

Non-invasive Ventilation in Preterm Infants: A Clinical Review

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Abstract

Non-invasive ventilation (NIV) has gained increased popularity in the neonatal intensive care unit, because it is less likely to cause the short and long-term pulmonary complications associated with invasive mechanical ventilation. There are now number of NIV strategies available for the routine respiratory care of preterm infants including nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), nasal high frequency oscillatory ventilation (NHFO) and high flow nasal cannula (HFNC). These strategies are often used in combination with less invasive surfactant administration (LISA) and methylxanthines to augment respiratory drive. This review describes these various modes of NIV evaluating their impact on neonatal mortality and morbidity in preterm infants.

Abbreviations

NIV: Non-invasive ventilation, NCPAP: Nasal continuous positive airway pressure, PEEP: Positive end-expiratory pressure, PIP: Positive inspiratory pressure, CMV: Conventional mechanical ventilation, HFV: High frequency ventilation, NIPPV: Nasal intermittent positive pressure ventilation, SIMV: Synchronised intermittent mandatory ventilation, SNIPPV: Synchronized NIPPV, NSNIPPV: Non synchronized NIPPV, BiPAP: Bi-level-phasic positive airway pressure, NAVA: Neurally adjusted ventilatory drive, NHF: Nasal high frequency ventilation, NHFO: Nasal high-frequency oscillatory ventilation, HFNC: High-flow nasal cannula, NICU: Neonatal intensive care unit, ELGAN: Extreme low gestational age neonates, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, INSURE: Intubation surfactant administration and rapid extubation, LISA: Less invasive surfactant administration

Introduction

With the increased survival of extreme low gestational age neonates (ELGAN) < 28 week's non-intubated, non-invasive ventilation (NIV) has gained increased popularity in the neonatal intensive care unit (NICU). The primary aim of NIV is to provide respiratory support without the pulmonary and non-pulmonary complications associated with intubation and mechanical ventilation. One serious long-term pulmonary complication associated with positive pressure ventilation is bronchopulmonary dysplasia (BPD), commonly defined as oxygen dependency at 36 weeks' postmenstrual age. There are a number of ways NIV can be applied, including nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), nasal high frequency oscillatory ventilation (NHFOV) and humidified high flow nasal cannula (HFNC). Of these, NCPAP, started soon after birth has become the first line strategy for the management of preterm infants with respiratory distress syndrome (RDS) (figure 1), especially in combination with INSURE (intubation surfactant administration followed by immediate extubation) [1,2]. Caffeine is often used as an adjunct therapy in infants receiving NIV to augment the respiratory drive [3]. The purpose of the review is to describe various modes of NIV and to evaluate their impact on neonatal mortality and morbidity. For a more comprehensive discourse on this hot topic of non-invasive respiratory support in preterm infants I refer to very recently published clinical and systematic reviews and meta-analysis [4-6].

Modalities of NIV

NCPAP

Maintaining a normal functional residual capacity to improve gas exchange is a fundamental therapeutic concept for the atelectatic lung in neonates with RDS. In 1971 Gregory reported a small clinical trial in which NCPAP was used successfully in 20 infants (birth weight 930 to

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3800 g) with severe RDS [7]. Oxygenation was significantly improved and 16 patients survived. In a retrospective observational study of eight tertiary centers [8] in 1987, Avery et al. reported a significant lower incidence of CLD (arbitrarily defined as the need for increased inspired oxygen at 28 days of age) in one center where the predominant mode of respiratory support was the use of NCPAP (pressure around 5 mmHg); there were no significant differences in mortality. Despite the

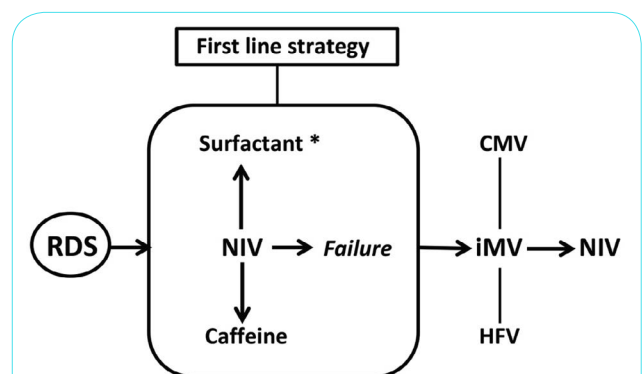


Figure 1: Respiratory support strategies in preterm infants with RDS.
* INSURE or LISA

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success with CPAP at one center, most other centers continued to prefer conventional mechanical ventilation (CMV) as a first line treatment for RDS. In the early 1990's randomized clinical trials of surfactant administration demonstrated significant reductions in neonatal mortality and pulmonary air leaks. The acceptance of surfactant therapy in combination with improvements in the performance of neonatal ventilators further supported the dominant role of CMV for the respiratory management of preterm infants with RDS. But despite the widespread use of surfactant therapy, rates of BPD did not change [9]. That led to a renewed interest in NIV. NCPAP can be delivered using a ventilator or by special CPAP-systems, which differ mainly in the way the end expiratory pressure is generated (table 1). In ventilators an expiratory valve is used to adjust the expiratory pressure. In so called NCPAP "flow-driver" systems the pressure is generated by adjusting the inspiratory flow or altering the expiratory resistance. However, the most widely used CPAP system is bubble-CPAP. In this system, the pressure is produced by inserting the distal end of the expiratory limb in water and the depth to which the tube is immersed equals the CPAP pressure. The gas flow leaving the circuit via the expiratory limbs produces continuous bubbling and pressure oscillations which may facilitate gas exchange. The most common interface used with CPAP systems are binasal prongs. However, a mask or nasopharyngeal tube can also be used. In infants with RDS a starting pressure of about 5-8 mm Hg [1] is commonly selected.

Recent meta-analyses have shown that early NCPAP compared to routine endotracheal intubation and prophylactic surfactant administration reduces the combined outcome of death and BPD [6,10,11] in preterm infants with RDS. Some guidelines continue to recommend the INSURE technique as an adjunct strategy for preterm babies with RDS placed on NCPAP [1,2], however, there is no evidence that the INSURE technique decreases the incidence of BPD above that of NIV. Less invasive methods to administer surfactant (LISA e.g., using a thin plastic catheter) [12] are not yet recommended, but may decrease the combined outcome of death and BPD [6].

NIPPV

There are a number of overlapping NIPPV terms used in the literature such as Bi-level CPAP, N-BiPAP, Si-PAP, DUOPAP describing basically the same functional principle, namely providing cycling inspiratory pressures in addition to the single, basic CPAP pressure, which is unchanged throughout the respiratory cycle (figure 2)[13]. This strategy may be beneficial in preterm infants with increased work of breathing and or inconsistent respiratory drive. NIPPV may be synchronized with the patient spontaneous inspiration (SNIPPV), by using a pneumatic and abdominal capsule, a flow sensor or by using a special ventilator responding to the patient's diaphragm activity. This latter synchronization technique is called neurally adjusted ventilatory assist (NAVA) and is used for or invasive and non-invasive ventilation [14,15]. The use of NAVA seems to be safe, though larger studies are needed. The technology for applying NIPPV has not been not standardized and different trials have used varying modes (table 1). When applied with a neonatal ventilator NIPPV can be performed in an assist control mode in which every breath of the infant is supported by a ventilator inflation [16]. NIPPV modes are commonly used to support extubation and as a rescue therapy after NCPAP failure. In a prospective study of 78 preterm infants less than 32 weeks's gestation the application of SNIPPV avoided intubation in more than 70% of the infants; no adverse effects were detected [17]. However, it remains unknown if NIPPV is better than NCPAP or if SNIPPV is better than non-synchronized forms of NIPPV [18,19]. Data suggest that SNIPPV seems to be more effective than non-synchronized NIPPV or NCPAP in treating apnea of prematurity [16]. In a recently published Cochrane meta-analysis comparing the use of various NIPPV modes versus NCPAP, NIPPV reduced the incidence of extubation failure, but had no effect on chronic lung disease or mortality [20]. General complications with the use CPAP and NIPPV may include gastric distension ("CPAP-belly") from swallowing excessive air, nasal septum erosion or necrosis, nasal obstruction from secretions or improper application of nasal prongs and air leaks [21-23].

Mode	Type of pressure assist PEEP-Generation	Settings Flow L/min	PEEP mbar	PIP mbar	Freq /min	Ti sec
A. NCPAP	single continuous 6-8 pressure (PEEP)	6-8	4-6 (8)			
Ventilator derived	expiratory valve					
Infant Flow driver*	kinetic energy of flow (flow generator)					
Bubble CPA	Distal expiratory tubing placed in water	5-10				
B. NIPPV	2 pressure levels (PEEP + PIP)	variable, depending on device, strategy				
NSNIPPV	not synchronized	} mimick CMV/SIMV				
SNIPPV	synchronized					
N-BiPAP	synchronized or not	} use of lower PIP and Frq and longer Ti ,allows				
DUOPAP*	not synchronized					
NHFOV	Pressure oscillations	mimicks HFOV				
C. HFNC	flow dependent PEEP	> 2L/ min, no pressure control				

Table 1: Modes and settings of non-invasive pressure assist for preterm infants.

*Preferred mode of NCPAP/NIPPV and settings in our NICU-Graz (PEEP 5 cm H₂O, PIP 8-12 mbar, Frequency (Frq) 20-40/min, inspiration time (Ti) 0,4-0,6 sec

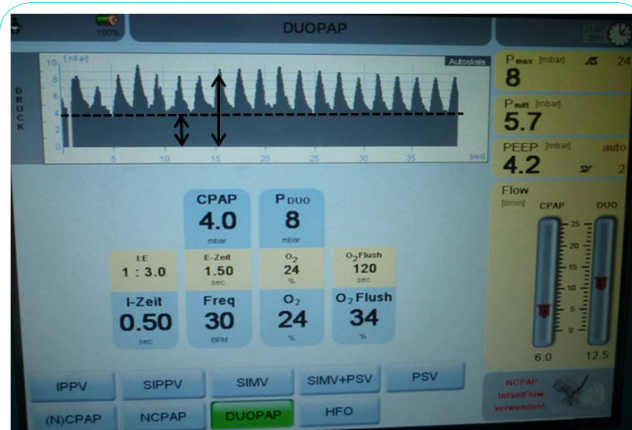


Figure 2: DUOPAP-mode and settings in a neonatal ventilator (Fabian, Acutronic, Switzerland) in the post-extubation phase of a preterm infant with RDS, DUOPAP uses infant flow generator for PEEP generation, double arrows show CPAP=PEEP (4 mbar) and PDUO=PIP (8 mbar, delta PIP = 4 mbar), giving a flow of 6 and 12,5 L/min respectively. The dotted line indicates the CPAP=PEEP level throughout the respiratory cycles.

Nasal High Frequency Ventilation (NHFV)

NHFV is a noninvasive form of HFV used with different ventilators and delivered through nasal interfaces [24-26]. Nasal high frequency oscillatory ventilation (NHFOV), might be considered an alternative to CMV and other modes of NIV. NHFOV generates CPAP using a bias flow with oscillations of constant frequency and active expiratory phase superimposed on spontaneous tidal breathing. It has similarities to bubble CPAP, but the oscillations on bubble CPAP are much smaller, irregular and have no active expiratory phase. There are a limited number of small and uncontrolled published clinical NHFOV studies suggesting that NHFOV is safe and feasible [25]. In a recently published pilot randomized controlled trial in 39 infants < 1500 g NHFV was not superior to biphasic-CPAP following CPAP failure [26]. Larger multicenter studies are necessary before widespread implementation of this NIV-technique.

High Flow Nasal Cannula (HFNC)

HFNC is gaining popularity in the NICU as an alternative for NCPAP. By delivering high flow rates, usually in the range of 4-8 L/min. HFNC supports ventilation and oxygenation by reducing inspiratory resistance, washing out carbon dioxide from the nasopharyngeal space and by providing a small amount of positive airway pressure [27]. With increasing flow rates nasopharyngeal pressure rises linearly providing additional CPAP [28]. HFNC may be more comfortable for the infant than NCPAP. Furthermore, it induces less nasal trauma and is preferred by nurses for large preterm infants [29,30]. A recent Cochrane meta-analysis including 14 studies in preterm infants of various gestational age and birth weight comparing HFNC with other non-invasive forms of respiratory support in preterm infants immediately after birth or following extubation, showed equivalent rates of treatment failure following mechanical ventilation and similar rates of BPD [31]. However, there are relatively few studies in infants < 1,000 grams. When used as primary support for preterm infants > =28 weeks of gestation with early respiratory distress not treated with surfactant, HFNC resulted in a significantly higher rate of treatment failure than did NCPAP [32]. Based on evidence from recent clinical trials, HFNC is currently not recommended as an alternative for

NCPAP during the acute phase of RDS but may be of benefit on some patients during the weaning phase [1,33].

Future Directions

Despite the enthusiasm for NIV, in preterm infants a number of infants will require intubation and positive pressure ventilation. Therefore, potential lung-protective strategies during positive pressure ventilation should be further investigated [34]. It will be important to evaluate and implement other non-invasive modalities and techniques to prevent lung and/or brain injury such as the administration of surfactant by inhalation, neuroprotective drugs, automated control of inspired oxygen, NAVA and combined respiratory and cerebral monitoring [35]. BPD is a multi-factorial disease and its prevention requires optimization of all clinical aspects in modern perinatal and neonatal care [36].

Conclusion

Based on the current best evidence from the literature it seems that early NCPAP applied via binasal prongs, may be the optimal strategy for preterm infants with RDS. Furthermore, it reduces the risk of death or BPD. NIPPV may offer advantages in terms of less extubation failure and a lower reintubation rate, but has no effect on mortality or BPD. HFNC, should not be considered an alternative to NCPAP or NIPPV in the acute phase of RDS, but may be equivalent to NCPAP post-extubation. In general, success rates of NIV may vary considerably and in part depends how success or failure is defined and how NIV is utilized.

Competing Interests

The authors declare that they have no competing interest.

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