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Optimal Ventilatory Strategies and Surfactant to Protect the Preterm Lungs

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Key Words
Bronchopulmonary dysplasia · Respiratory distress syndrome · Ventilatory strategy · Preterm infants

Abstract
Invasive ventilation via the endotracheal tube is one of the most common therapeutic interventions performed in preterm infants with respiratory failure. Respiratory distress syndrome (RDS) occurs in about 50% of preterm infants born at less than 30 weeks of gestational age. Mechanical ventilation using conventional or high-frequency ventilation and surfactant therapy have become the standard of care in management of preterm infants with RDS. However, bronchopulmonary dysplasia (BPD) remains as a major morbidity with adverse pulmonary and nonpulmonary outcomes in preterm infants despite these interventions. Ventilator-associated lung injury appears to be related to the duration of invasive ventilation via the endotracheal tube rather than the mode of ventilation. Randomized controlled trials comparing conventional mechanical ventilation and high-frequency ventilation, using 'optimal ventilatory strategies', have shown no significant difference in rates of BPD. Use of noninvasive ventilation, such as nasal continuous positive airway pressure and nasal intermittent positive pressure ventilation has shown a significant decrease in postextubation failure as well as reduced incidence of BPD. Optimal ventilatory strategy in preterm infants with RDS may begin in the delivery room with application of sustained inflation to establish functional residual capacity, followed by surfactant therapy and rapid extubation to noninvasive ventilation to decrease the incidence of BPD and improve overall outcome.

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Introduction

Bronchopulmonary dysplasia (BPD) remains as a major morbidity among preterm infants treated with invasive ventilation via an endotracheal tube (IVET) and surfactant for respiratory distress syndrome (RDS). Duration of IVET has a direct effect on the incidence of BPD. However, the incidence of BPD varies among different centers. This may be due to different criteria used to make the diagnosis of BPD and ventilatory strategies employed in different centers. Given the importance of a consistency, a new definition of BPD was proposed in 2001 based on gestational age, postmenstrual age, duration of oxygen and mechanical ventilation, and the need of positive pressure ventilation [1]. A limited number of studies have reported incidence of BPD based on the NIH-proposed new definition for BPD [2, 3]. Because of varied use of supplemental oxygen and saturation targeting in pre-

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Table 1. HFV versus conventional ventilation studies from 1989 to 2003 in preterm infants and bronchopulmonary dysplasia[1]

	Infants	Study population	Results
Pre-surfactant era studies (n = 6)			
HIFI, 1989	673	750–200 g	HFOV: no change in BPD; increase in IVH/PVL
Carlo, 1990	42	1,000–2,000 g	HFJV: no change in BPD
Keszler, 1991	144	≥750 g with PIE	HFJV: improved survival
Clark, 1992	83	≤1,750 g	HFOV: decrease in BPD
HiFO, 1993	176	≥500 g	No change in BPD
Ogawa, 1993	92	750–2,000 g	HFOV: no change in BPD
Surfactant era studies (n = 3)			
Gerstmann, 1996	125	≤35 weeks	HFOV: decrease in BPD and surfactant use
Wiswell, 1996	73	>500 g; <33 weeks	HFJV: no change in BPD; increase in severe IVH/PVL; trial stopped early
Keszler, 1997	130	700–1,500 g; ≤35 weeks	HFJV: decrease in BPD
Surfactant and SIMV era studies (n = 8)			
Rettwitz-Volk, 1998	96	<32 weeks	HFOV: no change in BPD
Plavka, 1999	43	500–1,500 g	HFOV: decrease in BPD
Thome, 1999	284	24–30 weeks	HIFI: no change in BPD; increase in air leaks
Moriette, 2001	273	24–29 weeks	HFOV: no change in BPD
Courtney, 2002	498	601–1,200 g	HFOV: decrease in BPD
Johnson, 2002	797	23–28 weeks	HFOV: no change in BPD
Craft, 2003	46	<1,000 g	HIFI: No change in BPD; increase in air leaks
Van Reempts, 2003	300	<32 weeks	HFOV/HIFI: No change in BPD

[1] Adapted from Keszler [6].

term infants, Walsh et al. [4] suggested the term 'physiological BPD', based on a timed room-air challenge at 36 ± 1 weeks' postmenstrual age in preterm infants in an attempt to compare incidence of BPD among different centers. Preterm infants receiving mechanical ventilation or requiring >30% oxygen to maintain oxygen saturation between 90 and 96% were considered to have 'physiological BPD'. Infants receiving ≤30% oxygen or effective oxygen >30% with saturations >96% were given room-air challenges for 30 min. Infants in whom saturations decreased to <90% were considered to have 'physiological BPD'. However, differences in incidence of BPD remain even with use of this standardized definition.

Invasive Ventilation via Endotracheal Tube

Significant improvements have been made in the use ventilatory strategies in preterm infants. However, IVET remains as a major contributing factor for BPD. IVET even for less than 48 h is associated with a longer length of stay in hospital [5]. Tidal ventilation using conventional mechanical ventilators and nontidal ventilation using high-frequency ventilators has been extensively studied in preterm infants with RDS. Nontidal ventilation strategies using high-frequency oscillatory ventilation (HFOV), high-frequency flow interruption (HIFI) and high-frequency jet ventilation (HFJV) have been evaluated before and after surfactant therapy for RDS became available and they have been compared with intermittent mandatory ventilation (IMV) and synchronized IMV (SIMV) [6].

Among the 6 studies [7–12] conducted during the pre-surfactant era, one reported a decrease in BPD with HFOV when compared to IMV [10] (table 1). However, the incidence of severe intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) was significantly higher in one of the HIFI trials published in 1989 [7]. Three trials were published during surfactant era [13–15] (table 1). Two of these studies reported a lower incidence of BPD with high-frequency ventilation (HFV) when compared to IMV [13, 15], while one study was terminated prematurely because of an increase in IVH or PVL among infants randomized to HFJV [14].

Among the 8 HFV trials [16–23] published between 1998 and 2003, when surfactant therapy and SIMV were

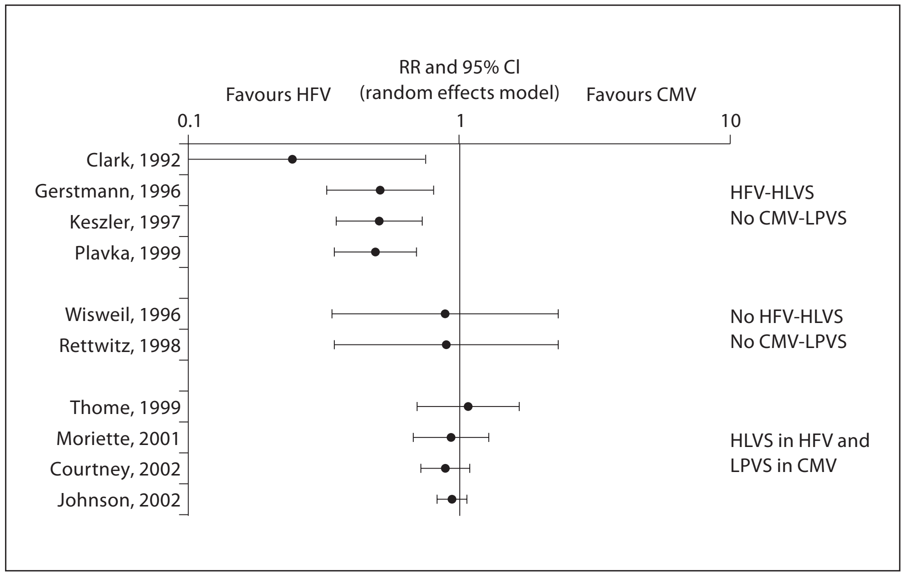

Fig. 1. A cumulative meta-analysis of trials of HFV versus conventional mechanical ventilation with and without lung protective ventilatory strategies and BPD. Reproduced with permission from Bollen et al. [24].

commonly used, only 2 studies reported a decrease in BPD with HFOV use [17, 20] and 2 studies reported increase in air leaks with HIFI use [18, 22]. Three trials [19–21] compared elective use of HFV in RDS. One study reported a decrease in BPD [20] and a second study reported a nonsignificant increase in IVH among infants treated with HFOV [19]. A third trial demonstrated no significant difference in pulmonary or central nervous system outcomes [21]. Differences in outcomes between HFV and IMV trials were primarily related to whether an optimal lung protective ventilatory strategy was employed or not for both of these modes of invasive ventilation. In studies where optimal lung volume strategy was attempted, there was no difference in BPD between tidal and nontidal ventilation modes [24] (fig. 1).

Different modes of patient-triggered ventilation (PTV), such as SIMV, assist-control, volume limit or volume guarantee, and pressure or volume support ventilation, are widely used in preterm infants. Randomized controlled trials using different modes of PTV have shown short-term benefits such as decrease in the duration of mechanical ventilation or days on oxygen [25, 26]. Volume-guaranteed or volume-targeted ventilation results in improved ventilation and stable gas exchange. None of these studies demonstrated a significant reduction in BPD. Evidence of long-term benefits from PTV is inconclusive. Use of PTV is more 'physiological' and should be considered whenever feasible in infants receiving IVET.

Noninvasive Ventilation Strategies

Since duration of mechanical ventilation via the endotracheal tube has a direct correlation with BPD, noninvasive ventilation (NIV) after a brief period of IVET using nasal continuous positive airway pressure (nCPAP) and nasal intermittent positive pressure ventilation (NIPPV) are being evaluated as ways of protecting the lungs of preterm infants [27]. NIV appears to be beneficial in the management of apnea of prematurity, for prevention of extubation failure, as well as in the initial management of RDS [28–30]. nCPAP can be delivered using conventional mechanical ventilators, bubble CPAP or infant flow driver systems. The infant flow driver uses a fluidic flip system which has been shown to assist spontaneous breathing and reduce work of breathing by reducing expiratory resistance and maintaining a stable airway pressure throughout the respiratory cycle [31]. High-flow (>2 l/min) nasal cannulae are used to deliver CPAP in some centers. Binasal prongs are more effective than single prongs in preventing extubation failure even among extremely low birth weight (ELBW) infants (24 vs. 88% failure rates, respectively) [32].

Optimal Delivery Room Management

Isovolemic transformation from a fluid-filled to air-filled lung during the transitional period at birth requires establishment of functional residual capacity. Use of only

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1 or 2 large inflations during resuscitation of ELBW (<1,000 g birth weight) infants immediately after birth may initiate lung injury. Sustained inflation and/or application of CPAP may be used to establish functional residual capacity. There is no consensus regarding the optimal mode of initiating respiratory support at birth in ELBW infants. Recently, te Pas and Walther [3] compared sustained inflation for 10 s at 20 cm H_2O applied via a nasopharyngeal tube followed by nCPAP versus manual inflations with a self-inflating bag and mask followed by nCPAP in 207 preterm infants. Need for intubation, days on mechanical ventilation and days on nCPAP, air leaks and moderate to severe BPD were significantly lower when a sustained inflation was used to recruit the lung instead of bag and mask ventilation. Additional studies are needed to evaluate delivery room practices in preterm infants [33]. Flow-controlled pressure-limited mechanical devices, such as Neopuff™ Infant Resuscitators (Fisher & Paykel Healthcare Corp. Ltd., Irvine, Calif., USA) to deliver consistent CPAP in the delivery room are recognized as an acceptable method of administering positive pressure ventilation during resuscitation, especially in preterm infants [34, 35]. The European CURPAP study is currently evaluating the efficacy of early nCPAP and natural surfactant as a combination therapy for very preterm infants at risk of RDS [36].

Early Ventilatory Management

It has been a common practice in many centers to intubate ELBW infants at birth. In a retrospective, cohort study, selective intubation of ELBW infants resulted in a significantly reduced need for intubation, lower incidence of BPD, IVH and decreased length of hospital stay as compared to routine intubation [37]. Use of bubble CPAP in ELBW infants was associated with a significantly improved survival without BPD [38]. Sahni et al. [2] reported a very low incidence of BPD (7.4%) in infants <1,250 g treated with bubble nCPAP. A limited number of studies compared nCPAP delivered using conventional mechanical ventilators and infant flow drivers. No significant differences were found in clinical outcomes when applying CPAP with the infant flow driver versus a conventional nasal CPAP device [39]. Sandri et al. [40] in a multicenter trial demonstrated no difference in BPD in infants between 28 and 31 weeks' gestational age treated with prophylactic or rescue nCPAP.

A major limitation of nCPAP is the need for intubation due to frequent apnea, bradycardia or desaturations in preterm infants. Approximately a third of infants extubated from IVET to nCPAP fail extubation and require reintubation. At present, there are no good tests to predict successful extubation in preterm infants. Kamlin et al. [41] used a spontaneous breathing test to predict successful extubation in preterm infants with a birth weight <1,250 g. A failed SBT was recorded if the infant had either bradycardia lasting for longer than 15 s and/or a drop in saturation below 85% despite a 15% increase in FiO_2 when infants were on CPAP via endotracheal tube (ET CPAP) prior to a planned extubation. No pressure support for spontaneous breaths was given during ET CPAP in this study. Sensitivity and specificity for SBT in predicting successful extubation were 97 and 73%, respectively. Additional studies are needed to evaluate if SBT may be used as a predictor of an infant's readiness prior to extubation.

Nasal cannulae have been used to deliver oxygen at flow rates of 0.5 l/min to as high as 8 l/min flow, with no intention of delivering CPAP. However, use of flow rates of 2 l/min via a nasal cannula with an outer diameter of 3 mm results in a mean CPAP of 9.8 cm H_2O [42]. Complications reported with the use of high-flow nasal cannulae include increased incidence of air leaks, gas trapping, and volutrauma. One must exercise caution when delivering flow rates greater than 2 l/min via nasal cannulae without knowing the amount of pressure delivered. Techniques to measure pressure delivered at the level of the nasal interface are urgently needed since use of nasal cannulae to deliver CPAP intentionally or not have become very common in the USA and elsewhere.

Nasal Intermittent Positive Pressure Ventilation

NIPPV is an alternative option when infants are extubated from IVET or for infants failing nCPAP. NIPPV is a form of NIV that combines nCPAP with IPPV breaths. NIPPV may augment nCPAP, prevent postextubation failure, minimize SIMV duration and potentially decrease the incidence of BPD. NIPPV has been shown to decrease postextubation failure significantly compared to nCPAP. Two randomized studies using synchronized NIPPV at the time of extubation showed significant reduction in extubation failure with NIPPV compared to NCPAP [29, 43]. In a retrospective study, Kulkarni et al. [44] showed that after introduction of NIPPV in their unit following a 2-week education to their staff, a significant reduction in BPD occurred.

Recently, studies comparing NIPPV and SIMV have shown promising results. Kugelman et al. [45] compared nCPAP with NIPPV as a primary mode of respiratory support in preterm infants <35 weeks' gestational age with RDS. NIPPV was more successful than nCPAP in decreasing the need for endotracheal intubation and the incidence of BPD was less. These authors did not report any adverse effects of NIPPV. This was the first study using NIPPV as a primary ventilatory mode for treatment of RDS, but study infants were larger and more mature than the control infants. Only 40 of the 84 infants studied were VLBW (<1,500 g). Studies are currently underway in preterm infants treated with surfactant for RDS to determine if rapid extubation to NIPPV would be a more successful approach than continued SIMV.

Surfactant Therapy

Surfactant therapy has become the standard of care in management of preterm infants with RDS. Two types of surfactants – natural surfactants derived from animal sources and synthetic surfactants – have been extensively evaluated in preterm infants. To date natural, modified surfactants appear to be more effective than synthetic surfactants during the acute phase of RDS. Three natural surfactants commonly available worldwide include Survanta® (beractant), Infasurf® (calfactant) and Curosurf® (poractant alfa). They differ in their composition, plasmalogen content, onset of response, duration of action, dosing volume, viscosity, need for additional doses and outcomes. Multiple comparative studies have been performed using these 3 natural surfactants. Prospective as well as retrospective studies comparing beractant and calfactant have shown no significant differences in clinical or economic outcomes [46, 47]. However, comparison of beractant and poractant alfa in prospective trials have shown significantly faster weaning of oxygen, less need for additional doses and cost benefits in patients treated with poractant alfa [48–50]. Recent analysis of a database involving more than 24,000 preterm infants has demonstrated a significant decrease in mortality and cost benefits in infants treated with poractant alfa as compared to those who were given beractant or calfactant [51, 52]. Poractant alfa is the only natural surfactant that has shown a decreased mortality when compared with a synthetic or natural surfactant and decreased need for additional dos-

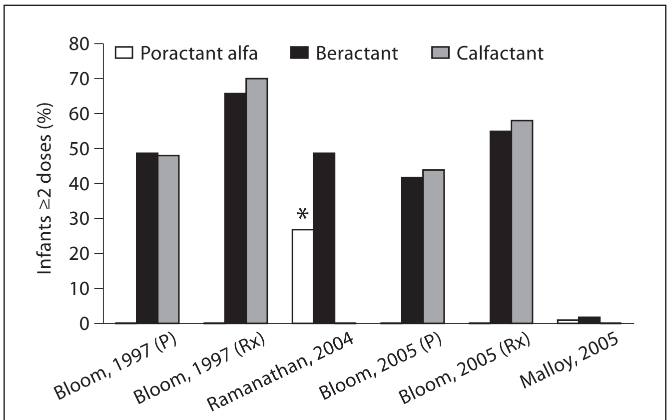

Fig. 2. Results from 6 comparative studies from 1997 to 2005 on the need for 2 or more doses of surfactant. P = Prophylaxis; Rx = rescue; * $p < 0.05$.

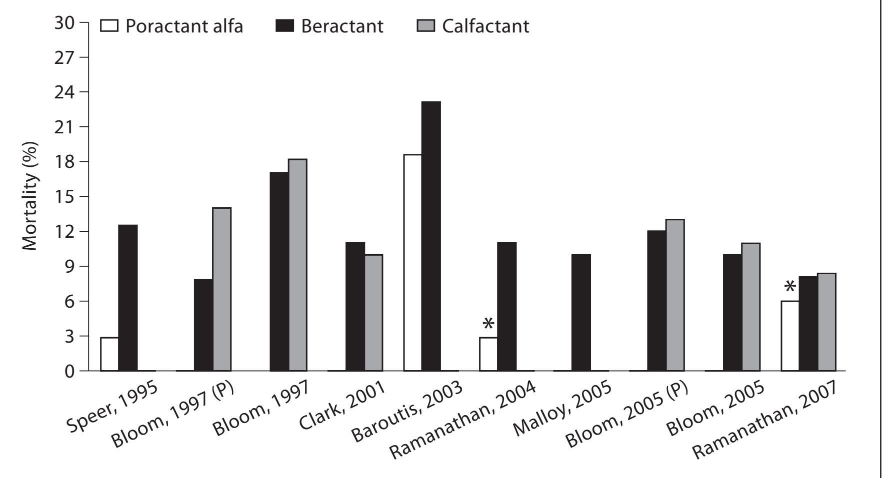

Fig. 3. Results from 10 comparative studies from 1995 to 2007 on the mortality among different surfactant-treated infants. P = Prophylaxis; * $p < 0.05$.

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es in comparative trials (fig. 2, 3). These differences in outcomes may be related to the fact that poractant alfa contains greater amounts of phospholipids distributed in a smaller volume as well as a greater amount of antioxidant phospholipids, namely plasmalogens.

Conclusion

BPD is associated with short- and long-term adverse pulmonary and nonpulmonary outcomes. High frequency and conventional ventilatory techniques have been extensively evaluated in the management of RDS in preterm infants [53]. When an optimal lung volume strategy is employed, there does not appear to be any significant difference between these two modalities. Data from physiological and clinical trials demonstrate that NIV significantly decreases BPD. Another area that requires further investigation includes synchronized NIV. NIPPV is a useful method of augmenting the beneficial effects of nCPAP in preterm infants with RDS. In summary, the use of NIV as a primary mode or following surfactant administration is associated with improved outcomes in preterm infants with RDS.

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