Review Article »»

Non-invasive Ventilation in Premature Infants: Based on Evidence or Habit

Shalabh Garg[1], Sunil Sinha[1,2]
[1]Consultant Neonatologist, The James Cook University, [2]Department of Paediatrics and Neonatal Medicine, University of Durham, Middlesbrough, United Kingdom

ABSTRACT

Despite surfactant and mechanical ventilation being the standard of care for preterm infants with respiratory failure, non-invasive respiratory support is increasingly being employed in neonatal units. The latter can be accomplished in a variety of ways but none of them have been proven so far to be superior to intubation and mechanical ventilation. Nonetheless, they appear to be safe and effective in experienced hands. This article relates to the use of non-invasive forms of respiratory support and evidence is reviewed from the clinical trials which have evaluated the use of these techniques.

Key words:
Newborn, non-invasive respiratory support, respiratory distress syndrome, respiratory failure

INTRODUCTION

Although life-saving, invasive mechanical ventilation in preterm neonates is a major risk factor for the development of Broncho-pulmonary Dysplasia (BPD)[1] and Ventilator-Induced Lung Injury (VILI). These concerns have prompted neonatologist to use non-invasive modes of ventilation, and this has been increasingly gaining acceptance in most neonatal units. Non-invasive Ventilation (NIV) in neonates has mainly been used to maintain effective breathing after a period of extubation and to avoid extubation failure. There has also been a recent trend to use NIV as primary mode of ventilation for early management of Respiratory Distress Syndrome (RDS) as an alternative to intubation and ventilation, but evidence of its superiority over traditional CPAP or intubation and ventilation is still lacking. Although the results of smaller studies have shown positive results in favor of NIV in preterm infants, this is not supported by the results of larger studies or systematic reviews. Moreover, the long-term safety and outcomes of this promising mode of ventilation need to be established before its widespread use as the primary mode of ventilation in this population can be recommended. This article aims to review the current available evidence for the use of non-invasive ventilation for treatment of RDS in preterm babies.

Historical background of NIV in neonates

The use of NIV in neonates is not a completely new concept and has been in use for almost over half a century. The first report on possible use of NIV in neonates[2] was published about 20 years before the Gregory's paper on continuous positive airway pressure (CPAP).[3] Negative pressure-assisted ventilation was used as a form of non-invasive ventilation but did not prove to be too beneficial.[4] NIV was found to achieve better gaseous exchange than simple oxygen therapy but was shown to be associated with significant head molding and cerebral hemorrhage due to the use of face mask straps.[5] Similarly, the reports of gastric perforations[6] with use of non-invasive ventilation made neonatologists reluctant to use NIV. With the advent of newer interfaces and devices, these complications are now less common,[7,8] and the clinicians are once again more interested in exploring the new ways of providing NIV as highlighted by recent surveys.[9,10] Various modes and ways of delivering NIV (synchronous or asynchronous) are being tested, and one can hope that this will further improve our understanding of use of NIV in preterm babies.

PHYSIOLOGICAL EFFECTS AND POTENTIAL BENEFITS OF NIV

The exact mechanism of action by which NIV works in preterm babies is not clear, but several physiological effects

Address for correspondence:
Prof. Sunil Sinha,
Professor of Pediatrics and Neonatal Medicine,
University of Durham and The James Cook University Hospital,
Middlesbrough, United Kingdom.
E-mail: sunil.sinha@stees.nhs.uk

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have been postulated. The immaturity of the respiratory system of preterm neonates along with unstable chest wall makes complaint airways easy to collapse and cause respiratory failure. One of the effects of NIV is simply to provide support and anchorage to these airways. This can be helpful in cases of obstructive apneas by stimulating the upper airways and make extubation successful after a period of invasive ventilation.[11,12] Non-invasive ventilation also helps to maintain functional residual capacity such as in the surfactant deficient alveoli of premature babies by augmenting their spontaneous respiratory effort and minute ventilation.[13,14]

The main proposed benefit of non-invasive ventilation is to avoid VILI and prevent development of BPD, but this has not been proven in large controlled trials. The other possible benefit is to prevent harmful effects of endotracheal intubation[15] including hemodynamic instability, increased airway resistance, acute and chronic airway trauma (potentially resulting in sub-glottic stenosis), increased infection risk due to colonization of trachea, and reduced clearance of secretions making frequent and traumatic suctioning less necessary, but there is not sufficient safety data to prove these hypotheses.

Modes of non-invasive ventilation

Non-invasive forms of ventilation in neonates can be provided either as a single level support such as CPAP and High Flow Nasal Cannula (HFNC) or bilevel support such as Nasal Intermittent Positive Pressure Ventilation (NIPPV). In NIPPV, CPAP provides a constant distending pressure (both during inspiration and expiration), while superadded ventilatory inflation (high level as in NIPPV or low level as in BiPAP and SiPAP) augments the tidal ventilation. The ventilator rate and inspiratory time (Ti) can be fixed as in traditional ventilation. The manufacturers use different names to describe these modes of NIV making the nomenclature confusing although the mechanism remains the same. Various modes of NIPPV include Synchronized Nasal Intermittent Positive Pressure Ventilation (SNIPPV),[16] Nasal Synchronized Intermittent Mandatory Ventilation (N-SIMV),[17] Nasopharyngeal Synchronized Intermittent Mandatory Ventilation (NP-SIMV),[18] Nasal Bi-level Positive Airway Pressure (N-BiPAP),[19] Nasal Intermittent Mandatory Ventilation (NIMV),[20] and Non-invasive Pressure Support Ventilation (NI-PSV).[21]

Nasal cannula oxygen with a flow of more than 2 liters per min (HFNC) has been shown to provide CPAP at these high flow rates[22] and has been becoming a favorable mean of providing single level non-invasive ventilation although the recent Cochrane Review by Wilkinson *et al.*,[23] has highlighted the insufficient evidence available at present to suggest long-term safety and efficacy of this modality. A recent review by Roehr *et al.*[24] highlighted the need to wait for the results of ongoing trials before HFNC use can be recommended widely. The main drawback of using HFNC is that the pressure generated is not measurable and cannot be regulated. One of the perceived benefits of HFNC is its ease of use and less nasal trauma, making it more popular amongst neonatal nurses.

Nasal high-frequency oscillation has been tested in animal models[25] as well as in preterm babies,[26] but its routine use as a non-invasive mode of ventilation warrants further studies.

CPAP on the other hand has been a time tested widely used modality of NIV and can be delivered by several different mechanisms and devices. The main difference between these delivery systems to provide CPAP is dependent on variations in the flow and/or pressure delivered. 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.*[27] compared the two modalities in a randomized controlled trial in 140 preterm infants (24 to 29 weeks gestational age), who were being weaned from mechanical ventilation (MV) and found no significant difference in extubation failure rate. However, in a sub-group analysis of infants ventilated for less than 14 days ($N = 127$), the extubation failure rate was significantly lower in those infants randomized to bubble CPAP (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. Large multicenter RCTs comparing the effectiveness of these devices will be required to detect differences between them.

Various interfaces have been used to deliver NIV such as by face masks, nasopharyngeal and nasal interfaces. The main drawback of these interfaces is the difficulty to maintain constant seal and to achieve the adequate pressure. The endotracheal tubes and nasopharyngeal interfaces have minimal leaks but increase the work of breathing significantly. Nasal interfaces are now commonly used, and short bi-nasal prongs are shown to be most effective and generate least amount of airway resistance and are minimally invasive.

CPAP VS. MECHANICAL VENTILATION

With better antenatal and perinatal care, it has become possible to manage even the smallest of the babies on CPAP from birth avoiding intubation and mechanical ventilation. Large randomized controlled trials published

Table 1: Trials comparing CPAP with Mechanical ventilation in preterm infants

Trial	Gestational age of included infants (weeks)	*N*	Comparison	Main conclusion
IFDAS[30] (Early nasal CPAP with prophylactic surfactant for neonates at risk of RDS)	27 to 29	237	nCPAP vs. MV	No difference with regards to primary outcome of death or BPD at 36 weeks gestational age
Coin[28] (CPAP Or Intubation at birth)	25 to 29 (excluding infants who required intubation within the first five minutes)	610	nasal CPAP vs. surfactant and MV	No difference with regards to primary outcome of death or BPD at 36 weeks gestational age
Support[29] (Early CPAP vs. Surfactant in Extremely Preterm Infants)	24 to 28	1316	nasal CPAP versus surfactant and MV	No difference with regards to primary outcome of death or BPD at 36 weeks gestational age

CPAP – Continuous positive airway pressure; BPD – Broncho-pulmonary dysplasia; RDS – Respiratory distress syndrome

recently[28-30] [Table 1] have shown safety of this approach, but CPAP has not been proven to show any significant long-term benefit in prevention of BPD and/or death over mechanical ventilation. Moreover, CPAP is not fully safe and can still result in serious complications in not managed properly. The clinicians, therefore, have to be careful in selecting and monitoring the babies managed on CPAP as the incidence of pneumothorax was significantly higher in the babies randomized to CPAP group in COIN Trail.[28] This might have been related to difference in standard of care provided in different units taking part in this trial.

NIPPV VS. CPAP

Whilst more and more neonatologists are using CPAP for primary treatment of RDS, this still fails in a significant proportion of babies necessitating re-intubation and invasive mechanical ventilation. This has prompted the use of NIPPV in many neonatal units with a hope that will reduce the chances of failure as compared to CPAP by improving respiratory mechanics due to increased minute ventilation and reduced work of breathing.

Several studies have shown short-term benefits of NIPPV over CPAP, but the data on incidence of BPD or long-term outcomes is not consistent. In some studies, NIPPV as compared to nasal CPAP has been shown to reduce extubation failure and apnea rates in preterm babies.[31,32] The evidence is in favor of NIPPV in reducing the need for invasive ventilation in the first few days of life.[33-36] A recent meta-analysis by *Meneses et al.*[37] found that NIPPV significantly decreases the need for invasive ventilation within the first 72 hours of life compared with nasal CPAP, but no difference between groups was found in the incidence of broncho-pulmonary dysplasia (risk ratio, 0.56; 95% CI, 0.09-3.49).

In the largest trial to date (1009 babies <30 weeks and/or <1000 gm) by Kirpalani *et al.*,[38] no significant difference was found in death or BPD rate in NIPPV or nasal CPAP group (published only in abstract form). Another recently finished randomized controlled trial comparing primary use of nasal CPAP vs. SiPAP (CoSi Trial,[39] abstract publication) for respiratory distress in premature babies (28-32 weeks gestation) again showed no significant difference in the primary outcome (failure of non-invasive respiratory support, necessitating intubation and ventilation, in the first 72 hours of treatment). The incidence of pneumothorax or BPD was not significantly different either in this trial.

How to wean patients from NIV

Preterm infants should be ready to wean from NIV once they reach the target PaO_2 or saturations with minimal oxygen requirement (e.g. below 0.3 for acute respiratory failure) and they have not experienced any apneas in previous 24 hours. Although there is not always a consensus as to the best practice of weaning, clinicians should familiarize themselves with the methods and equipments they are using on their units.

Weaning from CPAP may be done by decreasing the pressure by 1 cm of H_2O and closely monitoring for any clinical deterioration. Once the pressure has reached 4 cm of H_2O and infant is stable, they can safely be taken off. The nursing observations at the time of cares provide valuable information in deciding how likely a premature infant will manage off CPAP in addition to other parameters. The weaning from NIPPV is similar to that of MV (pressure, back up rate, and oxygen).

Future of non-invasive ventilation in neonates

NIV seems to be an attractive option of respiratory support in preterm infants and can prove to be effective in reducing the need for invasive mechanical ventilation and the complications associated with invasive mode including BPD. Although useful developments have been made over last 20 years in the understanding of NIV use in neonates, further research is still needed in the following areas for the best use of this approach:

- Should NIV be used with synchronization and, if yes, how best that can be achieved? New forms of

respiratory support, which are designed to improve synchronization of breaths between the patient and the ventilator are being developed, and it will be important to consider and evaluate their use in preterm infants. Neurally Adjusted Ventilatory Assist (NAVA)[40] is a novel form of non-invasive ventilation that is designed to improve synchronization and works by sensing the electrical activity of the diaphragm (electrode placed in esophagus).

- Best ventilatory settings and weaning strategies of non-invasive ventilation to avoid failure of NIV and need for intubation and mechanical ventilation.
- Can HFNC/CPAP/NIPPV be used as primary mode of ventilation and will they improve the long-term outcome?
- Long-term respiratory and neuro-developmental outcomes of NIV as compared to MV needs to be evaluated.

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