

Non-invasive respiratory support in preterm infants: do we need more evidence?

Although exogenous surfactant replacement and mechanical ventilation remain the standard of care for treatment of respiratory distress syndrome in preterm infants, non-invasive forms of respiratory support are increasingly used in the belief that they are associated with fewer complications and reduce the risk of bronchopulmonary dysplasia. This is not yet fully proven despite indications that non-invasive ventilation may be as effective as mechanical ventilation, at least in the short-term. Moreover, non-invasive respiratory support can be provided in a variety of ways and there is no consensus about the optimal use of these newer techniques.

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Key points

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1. Several studies have provided evidence for safety and efficacy of non-invasive respiratory support in preterm infants. Longer-term outcome data are still needed.
2. Non-invasive ventilation can be used either for primary treatment of respiratory distress syndrome or to facilitate extubation after a period of mechanical ventilation.
3. Continuous positive airway pressure (CPAP) is the method of choice for non-invasive respiratory support as no other modality has been shown to be superior to CPAP.

Like many other organ systems, the respiratory system of a preterm infant develops in stages. The respiratory centre's immaturity, unstable chest wall, compliant airways and surfactant deficiency altogether make it difficult for these infants to achieve effective respiration and cope with underlying lung pathology. The various modalities of non-invasive respiratory support help preterm infants in establishing their functional residual capacity and thus reduce the work of breathing. One of the other proposed mechanisms of action of non-invasive ventilation (NIV) is enhanced respiratory drive simply by stimulating the upper airways, which could be particularly useful in situations such as the immediate post-extubation period. Preterm infants are also more prone to obstructive apnoea and NIV may help to prevent this by providing anchoring support to the airways.

NIV in neonates is not a novel concept and its use has been reported in the literature for over half a century. Negative pressure ventilation was used as a form of NIV but without much benefit¹. The first report of possible use of NIV was published much before Gregory's article on continuous positive airway pressure (CPAP)^{2,3}. This modality lost interest among neonatologists over the next few decades because of associated complications including head moulding, cerebellar haemorrhage and gastric perforation. Newer and safer delivery devices have regenerated interest in NIV

and most neonatologists have started to use non-invasive modes of respiratory support in the belief that the complications associated with intubation and mechanical ventilation, especially ventilator-induced lung injury (VILI), are reduced⁴. The incidence of VILI still remains high despite newer modes of mechanical ventilation and lung protective strategies. Until now, NIV has mostly been used to facilitate extubation after a period of conventional ventilation; however, the evidence is also accumulating for the early use of NIV as the primary treatment for respiratory distress syndrome (RDS). Although appearing to be effective, the long-term safety and the outcome of NIV remain to be established fully. This article reviews current practice and evidence for individual techniques of NIV based on data in recently published trials.

Modalities of NIV

NIV in preterm neonates is broadly provided in two ways, single level support or bi-level support. CPAP and high flow nasal cannulae (HFNC) provide single level support whereas nasal intermittent positive pressure ventilation (NIPPV), bi-level positive airway pressure (BiPAP) and synchronised intermittent positive airway pressure (SiPAP) work by providing bi-level support (**TABLE 1**).

CPAP

CPAP is the most widely used modality of non-invasive respiratory support in the

	CPAP	NIPPV	HFNC	Nasal HFV
Pressure support	Constant distending pressure	Bi-level (constant distending pressure with intermittent rises)	High flow nasal cannula oxygen providing pressure support	Constant distending pressure with pressure oscillation around the mean pressure
Primary treatment of RDS	Yes	Yes	Not routinely	No (invasive HFV used in some centres)
Post-extubation period	Yes	Yes	Yes	Still in research stage
Apnoea of prematurity	Yes	Yes	Yes	Not tested
Synchronisation	No	Possible	No	No
Monitoring of pressure generated	Yes	Yes	No	Yes

TABLE 1 The characteristics of various modalities of non-invasive ventilation. Key: CPAP = continuous positive airway pressure, NIPPV = nasal intermittent positive pressure ventilation, HFNC = high flow nasal cannula, HFV = high-frequency ventilation, RDS = respiratory distress syndrome.

preterm population and there are different devices and ways of delivering CPAP in practice. Ventilators can also provide CPAP through an endotracheal tube. The CPAP devices differ from each other depending upon whether they provide constant or variable flow and/or pressure. The conventional ventilator and bubble CPAP are considered as constant flow systems, but the pressure achieved varies. Infant flow driver (IFD), on the other hand, is considered to be a variable flow system generating constant pressure. Gupta et al compared bubble CPAP and IFD in a randomised controlled trial in infants of 24–29 weeks' gestation and found no significant difference in the extubation rate in infants weaned from mechanical ventilation⁵. However, in infants ventilated for less than 14 days, the extubation failure rate was significantly less in the bubble CPAP group (14.1% vs 28.6%, $p=0.046$). No published trials have compared the effectiveness of bubble CPAP with that of IFD CPAP when used as the initial mode of respiratory support in preterm infants with RDS.

NIPPV

In NIPPV, a constant distending pressure in the form of CPAP (both in inspiration and expiration) and the superadded ventilator pressure over and above the CPAP pressure, enhance the tidal ventilation. NIPPV is a form of respiratory support very similar to intermittent positive pressure ventilation minus the use of an endotracheal tube. The pressure, in addition to the CPAP pressure, can be delivered as a high level support (as in NIPPV) or as a low level support (as in BiPAP). If the NIPPV mode is synch-

ronised, it is known as sNIPPV. Bi-level pressure support (BiPAP and SiPAP) describes the delivery of two different pressure levels during the respiratory cycle. A baseline continuous airway distending pressure is provided which is then augmented by intermittent pressure rises. These pressure rises may be timed, at a rate specified by clinicians (BiPAP), or 'triggered' by the patient's own inspiratory efforts (SiPAP). The other parameters (such as rate or inspiratory time) can be set as in a conventional ventilator. The nomenclature used by manufacturers to describe various modes of NIPPV is confusing but the underlying mechanism of providing pressure support remains the same.

HFNC

HFNC has recently become a frequently used alternative mode of providing NIV in preterm infants. It has become popular among neonatal nurses due to perceived advantages over CPAP in reducing local nasal trauma and facilitating easy access to the infant's face during care times. A blend of oxygen and air delivered through a nasal cannula at a rate $>2\text{L/min}$ ($1\text{--}8\text{L/min}$) has been postulated to provide effective CPAP pressure but this cannot be measured⁶. Hence, the main reservation among neonatologists about the use of HFNC is the unpredictability of pressure generated in the airway as this may vary according to the size of the infant and the diameter of the nasal interface used.

Nasal high-frequency ventilation (HFV)

Nasal HFV has been tested in animal models⁷ as well as in preterm infants⁸, but

its routine use as a non-invasive mode of ventilation warrants further studies. Colaizy et al⁸ reported the use of nasal HFV in 14 very low birthweight (VLBW) infants with respiratory failure. Infants who were receiving nasal CPAP and had a $\text{pCO}_2 > 5.6\text{kPa}$ were switched to nasal HFV for a two-hour period. Mean airway pressure was set to equal the previous level of CPAP and amplitude was adjusted to obtain chest wall vibration. After two hours, pCO_2 (mean = 5.8kPa) was significantly lower than the initial pCO_2 (mean = 6.5kPa ; $p=0.01$) and pH had increased significantly (7.40 vs 7.37 , $p=0.04$). In this study, a single nasopharyngeal tube provided both CPAP and nasal HFV. Nasal HFV may offer another important tool to be used for NIV support but further studies are required to assess its efficacy as a primary mode.

Evidence for safety and efficacy derived from recent publications

CPAP vs surfactant and mechanical ventilation

Improved antenatal and perinatal care has made it possible to manage more and more preterm infants on CPAP from birth instead of mechanical ventilation through an endotracheal tube. Several randomised controlled trials over recent years have demonstrated the efficacy of CPAP as a primary treatment of RDS but they do not confirm any advantage over mechanical ventilation in reducing death or BPD. However, the incidence of adverse neurodevelopmental primary outcomes at 18 months of age, as assessed in one trial, was no worse in the CPAP group as compared to their counterparts who

Study	Study population	Study design	Outcome measures	Key results
IFDAS 2002 ⁹	Preterm infants (27-29 weeks' gestation) n=237	Multicentre RCT Nasal CPAP vs MV	Primary outcome Death or BPD at 36 weeks	No significant difference
COIN 2008 ¹⁰	Preterm infants (25-28 weeks' gestation excluding those requiring intubation within the first five minutes) n=610	Multicentre RCT CPAP or intubation and ventilation (no surfactant)	Primary outcome Death or BPD at 36 weeks Secondary outcome Pneumothorax	No significant difference, 33.9% (CPAP) vs 38.9% (MV), p=0.19 9% (CPAP) vs 3% (MV), p=<0.001)
SUPPORT 2010 ¹¹	Preterm infants (24-27 weeks' gestation) n=1316	Multicentre RCT CPAP or intubation and surfactant	Primary outcome Death or BPD at 36 weeks Secondary outcomes Pneumothorax Severe retinopathy of prematurity	No significant difference, 47.8% (CPAP) vs 51% (surfactant group), p=0.53 No significant difference
SANDRI 2010 ¹²	Preterm infants (25-28 weeks' gestation) n=208	Multicentre RCT Prophylactic surfactant (and MV or extubation to CPAP) vs nasal CPAP (MV if CPAP failure)	Primary outcome Need for MV in first five days Secondary outcomes Death or BPD Pneumothorax Duration of hospital stay	No significant difference, 31.4% (prophylactic surfactant) vs 34% (CPAP), p=0.8 No significant difference
DUNN 2011 ¹³	Preterm infants (26-29 weeks' gestation) n=648	Multicentre RCT Prophylactic surfactant, MV (PS group) vs intubate, surfactant and extubation (ISX group) to CPAP vs nasal bubble CPAP	Primary outcome Death or BPD at 36 weeks Secondary outcomes Number of surfactant doses Use of postnatal steroids Days of assisted ventilation or CPAP	No significant difference (PS=36.5%, ISX=28.5%, nasal bubble CPAP=30.5%) RR: PS group vs ISX group (0.78; 0.59-1.03), PS group vs nasal bubble CPAP (0.83; 0.64 -1.09) No significant difference

TABLE 2 Randomised controlled trials comparing outcomes in preterm infants managed with mechanical ventilation versus nasal CPAP.

Key: CPAP = continuous positive airway pressure, RCT = randomised controlled trial, BPD = bronchopulmonary dysplasia, MV = mechanical ventilation, PS group = prophylactic surfactant and mechanical ventilation group, ISX group = intubate, surfactant and extubation group, RR = relative risk.

received mechanical ventilation (**TABLE 2**).

Schmölzer et al¹⁴ recently conducted a systematic review and meta-analysis of four of the aforementioned trials. The results indicate that nasal CPAP initiated in the delivery room compared with intubation was associated with marginally lower death or BPD in very preterm infants (41% vs 43%)¹⁰⁻¹³. According to this review, one additional infant could survive to 36 weeks' gestation without BPD for every 25 infants treated with nasal CPAP in the delivery room rather than being intubated and mechanically ventilated. The reduction

of BPD, however, achieved only a borderline statistical significance in the CPAP group (relative risk 0.91; 95% CI 0.82-1.01) and the pooled analysis showed a significant benefit for the combined outcome of death or BPD, or both, at 36 weeks' corrected gestation in favour of nasal CPAP (relative risk 0.91; 0.84-0.99, number needed to treat = 25). The authors of this systematic review highlight the significant heterogeneity in these trials and the results should be interpreted with caution. The overall data suggest that nasal CPAP can be a safe and efficacious option

for early management of RDS in preterm infants if used judiciously. However mechanical ventilation and exogenous surfactant replacement still remains the mainstay of treatment, especially in infants who are more immature, such as those born at less than 26 weeks' gestation and those who fail to improve on CPAP.

The only trial to assess the longer-term neurodevelopmental outcome is from the SUPPORT study group, which concluded that there are no significant differences in the composite outcome of death or neurodevelopmental impairment among

Study	Study population	Study design	Outcome measures	Key results
Manley et al 2013 ²⁰	Preterm infants (<32 weeks' gestation, <1.5kg) n=303	Multicentre RCT (non-inferiority)	Primary outcome Extubation failure (within 7 days) Secondary outcomes • Death before discharge • O ₂ at 36 weeks • Pneumothorax • Duration of hospital stay • Nasal trauma	No significant difference (risk difference 8.4%; 95% CI, -1.9-18.7) No significant difference apart from nasal trauma incidence 19% (HFNC group) vs 53% (CPAP), p=<0.001
Collins et al 2013 ²¹	Preterm infants (<32 weeks' gestation) n=132	Multicentre RCT	Primary outcome Extubation failure (within 7 days) Secondary outcomes • O ₂ at 36 weeks (BPD) • Pneumothorax • Nasal injury	No significant difference 22% (HFNC) vs 34% (CPAP), p=0.14 BPD: 36% (HFNC) vs 43% (CPAP), p=0.3 Nasal trauma: 7.2% (HFNC) vs 10.7% (CPAP), p=<0.001
Yoder et al 2013 ²²	Infants >28 weeks' gestation (28-42 weeks' gestation) n=432	Multicentre RCT (primary treatment of RDS or post-extubation)	Primary outcome Treatment failure (within 72 hours) Secondary outcomes • Days of non-invasive support • Pneumothorax • BPD • Nasal mucosal injury	No significant difference Fewer days on assigned mode in nasal CPAP group (median of two fewer days, p=<0.001) Nasal trauma significantly less in HFNC group (9% vs 16%), p=0.47

TABLE 3 Recently published trials comparing HFNC with nasal CPAP in preterm infants as an aid to facilitate extubation. Key: CPAP = continuous positive airway pressure, HFNC = high flow nasal cannula, RCT = randomised controlled trial, RDS = respiratory distress syndrome, BPD = bronchopulmonary dysplasia.

extremely premature infants randomly assigned to early CPAP or early surfactant administration (27.9% in CPAP group vs 29.9% in the surfactant group; relative risk 0.93; 95% CI 0.78-1.10; p=0.38)¹⁵.

CPAP vs NIPPV

Despite efficacy of CPAP for the primary treatment of RDS, failure rate still remains relatively high necessitating intubation and mechanical ventilation, especially in infants born at less than 30 weeks' gestation. This has prompted the use of NIPPV with an aim to reduce the chances of failure as compared to CPAP, on the assumption that NIPPV improves respiratory mechanics (increased minute ventilation and reduced work of breathing). The initial smaller studies favour the use of NIPPV as compared to CPAP in reducing the need for mechanical ventilation when used for primary treatment of RDS or post-extubation. However the results of these

trials have not been consistent in reducing the incidence of BPD, some showing results in favour of NIPPV and others showing no difference¹⁶. The reasons for these differences are not clear but can be accounted for by the varying gestations of the infants, different primary outcomes and the randomisation criteria.

One of the largest trials to date by Kirpalani et al (1,009 infants, <30 weeks' gestation and/or <1,000g) showed no difference in death or survival without BPD at 36 weeks' corrected age after non-invasive respiratory support with NIPPV or CPAP (38.4 in NIPPV vs 36.7 in CPAP group; adjusted odds ratio 1.09; 95% CI 0.83-1.43; p=0.56) when used either as post-extubation or primary treatment of RDS¹⁷.

CPAP vs SiPAP

The only prospective randomised controlled trial (120 preterm infants of 28⁺⁰

to 31⁺⁶ weeks' gestation) comparing nasal CPAP and SiPAP for the primary treatment of RDS has recently completed. It did not show any significant difference in the primary outcome of failure of treatment necessitating intubation and ventilation in the first 72 hours of treatment (7% in CPAP group vs 8% in SiPAP group; p=0.78)¹⁸.

CPAP vs HFNC

The last Cochrane review in 2011 concluded that there is insufficient evidence to establish the safety or effectiveness of HFNC as a form of respiratory support in preterm infants¹⁹. Since then, a number of randomised controlled trials have been conducted comparing HFNC vs CPAP in the post-extubation phase of preterm respiratory management. HFNC has been found to be non-inferior to CPAP in these trials (TABLE 3); however, these studies differ from each

other in design and inclusion criteria.

The studies conducted by Manley et al²⁰ and Collins et al²¹ included preterm infants of less than 32 weeks' gestation with a median of around 27 weeks' gestation, whereas the study by Yoder et al²² involved larger infants with a median gestation of 33 weeks. The other main difference is that in the study by Yoder et al, the entry point in the trial is a non-invasive mode (HFNC or CPAP) either for primary RDS or for post-extubation management. The incidence of nasal trauma is significantly less in the HFNC group in all the trials but still relatively large when the whole study population is considered.

Weaning from NIV

There is not always a consensus among neonatologists regarding best practice when weaning infants from non-invasive respiratory support. Preterm infants should be ready to wean from NIV once they have reached a target FiO₂ (less than 0.3 in acute respiratory phase), blood gases are normalised and they are free from any apnoea over the last 24 hours. This is a general guide that most neonatologists use in deciding the readiness from weaning but other factors such as growth, haemoglobin status and feeding should also be considered. On CPAP, pressure is generally decreased in increments of 1cmH₂O. For patients on HFNC, the flow is generally reduced by 1L/min every time the weaning criteria are achieved (usually every 24-48 hours) until a flow of 2L/min is reached, after which the support can be switched to low flow oxygen or air. Weaning from NIPPV is similar to that of invasive mechanical ventilation.

Complications of NIV

Gaseous abdominal distension is still one of the commonest problems of NIV and occurs more commonly with asynchronous support. This may sometimes cause feed intolerance in preterm infants. Being pressure support ventilation, some of the complications related to mechanical ventilation can occur with NIV as well, eg BPD and pneumothoraces. Equipment dysfunction should always be considered when an infant on NIV suddenly deteriorates. Other mechanical problems relating to nasal interfaces are displacement and obstruction of prongs, local irritation and trauma, but these do not seem to have long-term sequelae.

Future directions

In the last decade the use of NIV has increased substantially in the neonatal population. Several trials have demonstrated that it can be a safe approach in experienced hands and can prove to be at least as effective as mechanical ventilation. Although several useful developments have been made to improve understanding of NIV use in neonates, further research is still needed to compare the different strategies of NIV and identify optimal pressure and weaning strategies to prevent common complications such as pneumothoraces and gastric distension. The dilemma about the use of synchronised versus non-synchronised NIPPV and any differences in longer-term outcomes, needs to be further studied. Neurally adjusted ventilatory assist (NAVA) is a novel form of NIV that is designed to improve synchronisation – it works by sensing the electrical activity of the diaphragm (an electrode is placed in the oesophagus)²³. Longer-term follow up studies are needed to determine clinically relevant outcomes. It is also important that the beneficial effects of NIV are applicable across neonatal units to achieve generalisability and to maximise favourable outcomes.

Conclusion

This article describes the commonly used modalities of NIV and their efficacy and safety based on data from recent trials. This may have implications for clinical practice and provide a platform for future research in this area.

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