REVIEW ARTICLE

The Role of Continuous Positive Airway Pressure Therapy in the Management of Respiratory Distress in Extremely Premature Infants

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The use of mechanical ventilation for the treatment of respiratory distress syndrome (RDS) in low birth weight infants may cause barotrauma, volutrauma, and chronic lung disease. Different continuous positive airway pressure (CPAP) delivery systems exist, each with its own practical and clinical advantages and disadvantages. CPAP can be used as either a primary or an adjunctive respiratory support for RDS. Research demonstrates that CPAP decreases the incidence of respiratory failure after extubation. Clinical trials indicate that the optimal management of neonatal RDS consists of early surfactant treatment followed quickly by extubation and stabilization on CPAP. Early surfactant treatment combined with CPAP reduces the need for mechanical ventilation, compared to later surfactant treatment. Evidence suggests a synergistic effect between early surfactant administration and rapid extubation to nasal CPAP.

KEYWORDS continuous positive airway pressure, extremely premature infants, surfactant, respiratory distress syndrome

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INTRODUCTION

Treatment of respiratory distress syndrome (RDS) in low birth weight (LBW) infants involves surfactant administration, mechanical ventilation, and nutritional support.[1] Mechanical ventilation requires prolonged invasive intubation which is associated with physical trauma, including esophageal perforation, vocal cord damage, nasal septum damage (nasotracheal tubes), or acquired palatal groove (orotracheal tubes).[2] In addition, improper device settings may induce lung damage due to unnecessarily high pressures (barotrauma) or high gas volumes (volutrauma). Barotrauma and volutrauma, in turn, can result in bronchopulmonary dysplasia (BPD). BPD has several etiologies, the most important being excess oxygen exposure and barotrauma.[3-5] These may lead to inflammation and abnormal alveolar repair. Therefore, minimally invasive ventilation is beneficial in managing LBW infants with respiratory distress.[6]

ABBREVIATIONS BDP, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; FRC, functional residual capacity; IMV, intermittent mandatory ventilation; INSURE, early INtubation, SURfactant, and rapid Extubation to CPAP; LBW, low birth weight; MV, mechanical ventilation; NCPAP, nasal continuous positive airway pressure; NICHD, National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; NIPPV; nasal intermittent positive pressure ventilation; RDS; respiratory distress syndrome; sIMV, synchronized intermittent mandatory ventilation

A multivariate analysis comparing specific measures of respiratory care during the first postnatal week reveals that the only variable

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responsible for improved morbidity between two particular neonatal intensive care units (NICU) is the initiation of continuous positive airway pressure (CPAP) as opposed to mechanical ventilation.[7] Thus, minimally invasive ventilation in LBW infants with RDS should minimize persistent low-grade inflammation, barotrauma, and volutrauma.[8] As the LBW population continues to grow, and birth weights and gestational ages of surviving preterm neonates continue to decline, demand for a more gentle form of ventilation increases.

The use of CPAP within neonatal practice is expanding based upon such need for gentle, noninvasive ventilation approaches.[9,10] Thus, the focus of this article is to provide an overview of CPAP, its indications for use, and clinical benefits based upon key studies.

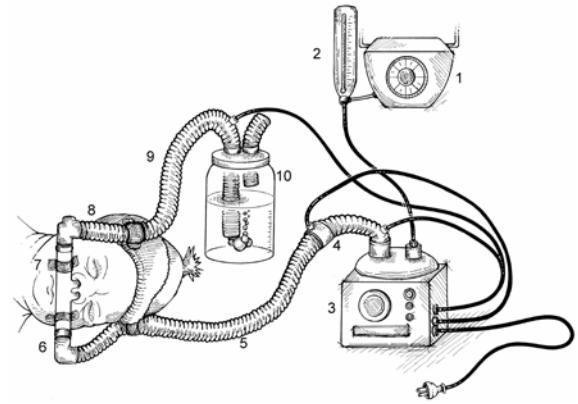

Figure 1. CPAP device and components 1) oxygen blender; 2) flowmeter (5-10 LPM); 3) heated humidifier; 4) Thermometer; 5) inspiratory tubing; 6) nasal cannulea; 7) Velcro; 8) manometer (optional); 9) expiratory tubing; 10) bottle containing 0.25% acetic acid solution filled up to 7 cm depth with distil end of expiratory tubing immersed to a depth of 5 cm to generated + 5cmH2O CPAP.
Reprinted, with permission, of the American Academy of Pediatrics.[17]

CPAP

In RDS, there is a deficiency of surfactant, which increases the surface tension at the air-liquid interface.[11] The alveoli progressively collapse if the surface tension is not reduced.[11] It is possible that CPAP can provide sufficient support to prevent a cascade of alveolar collapse. Introduced in 1971, CPAP therapy may provide a more gentle means of respiratory support than mechanical ventilation, maintaining an open airway, preventing lung collapse at the end of expiration, and establishing functional residual capacity in the treatment of acute respiratory distress in LBW infants.[2,12-15] CPAP also provides an alternative therapy that reduces the incidence of morbidities associated with intermittent mandatory ventilation (IMV) in the management of LBW infants.[16]

CPAP systems have three basic parts: 1) a supply of heated and humidified air, 2) a patient interface such as a nasal cannula, face mask, or head hood, and 3) an expiratory valve to provide positive air pressure within the system[17,18] (Figure 1). The greatest variation among CPAP systems is in the patient interface component. Several studies compare the interface methods of CPAP and find no difference in clinical outcomes. For instance, no difference is found when comparing the Infant Flow Driver versus a single-prong nasal CPAP device.[19,20] There are practical and clinical advantages and disadvantages with each delivery system[18] (Table 1). Many institutions leading in the use of CPAP as a first line therapy for RDS management in LBW infants use a nasal CPAP device with two short-curved nasal prongs (Figure 2). The use of CPAP systems with nasopharyngeal prongs reduces the likelihood of air leaks, but operates with higher resistance to airflow. Studies suggest that nasopharyngeal CPAP reduces the extubation failure rate from 30% to 5%.[21]

The heart of the CPAP system is the expiratory "positive pressure" valve. The expiratory valve may either be a variable pressure-flow valve or a threshold resistor.[14,22-24] Variable pressure-flow valves provide a constant level of resistance to air flow. Given the pressure/flow relationship (pressure = flow × resistance), pressures can fluctuate widely during spontaneous breathing in fixed resistance systems. Should an infant attempt to exhale into a fixed-resistance expiratory valve CPAP system, internal pressure will spike drastically which can potentially injure the infant's lungs. Conversely, threshold resistor CPAP systems provide a constant level of pressure. This is easily accomplished by submerging the expiration tube within a fluid column, allowing determination of the pressure by measuring the depth of submersion. Since pressure is independent of flow in threshold resistor systems, systems that submerge the expiration tube are considered to be more stable than systems with variable pressure-flow valves.[24]

Table 1. Advantages and disadvantages of various CPAP devices

Devices	Advantages	Disadvantages
Endotracheal tube	Secures open airway	Increase resistance from single long tube; Complications associated with endotracheal intubation
Head hood	No need for intubation; Easy to use	Impedes rapid access to head for rescue; Compresses vasculature in the neck; Prone to air leak; Noise from airflow
Face chamber	No need for intubation; Easy to use	Difficult to keep airtight; Necrosis of face
Face mask	No need for intubation; Easy to use	Difficult to keep airtight; Necrosis of face
Nasal mask	For infants with nasal septum injury from nasal prongs	Difficult to keep in place; Prone to air leak
Nasal prongs	No need for intubation; Easy to use; Allows neonate movement	Hudson[a] Easy to apply and keep in place; Anatomic curved prongs; Nasal septum erosion or necrosis INCA[b] Easy to apply and keep in place; Straight prongs may not point to nasal cavities; Nasal septum erosion or necrosis InfantFlow[c] Decrease work of breathing; Difficult to keep in place; Nasal septum necrosis; NeoPAP[d] High humidity; Difficult to keep in place; Nasal septum necrosis; Prongs too soft; Pressure measured may not be what patient receives
Nasal cannula	Vapotherm[e] Easy to apply; High humidity	CPAP pressure unknown, pending air flow rate and space between cannula and anterior nares
Nasal pharyngeal tube	No need for intubation; Easy to use	Increase of resistance from long tubes; Tubes may be pinched from nasal passage

a Hudson-RCI, Temecula, California
b Ackrad Laboratories, Inc, Cranford, New Jersey
c EME. Tricomed, Brighton, United Kingdom
d Respironics, Inc., Murrysville, Pennsylvania
e Vapoterm, Inc., Stevensville, Maryland
Adapted with permission from Ramanathan R, Sekar K, Soll RF, Wung J. Expert Opinions in Managing Neonatal Respiratory Distress Syndrome: Focus on Non-invasive Ventilation Strategies. Highlights from a 2005 Roundtable Discussion. Annenberg Center for Health Sciences, 1-20, 2005.[18]

INDICATIONS AND BENEFITS OF CPAP

CPAP can be used both as a primary mode to stabilize infants with respiratory insufficiency as well as an adjunct to other therapies after extubation from IMV. CPAP decreases the incidence of respiratory failure after extubation.[25] Although most clinical studies of CPAP were performed in patient populations that had previously been intubated, of which many were treated with surfactant, nasal CPAP is being used as the primary therapy in cases of mild to moderate RDS. That literature consistently demonstrates that the earlier a premature neonate is treated with surfactant, the better the clinical outcome.[1] For example, neonates treated

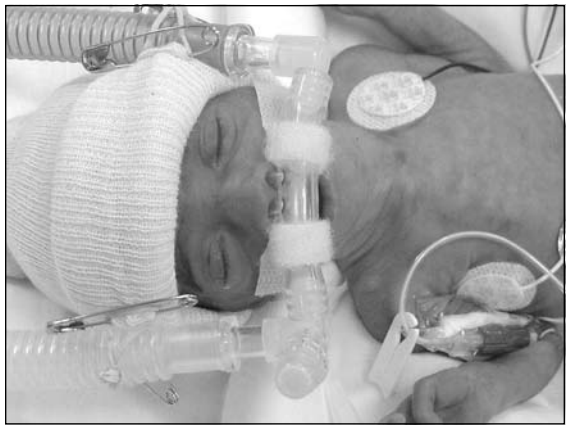

Figure 2. A low birth weight infant being treated with CPAP.
Photograph courtesy of Rangasamy Ramanathan, MD.

by two hours of age present better clinical outcomes than neonates treated by three hours of age.[26] The evidence from randomized controlled trials suggests that clinical outcomes are improved with early intubation and surfactant therapy followed by extubation to CPAP.[9,18,27-31]

Evidence shows that CPAP is an effective therapy when administered by well-trained and experienced personnel.[32,33] CPAP is indicated as a therapeutic intervention in infants with low functional residual capacity (FRC), or in patients with RDS. In addition, CPAP is useful in the treatment of transient tachypnea of the newborn, apnea of prematurity, airway closure disease such as BPD, and respiratory support after extubation.

SURFACTANT THERAPY FACILITATES EARLY EXTUBATION TO CPAP

Trial evidence has indicated that optimal management of the premature neonate consists of early treatment of surfactant-deficient LBW infants with surfactant, followed quickly by extubation and stabilization on CPAP.[27,34] Verder et al. examined the efficacy of poractant alfa in the management of premature neonates with RDS.[28] In a follow-up multi-center randomized controlled trial, Verder and colleagues[27] compared early versus late treatment with porcine surfactant, analyzing the reduced need for mechanical ventilation in LBW infants. The study was terminated early based on interim findings of a significant benefit with surfactant therapy followed by nasal CPAP over nasal CPAP alone. Infants who received early treatment presented with improved oxygenation six hours after randomization, with alveolar–arterial oxygen tension difference (a/APO_2) increasing to 0.48 in early-treated infants compared with 0.36 in late-treated infants. In addition, the need for mechanical ventilation before discharge was reduced, with 68% of late-treated infants needing mechanical ventilation and 25% of early-treated infants needing such intervention.

A meta-analysis (Table 2) evaluating the use of surfactant and rapid extubation to nasal CPAP (NCPAP) found that infants with RDS treated with early surfactant replacement therapy and NCPAP were less likely to need mechanical ventilation, and they were at lower risk for air leaks than infants treated with NCPAP and later surfactant therapy.[1] The analysis examined six randomized clinical trials of early surfactant administration in spontaneously breathing infants.

The National Institute of Child Health and Human Development (NICHD, 2002) study randomized and stratified LBW infants by birth weight and age at enrollment.[30] Early surfactant treatment followed by rapid extubation to CPAP reduced the need for mechanical ventilation from an average of 9.1 days to 3.5 days (standard deviation not available). The 2003 Vermont-Oxford study also found a reduced need for mechanical ventilation, with average duration on mechanical ventilation reduced from 1.9 ± 1.4 days to 1.7 ± 1.6 days in LBW infants stratified by center and birthweight.[35] Reininger et al. randomized LBW infants with no stratification and also found a significant reduction in the need for mechanical ventilation, with the average duration reduced from 2.65 days to 2.25 days.[29]

Dani and co-investigators compared nasal CPAP and mechanical ventilation in two nearly identical cohorts of neonates (based on gestational age and birth weight) treated with poractant alfa.[9] When used in lieu of MV, nasal CPAP significantly reduced the need for continued MV and reduced the days on mechanical ventilation and oxygen therapy, days on CPAP, days in the NICU, and the need for additional doses of surfactant.

Blennow and colleagues described this early intervention strategy as the INSURE approach

Table 2. Summary of CPAP studies involving surfactants

Reference	Surfactant + CPAP	Control	Infant Characteristics	Age at Surfactant Treatment	Key Findings
29	52	53 (Surfactant + IMV)	25-36 wk gestational age	24 hr	Less days on MV; early study termination
30	32	29 (Surfactant + IMV)	1250-2000 g	12 hr	Less days on MV; early study termination
31	35 (Poractant alfa)	33 (CPAP alone)	25-35 wk gestational age		Early poractant alfa + CPAP: decrease need for mechanical ventilation
27	33 (Early poractant alfa + CPAP)	27 (Late poractant alfa + CPAP)	<30 wk gestational age	5.2 vs. 9.9 hr	Early poractant alfa + CPAP: decrease need for MV; improved oxygenation
35	138	132 (CPAP with later rescue surfactant + IMV)	1501-2000 g	2-24 hr	Decreased days on MV
9	13 (Poractant alfa)	14 (Poractant alfa + IMV)	<30 wk gestational age	2.7 vs. 3.5 hr	Decreased days on MV, O_2, NICU length of stay and second dose of poractant alfa

IMV, Intermittent Mechanical Ventilation; MV, Mechanical Ventilation; GA, Gestational Age; NICU, Neonatal intensive care unit. Copyright Cochrane Library, adapted with permission.[1]

(early INtubation, SURfactant, and rapid Extubation to CPAP).[34] Early trial data indicates that neonates maintained on CPAP begin to produce endogenous surfactant within two hours.[36] Evidence from randomized controlled clinical trials demonstrate a synergistic effect between early surfactant administration and rapid extubation to nasal CPAP.

Between 1999 and 2002, CPAP in neonates with birth weights less than 750 grams produced a success rate of 37%.[18] The success rate increased to 72.7% when neonates with birth weights between 750 and 1000 grams were included. CPAP was successful in more than 91% of neonates with birth weights above 1000 grams. The success rate in neonates with gestational birth ages of 26 weeks or more was similarly high at 84.6%.

NIPPV AND FUTURE DIRECTIONS

As many institutions are incorporating the benefits of early extubation to CPAP into regular practice, research is proceeding to optimize outcomes in the neonatal population with RDS. One area of current investigational interest is extubation to nasal intermittent positive pressure ventilation (NIPPV). NIPPV incorporates the benefits of CPAP while supplementing intermittent breaths from the ventilator in coordination with respiratory efforts by the infant. Clinical trials indicate that NIPPV may reduce the need for reintubation,[37-39] thereby reducing the risks associated with prolonged intubation. Furthermore, NIPPV may reduce atelectasis, improve ventilation-perfusion matching, and reduce apnea of prematurity when compared to CPAP.[40] Meta-analyses support the benefits of NIPPV in reducing the rate of reintubation[41] and apnea of prematurity.[42]

To date, studies of NIPPV have involved a small number of infants. Clearly, larger studies are needed to confirm the benefits of NIPPV, as well as to compare the long-term outcomes of NIPPV compared to CPAP, for example in the development of BPD. Ramanathan and colleagues are currently conducting a multicenter trial that compares the benefits of extubation to NIPPV versus synchronized intermittent mandatory ventilation (sIMV) after surfactant administration in preterm infants with RDS. These results will surely be anticipated and may help to shed light on the prospective role of NIPPV in the treatment of neonates with RDS.

High flow nasal cannula have been tried to prevent re-intubation in premature infants as high flow cannula may generate positive airway pressure. In a study that compared high flow cannula and CPAP generated by an infant flow nasal CPAP system (VIASYS, Conshohocken, PA, USA), high flow nasal cannula was not

found to be superior to the infant flow CPAP system. More infants in the high flow cannula group were re-intubated compared to the nasal CPAP group. In addition, the high flow nasal cannula group also experienced more apneas and bradycardias post extubation.[43]

CONCLUSIONS

There is a significant learning curve associated with the clinical application of CPAP.[18,44] Attention to detail in its application is necessary to minimize complications.[44] Surfactant therapy can help aid practitioners in the successful incorporation of CPAP as an effective strategy. Based on the literature, three strategies for the management of the LBW infants have emerged: 1) Intubation and surfactant treatment with stabilization on conventional ventilation; 2) Intubation and surfactant treatment with extubation to nasal CPAP, and; 3) Stabilization on nasal CPAP alone.

Preliminary studies suggest that these LBW infants may successfully be ventilated with nasal CPAP; however, a synergistic effect may occur when CPAP is combined with surfactant therapy and early extubation. The literature suggests that surfactant therapy with rapid extubation to CPAP reduces the need for mechanical ventilation. Based on these findings, neonatologists are currently conducting randomized prospective clinical trials to determine the optimal strategies for the management of neonatal RDS. The long-term goal is to reduce the incidence of chronic lung disease, specifically BPD.

DISCLOSURE Dr. Sekar is a member of the Speaker's Bureau and a consultant for Dey, LP.

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