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REVIEW

Respiratory management of the preterm newborn in the delivery room

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Abstract: The survival of preterm infants has improved significantly during the past several decades. However, bronchopulmonary dysplasia remains a major morbidity. Preterm infants have both structural and functional lung immaturity compared with term infants, making them more likely to require resuscitation and more vulnerable to developing bronchopulmonary dysplasia. Interventions in the delivery room may affect short-term and long-term outcomes for preterm infants. The paradigm of resuscitation of preterm infants has been changing over the past decade from being interventional and invasive to be observational and gentle. Recent developments in respiratory management of preterm infants in the delivery room include oxygen supplementation and monitoring, alveolar recruitment techniques, noninvasive ventilation, new surfactant preparations, and new techniques for administration of surfactant. Providing nasal continuous positive airway pressure (CPAP) rather than intubating has been identified as a potentially better practice. Experimental studies have demonstrated that early application of nasal CPAP is protective for the preterm lung and brain compared with mechanical ventilation. Several observational studies have suggested that early nasal CPAP and avoiding intubation leads to reduced oxygen requirements, intubation rates, duration of mechanical ventilation, and may decrease rates of bronchopulmonary dysplasia. Multicenter, randomized controlled trials support the use of nasal CPAP as a primary strategy in preterm babies with respiratory distress syndrome. This approach leads to a reduction in the number of infants who are intubated and given surfactant without an impact on bronchopulmonary dysplasia rates. On the other hand, half of the infants enrolled in these studies failed nasal CPAP treatment. New techniques for surfactant administration include INSURE ("intubate give surfactant and extubate"), administration through a laryngeal mask airway, nebulized surfactant administration, and minimally invasive surfactant therapy.

Keywords: continuous positive airway pressure, lung injury, oxygen, resuscitation, surfactants

Introduction

Preterm infants are at increased risk of morbidity and mortality because of the immaturity of all their body systems, especially the lungs. Survival of preterm infants has improved over the past several decades, mainly due to new interventions, such as use of prenatal corticosteroids, surfactant replacement therapy, and new modalities of mechanical ventilation.[1–4] This improvement in mortality has not been paralleled by a decrease in morbidity. The prevalence of complications, such as bronchopulmonary dysplasia, retinopathy of prematurity, severe intraventricular hemorrhage, and periventricular leukomalacia have not changed substantially.[4–6] Moreover, these infants continue to be at risk of adverse neurodevelopmental sequelae.[7] Delivery room practices during the

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first minutes of life have a great potential to improve these outcomes. The concept of a delivery room intensive care unit has recently been introduced, emphasizing the need to improve the technical equipment at the delivery room bed “as if it were a neonatal intensive care unit (NICU) bed”.[8]

Physiology

Respiratory management of preterm infants in the delivery room represents a great challenge for neonatologists because preterm infants are more likely to need significant resuscitation effort and are more likely to develop complications related to this effort.[9] Accordingly, understanding the physiological differences between the lungs of preterm infants and term infants is important to be able to provide effective and safe resuscitation. Preterm infants have both structural and functional lung immaturity compared with term infants. Intrauterine lung maturation has been divided into five phases, ie, embryonic (26 days to 6 weeks’ gestation), pseudoglandular (6–16 weeks’ gestation), acinar or canalicular (16–28 weeks’ gestation), saccular (28–34 weeks’ gestation), and alveolar (36 weeks’ gestation until 18 postnatal months).[10] Thus, preterm infants delivered at 23–34 weeks’ gestation during the acinar, canalicular, and saccular stages of development appear to be most susceptible to lung injury.[10,11] At these stages, the premature lung has poorly developed supporting structures in the airway and a smaller alveolar surface area.

Together with structural lung immaturity, preterm infants have both quantitative and qualitative immaturity of surfactant. Surfactant from immature lungs contains larger amounts of phosphatidylinositol, smaller amounts of phosphatidylglycerol, and has a lower protein to lipid ratio compared with surfactant from mature lungs.[12] Due to its lower content of phosphatidylglycerol, surfactant from premature lungs has lower surface activity. The phosphatidylglycerol content of surfactant begins to rise after 35 weeks’ gestation. Surfactant proteins are expressed at varying degrees at different stages of gestation, with surfactant protein A after 32 weeks’ gestation, surfactant protein B after 34 weeks’ gestation, surfactant protein C during early lung development, and surfactant protein D at late gestation. Owing to structural and functional immaturity, the lungs of preterm infants are more vulnerable to barotrauma, volutrauma, atelectrauma, and biotrauma.

Immature antioxidant defense systems increase the susceptibility of preterm infants to oxidative stress and concomitant morbidities of prematurity, including bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis.[13] Thus, the use of excess supplemental oxygen for resuscitation of preterm infants in the delivery room may be injurious. Hypothermia, perinatal infection, immaturity of respiratory drive, and weak respiratory muscles are cofactors that further add to the unique features of preterm infants and contribute to the need for neonatal resuscitation.

Resuscitation

Unlike for full term infants, there is no clear and approved consensus among neonatologists regarding delivery room resuscitation and respiratory management of preterm infants. The paradigm of resuscitation of preterm infants has been changing over the past decade from being interventional and invasive to be observational and gentle. This change is attributed to the accumulating evidence that early, even if brief, positive pressure ventilation, large tidal volume, and oxygen therapy initiate a process of inflammation, remodeling, and injury in premature lungs.[14] Recent developments in respiratory management of preterm infants in the delivery room include limitation of excess oxygen use in resuscitation, limitation of inflating pressure, use of a T-piece resuscitator, recognition of the value of a sustained lung inflation technique, early use of noninvasive ventilation, and the INSURE (“intubate give surfactant and extubate”) method for surfactant administration.

Oxygen therapy and target oxygen saturation

Over the past few years, evidence has been growing to indicate that routine use of 100% oxygen for neonatal resuscitation is not superior to room air and may be hazardous to newborn infants.[15,16] Although preterm infants are more susceptible to hyperoxia and oxidative stress with use of pure oxygen, the data suggest that room air may be insufficient to achieve target oxygen levels.[17] In an observational study of resuscitating preterm infants <30 weeks’ gestation with room air, 95% of the enrolled infants failed to achieve target oxygen saturation by five minutes of age and required supplemental oxygen.[18] In two trials, preterm infants <28 weeks’ gestation were randomly assigned to receive 30% with a step-up increment versus 90% oxygen with a step-down decrement during initial resuscitation, and no differences were found in mortality or pulse oximetry percent saturation (SpO_2) values from 1–20 minutes of life, but those resuscitated with 30% oxygen needed fewer days of oxygen supplementation and mechanical ventilation, and had a lower incidence of bronchopulmonary dysplasia.[19,20] Although the updated

American Heart Association guidelines recommended initial resuscitation of preterm infants with blended oxygen without specification,[21] it seems reasonable to start at a concentration of 30% and step up gradually according to response.

The target SpO_2 range that adequately meets metabolic demands and limits oxygen toxicity for the preterm infants has garnered the interest of investigators over the past decade. Four major trials have investigated target SpO_2 in preterm infants (Table 1),[22–25] but only one of these studies enrolled infants in the delivery room. Three levels of saturation were thoroughly evaluated in these trials, including low targeted saturation at 85%–90%, medium targeted saturation at 91%–95%, and high targeted saturation at 95%–99%. Data from the individual trials suggest that high targeted saturation over 95% was associated with bronchopulmonary dysplasia and oxygen dependency. Pooled data from premature infants <28 weeks from SUPPORT (the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial) and the BOOST (Benefits of Oxygen Saturation Targeting) II trial showed a higher survival rate in infants assigned to a target oxygen saturation of 91%–95% compared with the low saturation of 85%–89%.[24] Recently, nomograms for oxygen saturation and heart rate in the first minutes of life for preterm babies have been developed, showing a slow rise in oxygen saturation after birth.[26,27] SpO_2 values within the 90th and 10th centile could be considered a valid reference for assessing improvement and need for oxygen administration.[28]

Appropriate inflating pressure of the lungs

There is no consensus about the inflating pressure needed to resuscitate preterm infants. Experimental studies have suggested that lungs are injured if they are inflated with either a high pressure to volumes that exceed total lung capacity, or low pressures to small volumes below a normal functional residual capacity.[29] Overdistension of the lung (volutrauma) and insufficient lung volumes (atelectrauma) can initiate an inflammatory process, which may progress to bronchopulmonary dysplasia.[30,31] Bjorklund et al showed in preterm lambs that as few as six large insufflations with tidal volumes of 35–40 mL/kg, probably harmless in normal circumstances, forced into a surfactant-deficient lung immediately after birth can compromise the effect of subsequent surfactant rescue treatment. The immature lambs were more difficult to ventilate and had more widespread lung injury in histological sections.[32] Hoskyns et al reported that

Table 1 Studies addressing target oxygen saturation in preterm infants

Study	Population	Comparison	Primary outcome	Main results
STOP-ROP[22]	649 preterm infants ±25.4 weeks' gestation	High SpO_2 (96%–99%) versus low SpO_2 (89%–94%)	Progression to threshold retinopathy of prematurity and need for peripheral retinal ablation	No difference in mortality or progression of retinal disease High SpO_2 group were more likely to remain hospitalized, on oxygen, and have chronic lung disease at 50 weeks postmenstrual age
BOOST-I[23]	358 preterm infants <30 weeks' gestation	High SpO_2 (95%–98%) versus low SpO_2 (91%–94%)	Growth and neurodevelopmental measures at a corrected age of 12 months	No difference in neurodevelopmental outcome Six infants died of pulmonary cause in the high SpO_2 group High SpO_2 group received longer oxygen therapy, and were more likely to receive supplemental oxygen at 36 weeks postmenstrual age and at home
BOOST-II[24]	1200 preterm infants <28 weeks' gestation	High SpO_2 (91%–95%) versus low SpO_2 (85%–89%)	Survival without disability at 2 years corrected for gestation	The study was closed early after a safety analysis demonstrated a higher survival rate in the group that was randomly assigned to a high target SpO_2
SUPPORT[25]	1316 preterm infants ±26 weeks' gestation	High SpO_2 (91%–95%) versus low SpO_2 (85%–89%)	Composite of severe retinopathy of prematurity, death before discharge from the hospital, or both	Low target saturation group were less likely to have severe ROP but had a higher mortality rate before discharge

Abbreviations: STOP-ROP, Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity; BOOST, Benefits of Oxygen Saturation Targeting; SUPPORT, Surfactant, positive pressure, and pulse oximetry randomized; SpO_2, pulse oximetry percent saturation.

inflation pressures of 25–30 cm H_2O in preterm infants rarely led to tidal volumes of more than 4 mL/kg, although higher pressures were sometimes needed for optimal resuscitation.[33] In contrast, Hird et al found that a median inflation pressure of 22.8 cm H_2O was necessary to generate adequate chest wall expansion in preterm infants, with no infant requiring a peak inspiratory pressure >30 cm H_2O.[34] Assessment of chest rise as a measure of lung expansion is not very accurate and might lead to delivery of excessive tidal volumes.[35] Thus, monitoring of respiratory function has recently been suggested as a useful tool during resuscitation of preterm infants to minimize lung barotrauma and volutrauma.[36]

Use of a T-piece resuscitator

The T-piece resuscitator (Neopuff®) is similar to the flow-inflating bag in providing positive end-expiratory pressure, but with the addition of an adjustable flow control valve. The flow control valve allows for more precise control of the peak inspiratory pressure applied to the infant's lung, decreases the risk of lung barotrauma, and enables application of prolonged initial inflation breaths and positive end-expiratory pressure to be maintained between inflations, and can give continuous positive airway pressure (CPAP) when it is not being used as a ventilator. The T-piece resuscitator was found more consistently to deliver target pressures and prolonged inflation independent of the operator's expertise compared with manual bagging devices.[37] In a qualitative review of 30 trials comparing the T-piece resuscitator with self-inflating bags, two on infants and 28 on manikins, no superiority was found for the T-piece resuscitator over the self-inflating bag in the infant trials, but in the manikin studies the T-piece resuscitator was able to deliver inflating pressures closer to predetermined target pressures with minimal variation and to provide prolonged inflation breaths and more consistent tidal volumes.[38] Currently, target ventilation variables with the T-piece resuscitator include a respiratory rate of 40 breaths per minute, a peak inspiratory pressure of 20 cm H_2O, and a positive end-expiratory pressure of 4 cm H_2O.[39]

Value of sustained lung inflation technique

The first breaths in a full term newborn have a prolonged expiratory phase associated with a high positive intrathoracic pressure, and a brief inspiratory component to facilitate the distribution of air within the lungs and to assist in formation of the functional residual capacity.[40] In an experimental study, it was found that sustained inflation of preterm rabbit lungs for durations of 10 or 20 seconds increased the inspiratory volume and produced a greater functional residual capacity compared with durations of one or 5 seconds.[41] Sustained lung inflation for 20 seconds in combination with positive end-expiratory pressure was found to improve the functional residual capacity of preterm rabbit pups.[42] In asphyxiated full term infants, sustained lung inflation during resuscitation was found to increase their tidal volume and the functional residual capacity.[43] The European Resuscitation Council has recommended that initial inflation of the lung should be 2–3 seconds in duration to achieve a sustained lung inflation technique.[44,45] In preterm infants, sustained lung inflation for 5 seconds compared with traditional lung inflation for 2 seconds did not reduce lung injury, as measured by inflammatory cytokines.[46] Lindner et al compared sustained lung inflation with nasal intermittent positive pressure ventilation (IPPV) for treatment of preterm infants with respiratory distress syndrome in the delivery room, and found no significant difference in the need for mechanical ventilation or rate of adverse effects.[47] te Pas and Walther found a decrease in need for intubation and bronchopulmonary dysplasia in preterm infants of more than 28 weeks' gestation treated by sustained lung inflation at a pressure of 20 cm H_2O for 10 seconds using a T-piece resuscitator compared with a self-inflating bag and mask in the delivery room.[48] In preterm infants with respiratory distress syndrome, sustained lung inflation at a pressure of 25 cm H_2O for 15 seconds using a T-piece resuscitator was found to decrease the need for mechanical ventilation compared with using a T-piece resuscitator without sustained lung inflation, without inducing evident adverse effects.[49] However, issues like appropriate duration and pressure, hemodynamic changes, and risk of barotrauma, should be further evaluated before recommending routine use of sustained lung inflation in the resuscitation of preterm infants.

Continuous positive airway pressure

Mechanism of action

CPAP is a technique of respiratory support that generates a continuous distending pressure to the lung and is delivered to spontaneously breathing infants. Usually, a pressure of 4–8 cm H_2O is used to distend the airways and alveoli. CPAP improves oxygenation without increasing peripheral arterial carbon dioxide tension ($PaCO_2$) through stabilization and recruitment of collapsed alveoli. The functional residual capacity is increased, resulting in an increased alveolar surface area for gas exchange and a decrease in intrapulmonary shunting. CPAP enhances the release of surfactant and helps maintain the surfactant present on the alveolar surface. It stabilizes the chest wall and dilates the airways, reduces inspiratory resistance, increases lung compliance, counteracts paradoxical movement, and reduces thoracoabdominal asynchrony of the chest wall and reduces the work of breathing.[50,51]

Evidence for early use of CPAP in preterm infants

CPAP was first used as a method of supporting breathing in preterm infants in 1971.[52] Even after the introduction of surfactant replacement therapy and new mechanical ventilation strategies in the management of respiratory distress syndrome, bronchopulmonary dysplasia remained a frequent sequel of prematurity, and mechanical ventilation was described as the important predisposing factor for bronchopulmonary dysplasia; thus, by avoiding intubation and mechanical ventilation, many of these infants will not develop bronchopulmonary dysplasia.[53] Today, there is increased interest in the use of nasal CPAP in extremely low birth-weight (ELBW) and very low birth-weight (VLBW) infants,[54] and providing nasal CPAP rather than intubation has been identified as a potentially better practice according to basic quality improvement criteria.[55,56] The evidence for early application of nasal CPAP in this population comes from experimental, observational/retrospective, and randomized controlled trials.

Experimental studies

Experimental studies demonstrated that early application of CPAP is protective for the preterm lung and brain compared with mechanical ventilation. The ventilatory strategy of "open up the lung and keep it open" will minimize lung damage, therefore starting nasal CPAP directly after resuscitation is a gentle, noninvasive attempt to keep the lung open.[57] Jobe et al showed in preterm lambs that nasal CPAP after birth results in lower indicators of acute lung injury than conventional mechanical ventilation during the first 2 hours of life.[58] More recently, the same research group randomized preterm lambs to bubble CPAP (5 or 8 cm H_2O) or conventional mechanical ventilation for a period of 2–6 hours. They demonstrated larger lung volumes and better oxygenation with CPAP 8 cm H_2O compared with CPAP 5 cm H_2O, and lung dry/wet ratios were greater for both CPAP groups than for the mechanical ventilation group. Lambs that demonstrated terminal respiratory failure on CPAP within 2 hours had smaller surfactant pools (supporting early administration of surfactant to the most immature infants who are likely to be surfactant-deficient).[59] The value of surfactant replacement therapy coupled with CPAP has been demonstrated in another study showing that animals treated with surfactant prior to CPAP had less acute lung injury, suggesting that surfactant administration may modulate pulmonary inflammation and that CPAP alone without surfactant may not provide optimal pulmonary protection.[60] The lungs of premature baboons maintained on CPAP for 28 days demonstrated thin-walled airspaces with minimal fibroproliferation and scattered secondary crests. Pressure-volume curves were nearly identical to those observed at term gestation, but significantly better than those from preterm baboons ventilated with low tidal volume ("gentle") positive pressure ventilation.[61] In contrast with these findings, another study[62] demonstrated comparable acute effects on lung and systemic inflammation of CPAP (8 cm H_2O) and gentle conventional mechanical ventilation (tidal volume 8 mL/kg), leading to the conclusion that CPAP given shortly after birth fails to attenuate lung injury, supporting the results of randomized controlled trials of early use of CPAP where no reduction of bronchopulmonary dysplasia in preterm infants was observed.[63–66] Early CPAP was associated with less cerebral injury,[67] higher cerebellar weight,[68] and less damage to specific classes of neurons in the visual cortex expressing gamma aminobutyric acid[69] compared with delayed CPAP preceded by positive pressure ventilation in premature baboons.

Observational/retrospective studies

Several observational/retrospective studies have evaluated early use of CPAP in preterm infants[70–83] (Table 2), with most of these studies suggesting that early use of nasal CPAP and avoiding intubation leads to reduced oxygen requirements, intubation rates, and duration of mechanical ventilation, and some studies reporting decreased rates of bronchopulmonary dysplasia.[72,73,75,76,79,80,83] Other observational studies compared the rates of bronchopulmonary dysplasia in centers using early nasal CPAP with centers preferring intubation and mechanical ventilation. The pioneering work of Avery et al[84] found that NICUs using less intubation and mechanical ventilation reported less bronchopulmonary dysplasia compared with other NICUs. Van Marter et al[53] observed marked differences in the incidence of bronchopulmonary dysplasia (4% at the Babies Hospital, Columbia University, versus 22% at two Boston hospitals) despite similar mortality rates. Infants at the Babies Hospital were less likely to be mechanically ventilated, and those who did were ventilated for significantly shorter time periods. In multivariate logistic regression analyses, initiation of mechanical ventilation was associated with an increased risk of bronchopulmonary dysplasia.[53] Another study showed

Table 2 Studies evaluating respiratory outcomes after application of early nasal CPAP in preterm infants

Reference	Main results
Jacobsen et al[70]	Decreased need for mechanical ventilation (from 76% to 35%) Decreased IVH grade II–IV No difference in rate of death or BPD
Gittermann et al[71]	Decreased need for mechanical ventilation (from 53% to 30%) No difference in rate of death or BPD
Lindner et al[72]	Decreased need for mechanical ventilation (from 25% to 7%) Decreased rate of BPD and IVH, and shorter hospital stays No difference in mortality
De Klerk and De Klerk[73]	Decreased need for mechanical ventilation (from 65% to 14%) Decreased surfactant use, durations of ventilation and of oxygen therapy Decreased rate of death or BPD (from 16% to 3%)
Narendran et al[74]	Decreased need for intubation in the delivery room (60% versus 32%) Shorter duration of mechanical ventilation No difference in rate of death or BPD
Aly et al[75,76]	Decreased rate of death or BPD (from 65% to 27%) Over time, the incidence of BPD decreased significantly (from 33% to 11%) and average weight gain increased
Jegatheesan et al[77]	Shorter durations of mechanical ventilation and supplemental oxygen No difference in rate of death or BPD
Zecca et al[78]	No difference in duration of supplemental oxygen No difference in rate of death or BPD
Geary et al[79]	Decreased need for mechanical ventilation (from 99% to 60%) Shorter durations of mechanical ventilation and oxygen therapy Decreased the rate of moderate and severe BPD (from 43% to 24%)
Miksch et al[80]	Decreased intubation (from 81% to 58%) Shorter durations of oxygen therapy Decreased incidence of BPD (from 55% to 18%) for all surviving infants, and for ELBW infants (from 90% to 30%)
te Pas et al[81]	Decreased the need for intubation within 72 hours of age No difference in rate of death or BPD
Nowadzky et al[82]	Decreased the use of mechanical ventilation and its duration No difference in rate of death or BPD
Mulder et al[83]	Decreased the rate of BPD (from 47% to 37%) No difference in mortality

Abbreviations: NCPAP, nasal continuous positive airway pressure; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ELBW, extreme low-birth weight infants.

that rates of bronchopulmonary dysplasia and retinopathy of prematurity were significantly lower at the Neonatal Regional Tertiary Care Center, University of Vienna, compared with the Vermont Oxford Neonatal Network during the period 1994–2002, and this was attributed to more use of nasal CPAP and less use of mechanical ventilation during early respiratory management of VLBW infants.[85]

Improved respiratory outcomes for ELBW infants treated with a predominantly nasal CPAP approach were evident at Middlemore Hospital, New Zealand, compared with the Australian and New Zealand Neonatal Network data over a 3-year period (1998–2001). These infants spent a longer time on nasal CPAP and had less time on oxygen. Fewer of the Middlemore cohort were on oxygen at both 28 days, and 36 weeks corrected gestation, and fewer infants were discharged home on oxygen.[86] On comparing the resuscitation and ventilator techniques between two NICUs in Stockholm, Sweden and Boston, MA, a less aggressive approach with more nasal CPAP administration in the delivery room was used in Stockholm, which did not decrease the risk for bronchopulmonary dysplasia at 36 weeks; however, at 40 weeks, fewer infants were on oxygen support, and a strong association was found between site, mean airway pressure, and mechanical ventilation with bronchopulmonary dysplasia, indicating that CPAP could have a beneficial role in outcome.[87] In contrast with these findings, a recent study investigated whether the wide variation in frequency of bronchopulmonary dysplasia between Italian hospitals is due to differences in delivery room intubation rates in VLBW infants. Rates of bronchopulmonary dysplasia, delivery room intubation, and mechanical ventilation for >24 hours differed significantly between hospitals. It was demonstrated that delivery room intubation and brief (<24 hours) mechanical ventilation did not increase the risk of bronchopulmonary dysplasia.[88]

Five studies have evaluated neurodevelopmental outcomes in ELBW and VLBW infants managed with early CPAP.[51,89–92] Neurodevelopmental follow-up at 5 years of age in a cohort of ELBW infants treated mainly with nasal CPAP during the neonatal period in Denmark (the ETFOL study) showed similar proportions of adverse effects on the brain compared with those in published follow-up studies of preterm infants treated with mechanical ventilation.[51] Massaro et al demonstrated that ELBW infants managed with early nasal CPAP have neurodevelopmental morbidity at 3–6 months corrected age comparable with that of the National Institute of Child Health and Human Development

Neonatal Research Network cohort.[89] Dahl and Kamper demonstrated that VLBW infants treated with a regimen of early nasal CPAP/minimal handling had a relatively low incidence of handicap and impairment, with nearly 90% attending ordinary schools and near-average performance in mathematics and reading/spelling, which was not significantly different from their siblings.[90] Wintermark et al demonstrated that early application of nasal CPAP and avoidance of mechanical ventilation in VLBW infants showed no adverse effects on neurodevelopment and growth, and a significantly higher developmental quotient was found in the nasal CPAP group at a corrected age of 18 months.[91] Thomas et al demonstrated that ELBW infants receiving nasal CPAP had better Bayley Score of Infant Development Version II scores at a corrected gestational age of 18–22 months, and lower rates of bronchopulmonary dysplasia and death compared with those receiving mechanical ventilation at 24 hours of age and, after adjusting for acuity differences, the ventilatory strategy at 24 hours of age independently predicts the long-term neurodevelopmental outcome.[92]

Randomized controlled trials

Observational studies alone do not provide strong enough evidence to justify and promote new clinical practices. Early randomized controlled trials that evaluated the role of CPAP in preterm infants were done in the presurfactant era and included small numbers of cases. Two Cochrane reviews of these trials showed a reduction in mortality of preterm infants >1500 g with nasal CPAP, no significant differences in bronchopulmonary dysplasia, and a greater benefit from early application. They concluded that these trials provided insufficient information to make recommendations for clinical practice and called for a large randomized controlled trial.[93,94] Finer et al investigated the feasibility of randomizing ELBW infants <28 weeks' gestation to nasal CPAP/positive end-expiratory pressure or no nasal CPAP/positive end-expiratory pressure during resuscitation immediately after delivery, avoiding routine delivery room intubation for surfactant administration, and initiating nasal CPAP on admission to the neonatal unit. In the first group, nasal CPAP of 5 cm H_2O or IPPV (if necessary) with peak inspiratory pressure of 15–25 cm H_2O was given, and in the second group, no nasal CPAP and no positive end-expiratory pressure during IPPV was used. Nasal CPAP/positive end-expiratory pressure in the delivery room did not affect the need for intubation at birth or during the subsequent week, although this preliminary study was underpowered for detecting such a difference.[95]

Recently, five large multicenter, randomized controlled trials of appropriate design have tested the hypothesis that not intubating preterm babies with respiratory distress syndrome soon after birth would have a positive effect on outcome[63-66,96] (Table 3). These trials support the use of CPAP as a primary strategy in preterm babies with respiratory distress syndrome who are breathing spontaneously. This approach led to a reduction in the number of infants intubated and given surfactant. On the other hand, half of the infants enrolled in these studies failed CPAP treatment. It can be argued that such babies might have been disadvantaged because of the delay in receiving surfactant therapy. As far as we know, no meta-analysis of the results of these studies has been done until now, and none of these studies evaluated neurodevelopmental outcomes in the infants who participated in this research. Unfortunately, two of these trials were not published in full and are available only in abstract form.[63,96]

The strategy of early nasal CPAP in VLBW infants may be justified based on the current clinical evidence, because it has been shown to be safe, and reduces the need for mechanical ventilation.[95] However, to rely on nasal CPAP and "not to intubate" with the aim of reducing the incidence of bronchopulmonary dysplasia is not justified due to the low quality of evidence from retrospective/observational studies,[72,73,75,76,79,80,83] and the lack of evidence from randomized controlled trials that not intubating in the delivery room reduces bronchopulmonary dysplasia.[63–66,96]

Early nasal CPAP is not successful in all VLBW infants, and these infants will ultimately be ventilated mechanically. Forty-six percent of infants in the COIN (Continuous Positive Airway Pressure or Intubation at Birth) trial[63] and 83% of infants in SUPPORT[65] failed nasal CPAP. Ammari et al demonstrated that nasal CPAP was successful in 76% of infants with a birth weight of ≤1250 g and 50% of infants with a birth weight of ≤750 g, and that nasal CPAP failure was associated with a need for positive pressure ventilation at delivery, alveolar-arterial oxygen tension gradient >180 mmHg on the first arterial blood gas, and severe respiratory distress syndrome on the initial chest x-ray.[97] Another study reported a delivery room nasal CPAP failure rate of 51% in preterm infants (26–27 weeks). Medical history and initial blood gas values were poor predictors of subsequent nasal CPAP failure. Moreover, it was found that a threshold fraction of inspired oxygen (FiO_2) of ≥0.35–0.45 compared with ≥0.6 for intubation would shorten the time to surfactant delivery without a relevant increase in intubation rate.[98] A

Table 3 Randomized controlled trials evaluating early NCPAP in preterm infants

Study	Population	Comparison	Main results
IFDAS trial[63]	237 infants (27–29 weeks' gestation)	Early NCPAP with prophylactic surfactant versus early NCPAP with rescue surfactant versus early MV with prophylactic surfactant versus early MV with rescue surfactant	Less need for MV in the two NCPAP groups during the first 5 days of life 78% of infants in groups 1 and 2 were established on NCPAP by 6 hours of age No significant differences among the groups in mortality or oxygen dependency (at either 28 days of life or at 36 weeks' postmenstrual age)
COIN trial[64]	610 infants (25–29 weeks' gestation)	NCPAP versus intubation with MV	A 50% decrease in the use of surfactant in NCPAP group The NCPAP group also had fewer days of MV The combined outcome of death or oxygen dependency at 28 days was lower in the NCPAP group, but not significant at 36 weeks postmenstrual age Greater incidence of pneumothorax in NCPAP group (9% versus 3%)
SUPPORT trial[65]	1316 infants (24–28 weeks' gestation)	NCPAP at 5 cm H_2O in the delivery room without any surfactant versus intubation and surfactant treatment within 1 hour after birth	No difference in the primary outcome of death or BPD A high rate of intubation in the NCPAP group (83%) The NCPAP group had fewer days of MV No difference in the occurrence of air leak Less use of postnatal corticosteroids in the NCPAP group
VON trial[66]	648 infants (26–29 weeks' gestation)	Prophylactic surfactant followed by a period of MV versus prophylactic surfactant with rapid extubation to bubble NCPAP versus initial management with bubble NCPAP and selective surfactant treatment if required	The study was halted before the desired sample size was reached because of declining enrollment No difference in the primary outcome of combined death or BPD at 36 weeks No difference in the incidence of pneumothorax 48% of patients treated with NCPAP were not intubated, and 54% did not receive surfactant
REVE trial[96]	279 infants (25–27 weeks' gestation)	Early NCPAP after prophylactic surfactant versus MV with prophylactic surfactant	Intubation with early surfactant administration followed by NCPAP mostly benefits infants at 25–26 weeks' gestation

Abbreviations: MV, mechanical ventilation; NCPAP, nasal continuous positive airway pressure; IFDAS, Infant Flow Driver and Surfactant; COIN, CPAP or Intubation trial; SUPPORT, Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial; VON, Vermont Oxford Network trial; REVE, REduction of VEntilation trial.

clinical prediction score for nasal CPAP failure in VLBW infants was developed recently. On multivariate analysis, the authors found three variables, ie, gestation <28 weeks, preterm premature rupture of membranes, and product of CPAP pressure and FiO_2 ≥1.28 at initiation to maintain saturation between 88% and 93%, to be independently predictive of failure.[99] In another study, failure of the INSURE method was reported in 32% of preterm infants (23–28 weeks) receiving nasal CPAP. INSURE failure was significantly associated with the $PaCO_2$ and mean arterial-to-alveolar oxygen tension ratio as well as a severe radiological grade in preterm infants with respiratory distress syndrome.[100]

Alternative methods of noninvasive respiratory support in VLBW infants include heated, humidified high-flow nasal cannulation, bilevel nasal CPAP, and nasal IPPV. Although the humidified high-flow nasal cannula has been widely used in many NICUs,[101] there are scant data regarding its efficacy and safety.[102] Bilevel nasal CPAP was associated with better respiratory outcomes versus nasal CPAP, and allowed earlier discharge in preterm infants with respiratory distress syndrome.[103] Early use of nasal IPPV in preterm infants with respiratory distress syndrome reduced the need for intubation and mechanical ventilation,[104] and reduced the risk of bronchopulmonary dysplasia[105,106] compared with nasal CPAP. Although these findings are promising, further studies are needed to assess the potential benefits of these noninvasive ventilation techniques.

Surfactant

Surfactant therapy has been an excellent evidence-based measure of treatment for preterm respiratory distress syndrome since its introduction in 1990. In both VLBW[107] and larger[108–110] preterm infants, it has been shown to lead to a significant decrease in the risk of neonatal mortality and morbidity.[111] Surfactant replacement therapy has decreased the incidence of pneumothorax and intraventricular hemorrhage, and improved survival of preterm infants.[112]

Recent developments in surfactant therapy for respiratory distress syndrome in preterm infants include comparative trials of natural versus synthetic surfactants, exploration of alternative modes of administration of surfactant, time of surfactant administration, and evaluation of the concomitant use of surfactant with short-term or noninvasive ventilation as adjuvant therapy.

Natural versus synthetic surfactant

Natural and synthetic surfactant preparations commonly used for neonatal respiratory distress syndrome are shown in Table 4. Natural surfactants are generally derived from either lung lavage or minced lung of bovine or porcine origin. Synthetic surfactants are complex combinations of dipalmitoylphosphatidylcholine and other phospholipids, neutral lipids, lipoprotein, or alcohols.

Natural surfactant

Individual trials have compared the efficacy and safety of various natural surfactants in the treatment of respiratory distress syndrome. Most reported differences in effectiveness between natural surfactant preparations were from short-term studies. Poractant alfa was found to have a more rapid onset of action than beractant in most studies.[113–115] In a meta-analysis of five trials that compared poractant alfa with beractant in the treatment of preterm infants with respiratory distress syndrome, there was no difference in the primary outcome of bronchopulmonary dysplasia between the two different surfactant types (31.5% versus 29.9%, relative risk 0.98, 95% confidence interval 0.75–1.29), but a significant decrease in mortality rate was noted with the use of poractant versus beractant (relative risk 0.51, 95% confidence interval 0.3–0.89).[116] However, this difference in mortality was attributed to the use of higher doses of poractant alpha (200 mg/kg) compared with beractant (100 mg/kg) in three of the studies included in this meta-analysis. When the results were reproduced after exclusion of these trials, the difference in mortality was not statistically significant.[117] Calfactant was found to have a more rapid effect with fewer doses, without having an effect on overall incidence of bronchopulmonary dysplasia or mortality when compared with beractant.[118,119] Consistent with previous reports, the use of bovine lipid extract surfactant was associated with a more rapid improvement in oxygenation, but no effect on short-term outcome when compared with beractant.[120] On the basis of the currently available evidence, no preparation can

Table 4 Surfactant products for neonatal respiratory distress syndrome

Surfactant	Type	Preparation	Origin	Composition
Poractant alfa	Natural	Curosurf®	Porcine lung minces, lipid extraction with purification using liquid-gel chromatography	DPPC + PG + SP-B + SP-C
Calfactant	Natural	Infasurf®	Calf lung lavage with lipid extraction	DPPC + PG + SP-B + SP-C
Beractant	Natural	Survanta®	Bovine lung minces, lipid extraction, supplemented with DPPC, palmitic acid and tripalmitin	DPPC + PG + SP-B + SP-C
		Alveofact®	Cow lung lavage fluid with lipid extraction	DPPC + PG + SP-B + SP-C
BLES	Natural	BLES®	Bovine lipid extract surfactant	DPPC + PG + SP-B + SP-C
Colfosceril	Synthetic	Exosurf®	Synthetic DPPC in hexadecanol and tyloxapol (as spreading agents)	DPPC
Lucinactant	Synthetic	Surfaxin®	Recombinant SP-B analog	DPPC + POPG + palmitic acid + recombinant SP-B analog
Lusupultide	Synthetic	Venticute®	Recombinant SP-C analog	DPPC + PG + palmitic acid + recombinant SP-C analog

Abbreviations: BLES, bovine lipid extract surfactant; DPPC, dipalmitoylphosphatidylcholine; PG, phosphatidylglycerol; POPG, palmitoyloleylphosphatidylglycerol; SP-B, surfactant protein B; SP-C, surfactant protein C.

clearly be considered superior to another for the treatment of respiratory distress syndrome in preterm infants in terms of morbidity and mortality.

Synthetic surfactant

Although synthetic surfactants have theoretical advantages over natural surfactants, to date natural surfactants have been shown to be superior to synthetic surfactant in clinical trials due to the presence of protein B and C.[124,125] The use of natural preparations was associated with lower inspired oxygen concentrations, ventilator pressures, mortality, and rates of respiratory distress syndrome complications in preterm infants. When used for treatment of respiratory distress syndrome, colfosceril was associated with slower weaning and more pneumothorax but no difference in major clinical outcomes compared with calfactant. When used for prophylaxis, calfactant was more effective than colfosceril in reducing the severity of respiratory distress syndrome and the number of associated deaths, but had no impact on overall mortality or bronchopulmonary dysplasia.[124,125]

New-generation synthetic surfactants containing peptides that mimic surfactant protein B (lucinactant) or surfactant protein C (lusupultide) were developed to improve the efficacy of synthetic surfactants. Two large multicenter, randomized controlled trials compared the safety and efficacy of lucinactant with that of other surfactant preparations. The SELECT (Safety and Effectiveness of Lucinactant versus Exosurf in a Clinical Trial) study showed significant improvement in respiratory distress syndrome, related mortality through 14 days of life, and bronchopulmonary dysplasia when lucinactant was compared with colfosceril, as well as a reduction in total days on ventilation when compared with beractant.[126] Similarly, the STAR (SURFAXIN® Therapy Against Respiratory distress syndrome) trial found that lucinactant was noninferior to poractant with regard to survival without bronchopulmonary dysplasia. Infants treated with lucinactant required significantly fewer doses compared with poractant.[127] In summary, new-generation synthetic surfactant seems to have some advantages over previous synthetic surfactants containing only phospholipids, presumably because of the surfactant protein mimic, and is at least as good as currently used animal-derived surfactants.

Mode of administration

Intratracheal administration is presently the only approved means of delivering surfactant, due to its liquid nature. Accordingly, therapeutic use of surfactant is limited to infants who are intubated and/or undergoing mechanical ventilation. Furthermore, the process of surfactant administration requires a skilled attendant for endotracheal intubation. Tracheal intubation has potential risks, such as tracheal tube malpositioning or dislocation, hypoxia, bradycardia, and infection. Further, patients requiring tracheal intubation in an elective situation need to be treated with analgesic and sedative drugs that may have depressive respiratory effects.[128]

Alternative noninvasive techniques for administration of surfactant without tracheal intubation include administration through a laryngeal mask airway, nebulized surfactant, and minimally invasive surfactant therapy. Evidence for use of a laryngeal mask airway for surfactant administration comes from case reports and small uncontrolled trials.[129,130] A Cochrane review, which included only one small trial, compared late rescue laryngeal mask airway surfactant with no treatment in preterm infants ≥1200 g with respiratory distress syndrome, and administration of surfactant by a laryngeal mask airway was associated with no significant difference in need for subsequent mechanical ventilation and endotracheal surfactant, pneumothorax, days on IPPV, and days on IPPV or oxygen, but may have a short-term effect in reducing the requirement for oxygen.[131]

Administration of aerosolized surfactant has gained more interest because it is theoretically more gentle, noninvasive, and homogeneously distributed. Jorch et al demonstrated that CPAP and nebulized Alveofact® compared with CPAP alone resulted in an improved alveolar-arterial gradient and better $PaCO_2$ levels in infants at 28–35 weeks' gestation.[132] A comparison of nebulized Curosurf® and CPAP versus CPAP alone in infants at 23–36 weeks' gestation found no difference in clinical outcome, but demonstrated that nebulized surfactant was safe and well tolerated.[133] Similarly, Finer et al showed the safety of nebulized lucinactant (Aerosurf®) in 17 preterm infants at 28–32 weeks' gestation.[134] However, issues regarding development of nebulizer devices capable of administration, effective administration, dosing strategies, and cost-effectiveness remain unresolved.[135]

Kribs et al described another technique of administering surfactant, known as the MIST (minimally invasive surfactant therapy) technique, whereby surfactant is administered via a thin endotracheal catheter during spontaneous breathing together with application of nasal CPAP.[136] They reported that use of this technique increased between 2001 and 2004, and was associated with a significant increase in survival without bronchopulmonary dysplasia.[136] A multicenter German study involving 1541 infants at <31 weeks' gestational age demonstrated a decreased need for mechanical ventilation during the first 72 hours and a lower rate of bronchopulmonary dysplasia and rate of death or bronchopulmonary dysplasia in infants treated with this new technique compared with those who received standard care.[137] In a recent randomized controlled trial, preterm infants (26–28 weeks' gestation) randomized to this new technique required less mechanical ventilation and had fewer median days on mechanical ventilation compared with a standard treatment group.[138] In another report, it was demonstrated that there was no significant difference regarding neurodevelopmental outcome in school-aged children treated after implementing this technique, even though surviving infants were more immature and survival rates had increased.[139] Dargaville et al modified this technique using a 16-gauge vascular catheter inserted through the vocal cords under direct vision without the need for Magill forceps.[140]

The early use of noninvasive ventilation alone or in conjunction with surfactant may be as effective as intubation in preventing and treating respiratory distress syndrome in very premature infants. It has been suggested[54] that the high survival rates and low incidence of bronchopulmonary dysplasia experienced in some centers in Scandinavia and the US were further improved when nasal CPAP was combined with early surfactant treatment and early extubation to nasal CPAP.[128,141] The INSURE method, developed in Scandinavia, combines endotracheal intubation and surfactant application with early extubation to nasal CPAP.[142] Infants are usually anesthetized with morphine, sometimes in combination with thiopental, followed by naloxone application to reverse respiratory depression.[141,143]

Time of administration

Surfactant administered within 2 hours of life to infants ≤28 weeks' gestation reduced the incidences of pulmonary interstitial emphysema, bronchopulmonary dysplasia, pneumothorax, and mortality.[144] Preterm infants with respiratory distress syndrome who received surfactant within 30 minutes of life showed reductions in pulmonary interstitial emphysema, death, intraventricular hemorrhage grade III–IV, and the combined outcome of bronchopulmonary dysplasia and death in comparison with infants who receive surfactant later on.[145] However, most of the trials which studied the value of early versus late surfactant therapy were conducted before the era of routine antenatal steroids.[146] Accordingly, the previously observed difference between early and delayed surfactant therapy may be smaller in current practice.

CURPAP, an international randomized controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants, reported no difference in need for mechanical ventilation, bronchopulmonary dysplasia, or pneumothorax among infants born at 24–28 weeks' gestation who were randomized to receive prophylactic or early selective surfactant with nasal CPAP, suggesting early rescue surfactant is as good as prophylactic surfactant.[147] These results indicate that preterm infants (24–28 weeks' gestation) can be treated with nasal CPAP from birth, and that rescue INSURE should be used if nasal CPAP fails. In contrast, a multicenter study from Colombia randomized 279 preterm infants (27–31 weeks' gestation) with respiratory distress syndrome in the first hour of life to either an INSURE to CPAP protocol or to CPAP alone. The INSURE to CPAP group had lower mechanical ventilation requirements and less pneumothorax. No differences in rates of bronchopulmonary dysplasia or mortality were found.[148] In a recent multicenter study from South America, 256 VLBW infants (800–1500 g) were randomized to a CPAP/INSURE group (if respiratory distress syndrome did not occur, CPAP was discontinued after 3–6 hours; if respiratory distress syndrome developed and the FiO_2 was >0.35, the INSURE protocol was indicated) or to an oxygen/mechanical ventilation group (in the presence of respiratory distress syndrome, supplemental oxygen without CPAP was given, and if FiO_2 was >0.35, surfactant and mechanical ventilation were provided). They demonstrated a reduced need for mechanical ventilation and less use of surfactant in the CPAP/INSURE group, and no differences in mortality, pneumothorax, bronchopulmonary dysplasia, and other complications of prematurity between the two groups.[149]

Conclusion

The lungs of preterm infants are vulnerable to injury, especially immediately after birth. Improvements in respiratory support for preterm infants in the delivery room have great potential to improve the short-term and long-term outcome. There is a need to avoid routine intubation of ELBW infants in the delivery room. New techniques for monitoring and critical assessment of postnatal adaptation are currently available and may help to improve decision-making during resuscitation. New synthetic preparations and noninvasive techniques for surfactant administration may prove to be better than conventional techniques. Further research is urgently required to assess the potential benefits of these interventions.

Disclosure

The authors report no conflicts of interest in this work.

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