The role of surfactant and non-invasive mechanical ventilation in early management of respiratory distress syndrome in premature infants

Narayan Prabhu Iyer, Maroun Jean Mhanna
Cleveland, Ohio, USA

Review article

Background: **Surfactant replacement therapy has been used for few decades for the treatment of respiratory distress syndrome (RDS) and has significantly improved morbidity and mortality in premature infants. Non-invasive respiratory support has recently emerged as a strategy in the early management of RDS. In this review, we discuss the different strategies of early management of RDS.**

Data sources: **A literature search of PubMed database was conducted to review the subject. The quality of evidence of key clinical studies was graded according to a modified grading system of the international GRADE group.**

Results: **Continuous positive airway pressure (CPAP) with selective surfactant is a safe alternative to routine intubation, surfactant and mechanical ventilation in preterm infants with spontaneous breathing, and such an approach has been associated with decreased risk of death and bronchopulmonary dysplasia. There is a risk of pneumothorax when using a high pressure of CPAP (≥8 cm of H_2O), a high partial pressure of carbon dioxide (PCO_2 >75 mm of Hg), and a high fraction of inspired oxygen (FiO_2 >0.6) as a threshold for intubation while on CPAP.**

Conclusion: **Not all preterm infants need surfactant treatment, and non-invasive respiratory support is a safe and effective approach.**

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Key words: **non-invasive mechanical ventilation; prematurity; respiratory distress syndrome**

Author Affiliations: Department of Pediatrics, Division of Neonatology, Case Western Reserve University School of Medicine, MetroHealth Medical Center, Cleveland, Ohio 44109, USA (Iyer NP, Mhanna MJ)

Corresponding Author: Maroun Jean Mhanna, MD, MPH, Department of Pediatrics, Metro Health Medical Center, 2500 Metro Health Drive, Cleveland, OH 44109, USA (Tel: 216-778-1346; Fax: 216-778-4223; Email: mmhanna@metrohealth.org)

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Introduction

It has been more than 50 years since surfactant deficiency was identified as the cause of respiratory distress syndrome (RDS) of the newborn.[1] Once surfactant became commercially available, it revolutionized the therapeutic armamentarium available for the management of RDS in premature infants. Next to surfactant replacement therapy, great strides have been taken in the provision of non-invasive and invasive respiratory support to infants with RDS. These recent advances have led to significant improvement in morbidity and mortality of prematurely born infants. Advancements in respiratory care remain the focus of ongoing efforts to improve survival of premature infants and reduce lung disease associated with prematurity such as bronchopulmonary dysplasia (BPD). Ongoing efforts to improve the respiratory outcome of premature infants have been attempted to individualize respiratory care, avoid invasive mechanical ventilation, and optimize non-invasive surfactant delivery in infants with RDS. This review aims to discuss the management of RDS with an emphasis on the early postnatal period.

A literature search of PubMed database was conducted in August of 2013. MeSH terms including infant, newborn, positive-pressure respiration, continuous positive airway pressure (CPAP), continuous distending pressure, and pulmonary surfactants were used for the search. In addition, surfactant and non-invasive ventilation were also used as key words to include articles not included by MeSH terms.

Cross-references of the relevant articles were also searched for additional studies. Studies were restricted to English language. Search was limited to studies involving newborn infants. Clinical studies as well as animal and bench research studies were reviewed. A total of 1639 abstracts were identified, 165 articles were assessed, and 60 articles were found to be relevant to the review. The quality of evidence of several key clinical studies included in this review was graded according to the American College of Chest Physicians (ACCPs) grading guidelines, a modified grading system of the international GRADE group. The grading system

classifies recommendations into the following grades: strong (grade 1) or weak (grade 2), and quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to the study design, the consistency of the results, and the directness of the evidence.[2]

Characteristics of RDS

RDS is characterized by an increased respiratory effort in the newborn period, and it is associated with alveolar surfactant deficiency. Preterm infants with RDS have approximately 1/10th of the surfactant pool of healthy term infants;[3,4] and their lungs are at a stage of development where gas exchange is inefficient. For instance the lungs are in a saccular stage of development when infants are born at less than 28 weeks GA or they are extremely low birth weight (ELBW) infants; and it is not until 32 weeks GA that the alveolarization stage begins. Also, postnatal lung injury and inflammation lead to pulmonary edema and surfactant inactivation which in turn cause worsening of the respiratory failure. As will be discussed later, preterm lungs with low amounts of surfactant may not develop severe RDS unless they are injured. Therefore an attempt should be made to minimize postnatal lung injury.

Surfactant

The role of surfactant deficiency in the pathogenesis of RDS was first described by Avery and Mead in 1959.[1] Subsequently, Enhorning and Robertson[5] in 1972 showed an improvement in the pulmonary hysteresis loop after tracheal deposition of surfactant in rabbit fetuses. In 1980, Fujiwara et al[6] first showed clinical benefit of surfactant use in infants with RDS. Since then, multiple randomized controlled trials (RCT) using 12 different types of surfactant products have revolutionized the field of neonatology. Below, we provide a brief description of evidence-based clinical use of surfactant.

Timing and patient selection for surfactant therapy

Timing and patient selection for surfactant therapy have been the focus of multiple research studies in the last decade. The issue of timing can be broken down into two distinct questions: Do all preterm infants need surfactant? And if selective surfactant strategy is used, how soon after birth should surfactant be given? We will discuss the issue of patient selection later (see under the heading: Surfactant or non-invasive support). In infants with established RDS (defined as infants who are intubated because of clinical RDS) early surfactant (within two hours of life) reduces the combined outcome of death and/or BPD by 17% (grade 1A).[7]

Synthetic versus natural surfactant therapy

Synthetic and natural forms of surfactants have been marketed in the last two decades. There are two types of synthetic surfactants based on synthetic peptides presence or absence, and two types of natural surfactants based on bovine or porcine origins. Multiple studies have been conducted in the 1990s and early 2000 comparing the different types of surfactant. In a meta-analysis of multiple studies, natural surfactant was associated with a significant reduction in pneumothoraces (37%), mortality (13%), and BPD (5%) (grade 1A);[8] whereas in a meta-nalysis of two other studies, synthetic surfactants with added peptides did not show any significant difference in outcome in comparison with the natural forms.[9]

Among natural surfactants, there has been controversy regarding the efficacy of different forms. In a meta-analysis of 529 patients from 5 different randomized controlled studies, a high dose (200 mg/kg) porcine derived surfactant (Poractant) was associated with a reduction of mortality by 71% and a reduction of surfactant re-dosing by 36% compared with a bovine derived surfactant (Beractant) (grade 2A).[10] In a recent comparative effectiveness study (cohort study design) involving 51 282 infants, there were no differences in outcome between beractant, calfactant, and poractant preparations (grade 2B).[11] In that study, the authors attributed the previously described differences between different surfactant preparations to unmeasured site variations in outcomes.

Dosing of surfactant therapy

Few human studies regarding the pharmacokinetics of surfactant have been published. Early trials have shown that higher starting doses of 200 mg/kg produce faster and more sustainable improvement in oxygenation than lower doses of 100 mg/kg of poractant (grade 2A).[12] Other trials have also shown similar benefits of high dose poractant over 100 mg/kg of beractant.[13-15] In a recent study, using carbon-13 labeling to study the pharmacokinetics of surfactant in humans, Cogo et al[16] have shown that a high dose of 200 mg/kg resulted in a significantly longer half-life than a smaller dose of 100 mg/kg of poractant (32±19 *vs.* 15±19 hours). The same authors also found that the endogenous production of surfactant was the same in both groups, leading to the speculation that recycling of surfactant proteins might be responsible for the longer half-life of the exogenous surfactant.

Individualized responses to surfactant therapy

Individualized clinical responses to surfactant therapy are often seen in preterm infants with RDS. The response to surfactant is clearly modulated by gestational age, antenatal steroids and presence of co-morbid factors such as sepsis and maternal diabetes. The responses

can be categorized as acute, responses lasting hours and responses lasting days.[4] The acute response to surfactant results from the biophysical properties of surfactant. The acute response is dependent on the rapid and even distribution of surfactant to the distal lungs. In preterm lambs, surfactant distribution is better with larger volumes (4 mL/kg) if it is delivered prior to the implementation of positive pressure ventilation (as soon as possible after birth). Surfactant distribution is also better when it is delivered as a bolus instead of an installation over 15 minutes (grade 2C).[4] Following the administration of surfactant lung compliance changes over hours, and the additional surfactant effects are dependent on the catabolism and recycling/integrating of the exogenous surfactant into the endogenous pool. Therefore, a large initial dose of surfactant results in a longer half-life. However, some infants require repetitive doses of surfactant. In these infants, the presence of lung injury (ventilatory trauma and infection) along with a low surfactant pool size result in propagation of RDS. Another category of patients have been noted to have the "post surfactant slump" which is typically described in extremely premature infants with moderate to severe RDS, who would temporary response to a repetitive dose of surfactant a week later (grade 2C).[17]

Frequent dosing of surfactant

Although a single high dose of surfactant can last a few days, rapid catabolism in certain infants and extreme prematurity can lead to a need for repeated dosing. In a meta-analysis of two trials using natural surfactants, there was a 50% reduction in the risk of pneumothorax and a trend towards a reduction in the risk of mortality with repeated dosing (grade 1B).[18] It remains unclear if more than two doses of surfactant are beneficial.

Newer approaches to surfactant administration

Given that there will always be a subset of VLBW infants who will benefit from surfactant therapies, studies have been conducted to identify less invasive modes of surfactant deliveries, such as using aerosolized surfactant and using catheters and laryngeal mask airways (LMA) to deliver surfactant to the lungs. Aerosolized surfactant was first described in the 1960s, but multiple technical problems related to the preparation and administration of the aerosolized product has led to a decline in its use. With increasing emphasis on non-invasive surfactant administration, there has been a renewed interest in aerosolized surfactant. Aerosolized lucinactant has been used in a pilot study to treat premature infants with RDS.[19] Ongoing trials using LMA to deliver surfactant are currently conducted.[20] The delivery of surfactant to spontaneously breathing infants who are not intubated has been successful. In the avoidance of mechanical ventilation (AMV) study, infants between the age of 26 and 28 weeks gestation and <1500 g birth weight were enrolled. In the experimental arm, surfactant was administered to infants on NCPAP who required greater than 30% FiO_2. Surfactant was administered into the trachea by direct visualization using a thin catheter and a Magill forceps. Standard treatment was provided in the control arm. The need for mechanical ventilation at 2-3 days of life was significantly less in the experimental group than in the control group with a number needed to treat (NNT) of 6 (95% CI: 3-20, P=0.008). The procedure was well tolerated and there were no differences in serious adverse events between the two groups.[21] In a similar study, the Take Care study compared the administration of surfactant with a feeding tube strategy to the intubate-surfactant-extubate (INSURE) strategy in infants of <32 weeks gestational age and who had RDS. The group of infants who received surfactant with a feeding tube while spontaneously breathing, had significantly less need for mechanical ventilation and BPD than the INSURE group.[22]

Non-invasive respiratory support in the management of RDS

The most common mode of non-invasive mechanical ventilation in newborn infants is nasal continuous positive airway pressure (NCPAP) ventilation. NCPAP prevents airway obstruction by splinting the upper airway, diminishes the work of breathing by reducing resistance to air flow and helps lung expansion by providing a continuous distending pressure (CDP). CDP can theoretically limit atelectotrauma and reduce lung inflammation.

Indications of CPAP

Animal studies as well as more recent human studies have shown the benefit of CPAP soon after birth (grade 1A).[23-25] Also NCPAP can be safe and effective as the only therapeutic intervention in selected patients with RDS.[26]

Devices available for CDP

NCPAP and heated humidified high flow nasal cannula (HHFNC) are two of the common devices that provide non-invasive respiratory support in newborn infants. NCPAP devices vary by the source of pressure and type of flow, such as underwater seal in bubble CPAP, constant flow ventilator driven CPAP, and variable flow infant flow driven CPAP (such as Infant Flow®, CareFusion, Yorba Linda, CA). For instance, variable flow devices have been shown to improve the work of breathing in infants (grade 2B).[27] The type of nasal interface is equally important and adds a level of complexity to the care of infant on non-invasive respiratory support. Results from a meta-analysis suggest that short bi-nasal prongs are better than single

nasal or nasopharyngeal prongs (grade 1A).[28]

HHFNC (flows >1 L/min) is relatively a new device. HHFNC has produced similar results to NCPAP in supporting infants less or equal to 28 weeks gestation post-extubation (grade 1A).[29-31] There is also less nasal trauma with HHFNC than with NCPAP (grade 2B).[29,30] In a recent large trial comparing HHFNC with NCPAP, HHFNC was found not to be inferior to NCPAP. Compared with NCPAP, HHFNC was also found to be associated with reduced nasal trauma.[32]

NCPAP settings and weaning

Few randomized controlled trials[33-35] have been conducted to determine the optimal settings and weaning parameters of NCPAP. Some authors[33] consider 5 cm H_2O NCPAP as to the lowest setting below which CPAP is likely to be ineffective (grade 1C).[33] Using respiratory inductive plethysmography, researchers[34] found maximum increments in tidal volume and thoraco-abdominal synchrony with 8 cm H_2O CPAP (grade 2C). Bedsides, clinical examination remains essential in order to adjust NCPAP pressures and individualize therapy. Weaning from CPAP has not been extensively studied. In a randomized controlled study, CPAP weaning was found to be less effective than increasing "time off" in infants with RDS.[35]

Non-invasive positive pressure ventilation (NIPPV)

NIPPV is often used in preterm infants to augment CPAP and as a way to manage frequent apneas. Synchronization in NIPPV is achieved by application of the Graseby pneumatic capsule on the abdomen. More recently, synchronization has been attempted using a flow sensor and by detecting neural output to diaphragm.[36,37] Synchronization has theoretical advantages of improving tidal volume and CO_2 clearance. Synchronization also reduces thoraco-abdominal asynchrony and reduces work of breathing.[37-39] NIPPV has been shown to improve post extubation success rates. In a pooled analysis, NIPPV was shown to reduce extubation failure by 71%.[40] NIPPV has been tried as a strategy to reduce days of mechanical ventilation and BPD. In a retrospective study, VLBW infants treated with synchronized NIPPV had lower CO_2 and less BPD/death than infants treated with NCPAP.[41] In a recent randomized controlled study, there was no significant difference in the rate of survival without BPD at 36 weeks of post menstrual age among ELBW infants treated with NIPPV or NCPAP (grade 1B).[42]

Complications of non-invasive mechanical ventilation

Complications secondary to non-invasive ventilation are not uncommon. Nasal trauma and occasionally perforation of the nasal septum have been described.[43] Pneumothoraces have also been described when high pressures are applied (such as 8 cm NCPAP in the COIN study).[44] The safety of HHFNC has not been fully studied, especially that intra-thoracic pressures generated by HHFNC are variables;[45] however nasal trauma tends to be less with HHFNC than with NCPAP.

Nasal high frequency ventilation

The use of nasal high frequency ventilation (NHFV) has been reported. NHFV has the theoretical advantage that it does not require synchronization with patient breaths; especially when lack of synchronization has been a limitation for most forms of synchronized NIPPV. NHFV requires the same ventilators that are used for invasive HFV except in the former the interface is a nasal prong. Small case series have elaborated on the safety of short-term use of NHFV in VLBW infants.[46-48] In a preterm lung model, long-term use of NHFV has shown a better alveolarization than endotracheal intubation and mechanical ventilation.[49] In a newborn mannequin, NHFV was superior to NCPAP and NIPPV in clearing CO_2.[50] Further trials are needed to establish the use of this novel form of non-invasive respiratory support.

Surfactant therapy versus non-invasive mechanical ventilation

Surfactant therapy is generally indicated in extremely premature infants (less than 26 weeks gestation) and preterm infants with clinical RDS. In these infants, prophylactic surfactant therapy is superior to rescue therapy. Meta-analysis of randomized controlled trials conducted in 1990 support the use of prophylactic surfactant (surfactant given within 15 min of birth), with a lower neonatal mortality of 31% if infants born before 32 weeks of gestation.[25] There was also a reduction in the rate of pneumothoraces and pulmonary interstitial emphysema in infants treated prophylactically without a significant reduction in the rate of BPD (RR: 0.96; 95% CI: 0.82-1.12). Studies conducted in 1990 differ from the current clinical practices, since in 1990 routine administration of antenatal steroids and routine application of postnatal CPAP were not widespread. Currently, most preterm infants are exposed to antenatal steroids and after birth, postnatal CPAP is usually available. In this context of widespread use of antenatal steroids and post natal CPAP, multiple randomized controlled trials have been conducted comparing different strategies for the early management of RDS (Table).[21,22,44,51-55] A meta-analysis of two recent studies, where antenatal steroids and postnatal CPAP use were common, demonstrated a small, but statistically significant increase in the risk of CLD or death with the prophylactic administration of surfactant when compared

to selective use of surfactant in infants who were stabilized on NCPAP after birth (relative risk 1.12, 95% CI: 1.02 to 1.24, number needed to treat 17).[25] Using slightly different inclusion criteria, two further meta-analyses have been reported.[56,57] Both meta-analyses reported remarkable homogeneity and a benefit from the regular use of NCPAP in the delivery room with selective use of surfactant for infants with established RDS. Fischer et al[57] in their meta-analysis, included studies that compared strategies of avoidance of endotracheal intubation [stabilization on NCPAP alone or surfactant without intubation (AMV and Take Care)] to strategies of routine intubation and prophylactic surfactant. Strategies avoiding intubation showed a better outcome with a lower rate of BPD or death. When a number to treat analysis (NNT) was performed, the results showed that for every 35 spontaneously breathing infants who were not intubated at birth one additional infant survived without BPD at 36 weeks corrected gestational age.[57] In their meta-analysis, Schmolzer et al[56] also included studies that compared NCPAP with routine intubation and prophylactic surfactant, but they did not include studies where surfactant was administered without intubation. In their pooled analysis, they found one additional infant could survive to 36 weeks without BPD for every 25 infants treated with NCPAP instead of routine intubation. Recognizing the evolving evidence on patient selection and timing of surfactant administration, the 2013 European Consensus Statement has recently provided updated guidelines on respiratory management of preterm infants.[58]

The results of the trials and meta-analysis lead us to the following conclusions regarding the early management of RDS: 1) CPAP is a safe alternative to routine intubation and mechanical ventilation in spontaneously breathing extremely preterm infants (gestational age <30 weeks) (grade 1B); 2) Not all extremely preterm infants require surfactant therapy, and some can be managed with CPAP alone (grade 1A); 3) There is probably an increased risk of pneumothorax, as shown in the COIN study, with high pressure CPAP (≥8 cm of H_2O) and when using a $PaCO_2$ >75 or FiO_2 >0.6 as a threshold for intubation while on CPAP (grade 1B); 4) With the widespread use of prenatal steroids and early stabilization on NCPAP, selective use of surfactant, as compared to universal use of prophylactic surfactant may be associated with a reduction in the incidence of BPD (grade 1B).[25] Further reductions in BPD rates may be possible with the AMV and take care strategy.

Conclusions

The goal has always been to treat RDS and avoid the development of chronic lung disease. Over the last decade, several studies have shown that not all preterm infants need surfactant treatment, and that non-invasive

Table. Randomized controlled trials of different strategies for the early management of RDS

Studies	Interventions	Inclusion criteria	Outcome BPD/death	Major findings
COIN[44] (grade A)	CPAP *vs.* Intubation (surfactant given at physician discretion)	25-28 wks, spontaneously breathing requiring assistance at 5 min	No difference	CPAP group had 50% less intubation rate and less O_2 days. CPAP group had higher rate of pneumothorax possibly related to CPAP of 8 cm.
SUPPORT[51] (grade A)	CPAP *vs.* Intubation+ Surfactant	24-27 wks, all infants	No difference	CPAP group had more infants alive without PPV at 7 days, had less PPV days and less postnatal steroid days.
Rojas et al[52] (grade A)	Bubble CPAP *vs.* INSURE and bubble CPAP	27-31 wks, spontaneously breathing requiring assistance at 15-60 min	No difference	Surfactant group had less need for further PPV and less rate of pneumothorax. The latter was possibly related to high threshold (FiO_2 >75% or $PaCO_2$ >65) for intervention in the CPAP group.
CURPAP[53] (grade A)	CPAP *vs.* INSURE and CPAP	25-28 wks, spontaneously breathing requiring assistance within 30 min	No difference	No difference between groups in PPV at 5 days or pneumothoraces. Indication for intubation in CPAP group was FiO_2 >40% or $PaCO_2$ >65.
Tapia et al[54] (grade A)	CPAP+INSURE *vs.* Oxygen+Surfactant and mechanical ventilation	<1500 g, spontaneously breathing requiring assistance at birth	No difference	INSURE group had less need for PPV and surfactant.
VON[55] (grade B)	3 way-prophylactic surfactant *vs.* ISX *vs.* CPAP	26-29 wks, all infants	No difference	Infants who were initially treated with NCPAP or PS with rapid extubation to NCPAP had a similar outcome to those treated with PS followed by a period of mechanical ventilation.
AMV[21] (grade A)	CPAP+Surfactant without Intubation *vs.* CPAP+Rescue Surfactant+Intubation	26-28 wks, all infants	No difference	Surfactant without intubation group had less days of mechanical ventilation.
Take Care[22] (grade A)	CPAP+Surfactant without intubation (Take Care) *vs.* CPAP+INSURE	<32 wks, spontaneously breathing requiring assistance <2h	27% less BPD in the Take Care group	Less days of mechanical ventilation in the Take Care group.

CPAP: continuous positive airway pressure; NCPAP: nasal continuous positive airway pressure; PS: prophylactic surfactant; O_2: oxygen; PPV: positive pressure ventilation; INSURE: intubate-surfactant extubate; FiO_2: fraction of inspired oxygen; $PaCO_2$: partial arterial pressure of carbon dioxide; ISX: intubation-surfactant and rapid extubation; BPD: broncho pulmonary dysplasia; RDS: respiratory distress syndrome.

respiratory support is a safe and effective approach to prevent BPD. Also recent developments have shown that surfactant can be delivered without intubation. In the hope of reducing BPD, studies are aiming at improving our ability to identify infants who will benefit from surfactant therapy.[59] Trials using surfactant in spontaneously breathing infants without intubation, development of newer forms of surfactants such as nebulized surfactants and synthetic surfactants with surfactant protein B and C analogs,[60] are promising future strategies.

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