta-analysis	
Comparison	Quality of evidence	Quality of evidence	Risk ratio (95% credible interval)	Quality of evidence
Outcome—mechanical ventilation				
HFNC vs NIPPV	Moderate ^a	Very low ^{b,c}	1.52 (1.01, 2.32)	Moderate
CPAP vs HFNC	Very low ^{b,c}	Moderate ^a	1.09 (0.77, 1.58)	Moderate
BiPAP vs HFNC	Low ^{d,a}	...	0.85(0.51, 1.46)	Low
CPAP vs NIPPV	Very low ^{b,c}	Moderate ^b	1.66 (1.26, 2.27)	Moderate
BiPAP vs NIPPV	Very low ^{b,c}	...	1.29 (0.81, 2.15)	Very low
BiPAP vs CPAP	...	Low ^c	0.78 (0.53, 1.15)	Low
Outcome—treatment failure				
HFNC vs NIPPV	Moderate ^a	Very low ^{b,c}	2.34 (1.59, 3.33)	Moderate
CPAP vs HFNC	Very low ^{b,c}	Moderate ^a	0.75 (0.58, 1.03)	Moderate
BiPAP vs HFNC	Very low ^{b,c}	...	0.53 (0.35, 0.81)	Very low
CPAP vs NIPPV	Very low ^{b,c}	Moderate ^b	1.78 (1.40, 2.26)	Moderate
BiPAP vs NIPPV	Low ^c	Low ^c	1.23 (0.87, 1.76)	Low
BiPAP vs CPAP	Low ^c	Low ^c	0.69 (0.51, 0.93)	Low
Outcome—mortality				
HFNC vs NIPPV	Low ^c	Very low ^{b,c}	0.79 (0.24, 2.37)	Low
CPAP vs HFNC	Very low ^{b,c}	Low ^c	2.14 (0.75, 6.59)	Low
BiPAP vs HFNC	Very low ^{b,c}	...	2.68 (0.80, 9.55)	Very low
CPAP vs NIPPV	Very low ^{b,c}	Low ^c	1.67 (1.12, 2.73)	Very low ^e
BiPAP vs NIPPV	Very low ^{b,c}	Low ^c	2.07 (1.05, 4.56)	Low
BiPAP vs CPAP	Low ^c	Very low ^{b,c}	1.24 (0.69, 2.26)	Very low ^e
Outcome—CLD				
HFNC vs NIPPV	Low ^c	Very low ^{b,c}	1.25 (0.66, 2.47)	Low
CPAP vs HFNC	Very low ^{b,c}	Low ^c	1.06 (0.59, 1.96)	Low
BiPAP vs HFNC	Low ^c	...	1.11 (0.54, 2.39)	Low
CPAP vs NIPPV	Low ^c	Low ^c	1.33 (0.91, 2.06)	Low
BiPAP vs NIPPV	Low ^c	Low ^c	1.39 (0.84, 2.47)	Low
BiPAP vs CPAP	Low ^c	Low ^c	1.05 (0.66, 1.67)	Low
Outcome—mortality or CLD				
HFNC vs NIPPV	Low ^c	Low ^c	0.79 (0.24, 2.37)	Low
CPAP vs HFNC	Low ^c	Low ^c	2.14 (0.75, 6.59)	Low
BiPAP vs HFNC	Very low ^{b,c}	...	2.68 (0.80, 9.55)	Very low
CPAP vs NIPPV	Low ^c	Low ^c	1.67 (1.12, 2.73)	Low
BiPAP vs NIPPV	Very low ^{b,c}	Low ^c	2.07 (1.05, 4.56)	Low
BiPAP vs CPAP	Low ^c	Very low ^{b,c}	1.24 (0.69, 2.26)	Low
Outcome—air leak				
HFNC vs NIPPV	Low ^c	Very low ^{b,c}	1.16 (0.52, 2.50)	Low
CPAP vs HFNC	Very low ^{b,c}	Low ^c	1.596 (0.83, 3.58)	Low
BiPAP vs HFNC	Very low ^{b,c}	...	2.41 (0.99, 6.67)	Very low
CPAP vs NIPPV	Very low ^{b,c}	Low ^c	1.86 (1.14, 3.30)	Low
BiPAP vs NIPPV	Very low ^{b,c}	Low ^c	2.80 (1.37, 6.26)	Low
BiPAP vs CPAP	Low ^c	Very low ^{b,c}	1.50 (0.83, 2.78)	Low
Outcome—severe IVH				
HFNC vs NIPPV	Low ^c	Very low ^{b,c}	1.16 (0.28, 4.31)	Low
CPAP vs HFNC	Very low ^{b,c}	Low ^c	1.50 (0.45, 6.52)	Low
BiPAP vs HFNC	Low ^c	...	1.73 (0.42, 9.05)	Low
CPAP vs NIPPV	Very low ^{b,c}	Low ^c	1.74 (0.80, 4.37)	Low
BiPAP vs NIPPV	Low ^c	Low ^c	1.99 (0.74, 6.04)	Low
BiPAP vs CPAP	Low ^c	Low ^c	1.14 (0.48, 2.68)	Low

TABLE 5 (Continued)

	Indirect evidence	Direct evidence	Network meta-analysis	
Comparison	Quality of evidence	Quality of evidence	Risk ratio (95% credible interval)	Quality of evidence
Outcome—NEC stage II or more				
HFNC vs NIPPV	Low ^c	Very low ^{b,c}	2.28 (0.56, 10.42)	Very low ^e
CPAP vs HFNC	Very low ^{b,c}	Low ^c	0.89 (0.21, 3.50)	Very low ^e
BiPAP vs HFNC	Low ^c	...	0.55 (0.10, 3.42)	Low
CPAP vs NIPPV	Very low ^{b,c}	Low ^c	2.00 (0.91, 4.88)	Very low ^e
BiPAP vs NIPPV	Low ^c	...	1.23 (0.33, 5.62)	Low
BiPAP vs CPAP	...	Low ^c	0.62 (0.22, 1.96)	Low
Outcome—PDA requiring treatment				
HFNC vs NIPPV	Very low ^{c,d}	...	1.29 (0.53, 3.24)	Very low
CPAP vs HFNC	...	Very low ^{c,d}	0.84 (0.39, 1.70)	Very low
BiPAP vs HFNC	Very low ^{c,d}	...	0.84 (0.31, 2.24)	Very low
CPAP vs NIPPV	Low ^c	Low ^c	1.10 (0.62, 1.82)	Low
BiPAP vs NIPPV	Low ^c	Low ^c	1.08 (0.57, 2.08)	Low
BiPAP vs CPAP	Low ^c	Low ^c	0.99 (0.52, 2.03)	Low
Outcome—severe ROP				
HFNC vs NIPPV	Low ^c	...	0.61 (0.11, 2.77)	Low
CPAP vs HFNC	...	Low ^c	1.77 (0.49, 8.41)	Low
BiPAP vs HFNC	Very low ^{b,c}	...	2.65 (0.50, 21.15)	Very low
CPAP vs NIPPV	Very low ^{b,c}	Low ^c	1.08 (0.48, 2.51)	Low
BiPAP vs NIPPV	Very low ^{b,c}	Low ^c	1.60 (0.54, 5.66)	Low
BiPAP vs CPAP	Low ^c	Very low ^{b,c}	1.49 (0.47, 5.25)	Low
Outcome—nasal trauma				
HFNC vs NIPPV	Very low ^{c,d}	Very low ^{b,c}	0.88 (0.04, 17.06)	Very low
CPAP vs HFNC	Very low ^{c,d}	Moderate ^a	6.75 (1.67, 72.94)	Moderate
BiPAP vs HFNC	...	...	...	...
CPAP vs NIPPV	Very low ^{b,c}	Very low ^{c,d}	5.84 (0.47, 178.5)	Very low
BiPAP vs NIPPV	...	...	...	...
BiPAP vs CPAP	...	...	...	...

Note: GRADE Ranking the Quality Of Evidence.

High quality—very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality—moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality—confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality—very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: BiPAP, bilevel CPAP; bmp, beats per minute; CPAP, continuous positive airway pressure; HFNC, humidified high flow cannula; NIPPV, noninvasive positive pressure ventilation.

^aImprecision.

^bLimitations (risk of bias).

^cSevere imprecision.

^dHeterogeneity.

^eInconsistency.

incidence of reintubation between NIPPV and BiPAP groups in the first week after randomization in the primary respiratory support group.⁷⁵ Similar to the BiPAP vs NIPPV comparison, there was paucity of direct evidence for studies evaluating HFNC vs NIPPV where only two RCTs contributed to the direct evidence.^{55,56} These reiterate the need for further RCTs comparing these interventions.

Sensitivity analysis by assessing NIPPV and BiPAP based on synchronization did not reveal any significant differences in efficacies between synchronized or NS-NIPPV or BiPAP devices. There

is a paucity of literature comparing these interventions in RCTs. Most of the evidence in this NMA comparing synchronized vs nonsynchronized devices came from indirect evidence. S-BiPAP, S-NIPPV, and NS-NIPPV were more efficacious than CPAP and HFNC for both the primary outcomes. Lemyre et al⁹ in their sensitivity analyses based on synchronization had reported that S-NIPPV had similar efficacy when compared to CPAP while NS-NIPPV resulted in the lesser requirement of MV and treatment failure compared to CPAP. This could be explained by the differences between the

present NMA and Lemyre et al's⁹ meta-analysis as described previously.

The analysis of secondary outcomes reveals that both BiPAP and CPAP were associated with an increased risk of air leak and mortality when compared to NIPPV. Also, the risk of combined outcome of mortality or BPD was higher in CPAP compared with NIPPV. Isayama et al¹⁰ in their NMA of different invasive and noninvasive modalities along with different methods of surfactant administration in preterm neonates with RDS had found no differences in the incidence of air leak, mortality, or BPD between CPAP and NIPPV.¹⁰ The differences in the findings between this NMA and Isayama et al's¹⁰ might be due to the fact that while this NMA had included only noninvasive modalities of respiratory support and had excluded neonates requiring invasive MV, Isayama et al¹⁰ had assessed interventions such as LISA, INSURE, nebulized surfactant, surfactant application through laryngeal mask airway and invasive MV in their NMA. Also, more recent studies that were published after Isayama et al's¹⁰ meta-analysis were included in the present analysis.^{39,40,52-54} The other reason might be the differences in the gestational ages of the neonates enrolled in Isayama et al¹⁰ study and our study. While Isayama et al¹⁰ included studies that have enrolled smaller neonates (mean gestational age of 29 weeks), ours had included neonates with a mean gestational of 31 weeks. It should be noted that the network assessing the outcome mortality in our NMA was inconsistent. In a scenario where inconsistency has been detected for an outcome in an NMA, the network estimates are not reliable and any changes in the included studies to address the inconsistency becomes a post hoc analysis and is not recommended.⁹⁰

The increased risk of air leak with BiPAP when compared to NIPPV could be explained by the different mechanisms of flows used by these two interventions.⁹¹ While NIPPV uses a fixed flow using a ventilator, BiPAP is a variable flow device. Some of the BiPAP studies have used very high pressure high of upto 15 cm H₂O which might require a very high gas flow rate.⁹² Also, the inspiratory times are typically higher in BiPAP compared to NIPPV which might result in the alveoli being exposed to higher pressures for a longer period of time as well as increasing the risk gas trapping, especially when higher respiratory rates are used. The risk of mortality or BPD was higher in CPAP compared with NIPPV in this NMA. This was not seen in the Isayama et al's¹⁰ NMA. This might be due to the differences in the inclusion criteria between the two meta-analyses as specified above. Also, the quality of evidence for most of the secondary outcomes of this NMA was low to very low and hence should be interpreted with caution.

5 | STRENGTHS AND LIMITATIONS

This is one of the largest NMA evaluating the different NRS modalities used as primary support for preterm neonates with RDS. It is PRISMA NMA extension compliant. The quality of evidence for all the outcomes was done in a very robust manner as per the GRADE working group recommendations.

Limitations in this NMA include that this did not include two of the recently introduced NRS modalities in neonatal respiratory care namely, nasal high-frequency oscillation ventilation (nHFOV) and neurally adjusted Ventilatory assist. Also, two of the secondary outcomes (NEC and mortality) had inconsistent networks. Finally, the event rates and the optimal information size for most of the secondary outcomes were low with the quality of the evidence being downgraded to low to very low for these outcomes.

6 | CONCLUSIONS

The overall quality of evidence for the primary outcomes was moderate to very low for the different comparisons. NIPPV appears to be the most effective primary NRS modality in preterm neonates with RDS to prevent MV and respiratory failure in the first few days of life.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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REFERENCES

1. Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. *Cochrane Database Syst Rev*. 2009;2: CD007836.
2. Rojas-Reyes MX, Morley CJ, Soll R. Pro-phylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2012;3(3):CD000510.
3. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome—2019 update. *Neonatology*. 2019;115(4):432-450.
4. Permall DL, Pasha AB, Chen XQ. Current insights in non-invasive ventilation for the treatment of neonatal respiratory disease. *Ital J Pediatr*. 2019;45(1):105.
5. Li J, Li X, Huang X, Zhang Z. Noninvasive high-frequency oscillatory ventilation as respiratory support in preterm infants: a meta-analysis of randomized controlled trials. *Respir Res*. 2019;20(1):58.
6. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev*. 2016;2:CD006405.
7. Hong H, Li XX, Li J, Zhang ZQ. High-flow nasal cannula versus nasal continuous positive airway pressure for respiratory support in preterm infants: a meta-analysis of randomized controlled trials [published online ahead of print April 24, 2019]. *J Matern Fetal Neonatal Med*. 2019;1-8. <https://doi.org/10.1080/14767058.2019.1606193>
8. Fleeman N, Dundar Y, Shah PS, Shaw BN. Heated humidified high-flow nasal cannula for preterm infants: an updated systematic review and meta-analysis. *Int J Technol Assess Health Care*. 2019;35(4): 298-306.
9. Lemyre B, Laughon M, Bose C, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. *Cochrane Database Syst Rev*. 2016;12:CD005384.
10. Isayama T, Iwami H, McDonald S, Beyene J. Association of non-invasive ventilation strategies with mortality and bronchopulmonary

- dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA*. 2016;316(6):611-624.
11. Viraraghavan V R, Kiran More BH Prathik, Charles Roehr. Efficacy of non-invasive modalities of primary respiratory support in preterm neonates with RDS: systematic review and network meta-analysis. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=177474. Accessed May 30, 2020.
 12. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784.
 13. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 gm. *J Pediatr*. 1978;92(4):529-534.
 14. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1):1-7.
 15. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991-999.
 16. Higgins J, Green S Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. <http://handbook.cochrane.org>. Accessed April 26, 2020.
 17. Shim SR, Kim SJ, Lee J, Rucker G. Network meta-analysis: application and practice using R software. *Epidemiol Health*. 2019;41:e2019013.
 18. Béléveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Med Res Methodol*. 2019;19(1):196.
 19. Brooks S, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat*. 1998;7(4):434-455.
 20. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7-8):932-944.
 21. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163-171.
 22. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014;349:g5630.
 23. Nair G, Karna P. Comparison of the effects of Vapotherm and nasal CPAP in respiratory distress. Paper presented at: Pediatric Academic Societies Meeting; May 14-17, 2005; Washington, DC. <http://www.abstracts2view.com/pas/>. Accessed April 2020. E-PAS2005:57:2054.
 24. Iranpour R, Sadeghnia A, Hesarakhi M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. *J Isfahan Med Sch*. 2011;29(143):1.
 25. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. *Pediatrics*. 2013;131:e1482-e1490.
 26. Kadivar MM, Mosayebi ZM, Razi NM, Nariman SM, Sangsari RM. High flow nasal cannulae versus nasal continuous positive airway pressure in neonates with respiratory distress syndrome managed with insure method: a randomized clinical trial. *Iran J Med Sci*. 2016;41:494-500.
 27. Roberts CT, Owen LS, Manley BJ, et al. Nasal high-flow therapy for primary respiratory support in preterm infants. *N Engl J Med*. 2016;375(11):1142-1151.
 28. Shin J, Park K, Lee EH, Choi BM. Humidified high flow nasal cannula versus nasal continuous positive airway pressure as an initial respiratory support in preterm infants with respiratory distress: a randomized, controlled non-inferiority trial. *J Korean Med Sci*. 2017;32:650-655.
 29. Murki S, Singh J, Khant C, et al. High-flow nasal cannula versus nasal continuous positive airway pressure for primary respiratory support in preterm infants with respiratory distress: a randomized controlled trial. *Neonatology*. 2018;113:235-241.
 30. Shokouhi M, Basiri B, Sabzehei MK, Mahdiankhoo M, Pirdehghan A. Efficacy and complications of humidified high-flow nasal cannula versus nasal continuous positive airway pressure in neonates with respiratory distress syndrome after surfactant therapy. *Iran Red Crescent Med J*. 2019;21(2):e83615.
 31. Sharma P, Poonia A, Bansal R. Comparison of efficacy of nasal continuous positive airway pressure and heated humidified high-flow nasal cannula as a primary mode of respiratory support in preterm infants. *J Clin Neonatol*. 2019;8(2):102-105.
 32. Demirel G, Vatansever B, Tastekin A. High flow nasal cannula versus nasal continuous positive airway pressure for primary respiratory support in preterm infants: a prospective randomized study [published online ahead of print September 28, 2019]. *Am J Perinatol*. 2019. <https://doi.org/10.1055/s-0039-1696673>
 33. Lista G, Castoldi F, Fontana P, et al. Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial. *Arch Dis Child Fetal Neonatal Ed*. 2009;95(2):F85-F89.
 34. Kong LK, Kong XY, Li LH, et al. Comparative study on application of duo positive airway pressure and continuous positive airway pressure in preterm neonates with respiratory distress syndrome. *Zhongguo Dang Dai Er Ke Za Zhi*. 2012;14(12):888-892.
 35. Wood FE, Gupta S, Tin W, Sinha S. Randomised controlled trial of synchronised intermittent positive airway pressure (SiPAP) versus continuous positive airway pressure (CPAP) as a primary mode of respiratory support in preterm infants with respiratory distress syndrome. *Arch Dis Child*. 2013;98(suppl 1):A1-117.
 36. Gao X, Yang B, Hei M, et al. Application of three kinds of non-invasive positive pressure ventilation as a primary mode of ventilation in premature infants with respiratory distress syndrome: a randomized controlled trial. *Zhonghua Er Ke Za Zhi*. 2014;52(1):34-40.
 37. Aguiar T, Macedo I, Voutsen O, et al. Nasal bilevel vs continuous positive airway pressure in preterm infants: a randomized controlled trial. *J Clin Trials*. 2015;5(3):221.
 38. Zhou B, Zhai J-F, Jiang H-X, et al. Usefulness of DuoPAP in the treatment of very low birth weight preterm infants with neonatal respiratory distress syndrome. *Eur Rev Med Pharmacol Sci*. 2015;19(4):573-577.
 39. Sadeghnia A, Barekateyn B, Badiel Z, Hosseini SM. Analysis and comparison of the effects of N-BiPAP and Bubble-CPAP in treatment of preterm newborns with the weight of below 1500 grams affiliated with respiratory distress syndrome: a randomised clinical trial. *Adv Biomed Res*. 2016;5:3.
 40. Lee MJ, Choi EK, Park KH, Shin J, Choi BM. Effectiveness of nCPAP for moderate preterm infants compared to BiPAP: a randomized, controlled non-inferiority trial. *Pediatr Int*. 2020;62(1):59-64.
 41. Bisceglia M, Belcastro A, Poerio V, et al. A comparison of nasal intermittent versus continuous positive pressure delivery for the treatment of moderate respiratory distress syndrome in preterm infants. *Minerva Pediatr*. 2007;59(2):91-95.
 42. Kugelman A, Feferkorn I, Riskin A, Chistyakov I, Kaufman B, Bader D. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. *J Pediatr*. 2007;150(5):521-526.
 43. Sai Sunil Kishore M, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Paediatr (Stockholm)*. 2009;98(9):1412-1415.
 44. Meneses J, Bhandari V, Alves JG, Herrmann D. Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial. *Pediatrics*. 2011;127(2):300-307.

45. Fu CH, Xia SW. [Clinical application of nasal intermittent positive pressure ventilation in initial treatment of neonatal respiratory distress syndrome]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2014;16(5):460-464.
46. Sasi A, Skariah T, Lewis L. Early nasal intermittent mandatory ventilation (NIMV) versus nasal continuous positive airway pressure (NCPAP) for respiratory distress syndrome (RDS) in infants 28 to 36 weeks gestation—a randomized controlled trial. *J Paediatr Child Health*. 2013;49(suppl 2):34-35.
47. Armanian AM, Badiee Z, Heidari G, Feizi A, Salehimehr N. Initial treatment of respiratory distress syndrome with nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure: a randomized controlled trial. *Int J Prev Med*. 2014;5(12):1543-1551.
48. Shi Y, Tang S, Zhao J, Shen J. A prospective, randomized, controlled study of NIPPV versus nCPAP in preterm and term infants with respiratory distress syndrome. *Pediatr Pulmonol*. 2014;49(7):673-678.
49. Salama GS, Ayyash FF, Al-Rabadi AJ, Alquran ML, Shakkoury AG. Nasal-IMV versus nasal-CPAP as an initial mode of respiratory support for premature infants with RDS: a prospective randomized clinical trial. *Rawal J Med*. 2015;40(2):197-202.
50. Chen L, Wang L, Li J, Wang N, Shi Y. Noninvasive ventilation for preterm twin neonates with respiratory distress syndrome: a randomized controlled trial. *Sci Rep*. 2015;5:14483.
51. Oncel MY, Arayici S, Uras N, et al. Nasal continuous positive airway pressure versus nasal intermittent positive-pressure ventilation within the minimally invasive surfactant therapy approach in preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2016;101(4):F323-F328.
52. Dursun M, Uslu S, Bulbul A, Celik M, Zubarioglu U, Bas EK. Comparison of early nasal intermittent positive pressure ventilation and nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome. *J Trop Pediatr*. 2019;65(4):352-360.
53. Gharehbaghi MM, Hosseini MB, Eivazi G, Yasrebinia S. Comparing the efficacy of nasal continuous positive airway pressure and nasal intermittent positive pressure ventilation in early management of respiratory distress syndrome in preterm infants. *Oman Med J*. 2019;34(2):99-104.
54. Ann Skariah T, Edward Lewis L. Early nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for respiratory distress syndrome (RDS) in infants of 28-36 weeks gestational age: a randomized controlled trial. *Iranian J Neonatol IJN*. 2019;10(2):1-8.
55. Kugelman A, Riskin A, Said W, Shoris I, Mor F, Bader D. A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS. *Pediatr Pulmonol*. 2015;50(6):576-583.
56. Wang Z, Xiang JW, Gao WW, et al. Comparison of clinical efficacy of two noninvasive respiratory support therapies for respiratory distress syndrome in very low birth weight preterm infants. *Zhongguo Dang Dai Er Ke Za Zhi*. 2018;20(8):603-607.
57. Salvo V, Lista G, Lupo E, et al. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT. *Pediatrics*. 2015;135(3):444-451.
58. Friedlich P, Lecart C, Posen R, Ramicone E, Chan L, Ramanathan R. A randomized trial of nasopharyngeal-synchronised intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants following extubation. *J Perinatol*. 1999;19(6 Pt 1):413-418.
59. Barrington KJ, Finer NN, Bull D. Randomised controlled trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. *Pediatrics*. 2001;107(4):638-641.
60. Khalaf MN, Brodsky N, Hurley J, Bhandari V. A prospective randomised controlled trial comparing synchronized nasal intermittent positive pressure ventilation (SNIPPV) versus nasal continuous positive airway pressure (NCPAP) as mode of extubation. *Pediatr Res*. 1999;45:204.
61. Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus infant flow for preterm infants. *J Perinatol*. 2006;26(9):546-549.
62. Bhandari V, Gavino RG, Nedrelo JH, et al. A randomized controlled trial of synchronized nasal intermittent positive pressure ventilation in RDS. *J Perinatol*. 2007;27(11):697-703.
63. 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;50:85-91.
64. Khorana M, Paradevisut H, Sangtawesin V, Kanjanapatanakul W, Chotigeat U, Ayutthaya JKN. A randomized trial of non-synchronized nasopharyngeal intermittent mandatory ventilation (nsNIMV) vs. nasal continuous positive airway pressure (nCPAP) in the prevention of extubation failure in preterm under 1500 grams. *J Med Assoc Thai*. 2008;91(3):S136-S142.
65. Gao WW, Tan SZ, Chen YB, Zhang Y, Wang Y. Randomized trial of nasal synchronized intermittent mandatory ventilation compared with nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome. *Chinese J Contemporary Pediatr*. 2010;12(7):524-526.
66. Ramanathan R, Sekar KC, Rasmussen M, Bhatia J, Soll RF. Nasal intermittent positive pressure ventilation after surfactant treatment for respiratory distress syndrome in preterm infants under 30 weeks gestation: a randomized, controlled trial. *J Perinatol*. 2012;32(5):336-343.
67. O'Brien K, Campbell C, Brown L, Wenger L, Shah V. Infant flow biphasic nasal continuous positive airway pressure (BP- NCPAP) vs. infant flow NCPAP for the facilitation of extubation in infants' $\leq 1,250$ grams: a randomized controlled trial. *BMC Pediatr*. 2012;12:43.
68. Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure post extubation in premature infants. *J Pediatr*. 2013;162(949-54):e1.
69. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS. A trial comparing noninvasive ventilation strategies in preterm infants. *N Engl J Med*. 2013;369(7):611-620.
70. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med*. 2013;369:1425-1433.
71. 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 Maternal-Fetal & Neonatal Med*. 2014;27(9):926-929.
72. Mostafa-Gharehbaghi M, Mojabi H. Comparing the effectiveness of nasal continuous positive airway pressure (NCPAP) and high flow nasal cannula (HFNC) in prevention of post extubation assisted ventilation. *ZJRMS*. 2015;17:984.
73. Liu C Collaborative Group for the Multicenter Study on Heated Humidified High-flow Nasal Cannula Ventilation. Efficacy and safety of heated humidified high flow nasal cannula for prevention of extubation failure. *Zhonghua Er Ke Za Zhi*. 2014;52:271-276.
74. Chen J, Gao WW, Xu F, et al. Comparison of clinical efficacy of heated humidified high flow nasal cannula versus nasal continuous positive airway pressure in treatment of respiratory distress syndrome in very low birth weight infants. *Zhongguo Dang Dai Er Ke Za Zhi*. 2015;17:847-851.
75. 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;101(1):F21-F25.

76. Jasani B, Nanavati R, Kabra N, Rajdeo S, Bhandari V. Comparison of non-synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as post-extubation respiratory support in preterm infants with respiratory distress syndrome: a randomized controlled trial. *J Maternal-Fetal & Neonatal Med.* 2016;29(10):1546-1551.
77. Silveira CS, Leonardi KM, Melo AP, Zaia JE, Brunherotti MA. Response of preterm infants to 2 noninvasive ventilatory support systems: nasal CPAP and nasal intermittent positive-pressure ventilation. *Respir Care.* 2015;60(12):1772-1776.
78. Hegde D, Mondkar J, Panchal H, Manerkar S, Jasani B, Kabra N. Heated humidified high flow nasal cannula versus nasal continuous positive airway pressure as primary mode of respiratory support for respiratory distress in preterm infants. *Indian Pediatr.* 2016;53:129-133.
79. Komatsu DF, Diniz EM, Ferraro AA, Ceccon ME, Vaz FA. Randomized controlled trial comparing nasal intermittent positive pressure ventilation and nasal continuous positive airway pressure in premature infants after tracheal extubation. *Rev Assoc Med Bras (1992).* 2016;62(6):568-574.
80. Lavizzari A, Colnaghi M, Ciuffini F, et al. Heated, humidified high-flow nasal cannula vs nasal continuous positive airway pressure for respiratory distress syndrome of prematurity: a randomized clinical noninferiority trial. *JAMA Pediatr.* 2016. <https://doi.org/10.1001/jamapediatrics.2016.1243>
81. Victor S, Roberts SA, Mitchell S, Aziz H, Lavender T. Biphasic positive airway pressure or continuous positive airway pressure: a randomized trial. *Pediatrics.* 2016;138(2):e20154095.
82. Soonsawad S, Tongsawang N, Nuntnarumit P. Heated humidified high-flow nasal cannula for weaning from continuous positive airway pressure in preterm infants: a randomized controlled trial. *Neonatology.* 2016;110:204-209.
83. Kang WQ, Xu BL, Liu DP, et al. Efficacy of heated humidified high-flow nasal cannula in preterm infants aged less than 32 weeks after ventilator weaning. *Zhongguo Dang Dai Er Ke Za Zhi.* 2016;18:488-491.
84. Esmaeilnia T, Nayeri F, Taheritafti R, Shariat M, Moghimpour-Bijani F. Comparison of complications and efficacy of NIPPV and nasal CPAP in preterm infants with RDS. *Iran J Pediatr.* 2016;26(2):e2352.
85. Elkhwad M, Dako J, Jennifer G, Harriet F, Anand K. Randomized control trial: heated humidity high flow nasal cannula in comparison with NCPAP in the management of RDS in extreme low birth infants in immediate post extubation period. *J Neonat Pediatr Med.* 2017;3(1):121.
86. Ribeiro SNS, Fontes MJF, Bhandari V, Resende CB, Johnston C. Noninvasive ventilation in newborns $\leq 1,500$ g after tracheal extubation: randomized clinical trial. *Am J Perinatol.* 2017;34(12):1190-1198.
87. Salvo V, Lista G, Lupo E, et al. Comparison of three non-invasive ventilation strategies (NSIPPV/BiPAP/NCPAP) for RDS in VLBW infants. *J Matern Fetal Neonatal Med.* 2018;31(21):2832-2838.
88. Bourque SL, Roberts RS, Wright CJ, et al. Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure to prevent primary noninvasive ventilation failure in extremely low birthweight infants. *J Pediatr.* 2020;216:218-221.
89. Ding F, Zhang J, Zhang W, et al. Clinical study of different modes of non-invasive ventilation treatment in preterm infants with respiratory distress syndrome after extubation. *Front Pediatr.* 2020;8:63.
90. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE NICE Decision Support Unit Technical Support Documents. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE). 2014.
91. Roberts CT, Davis PG, Owen LS. Neonatal non-invasive respiratory support: synchronised NIPPV, non-synchronised NIPPV or bi-level CPAP: what is the evidence in 2013? *Neonatology.* 2013;104(3):203-209.
92. Reiterer F, Polin RA. Non-invasive ventilation in preterm infants: a clinical review. *Int J Pediatr Neonat Care.* 2016;2:118.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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