



POLICY STATEMENT

Respiratory Support in Preterm Infants at Birth

COMMITTEE ON FETUS AND NEWBORN

KEY WORDS

respiratory distress syndrome, preterm infant, neonate, surfactant, continuous positive airway pressure, bronchopulmonary dysplasia

ABBREVIATIONS

BPD—bronchopulmonary dysplasia

CI—confidence interval

CPAP—continuous positive airway pressure

INSURE—intubation, surfactant, and extubation

RDS—respiratory distress syndrome

RR—relative risk

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abstract

FREE

Current practice guidelines recommend administration of surfactant at or soon after birth in preterm infants with respiratory distress syndrome. However, recent multicenter randomized controlled trials indicate that early use of continuous positive airway pressure with subsequent selective surfactant administration in extremely preterm infants results in lower rates of bronchopulmonary dysplasia/death when compared with treatment with prophylactic or early surfactant therapy. Continuous positive airway pressure started at or soon after birth with subsequent selective surfactant administration may be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. *Pediatrics* 2014;133:171–174

BACKGROUND

Current practice guidelines in neonatology recommend administration of surfactant at or soon after birth in preterm infants with respiratory distress syndrome (RDS).¹ However, recent multicenter randomized controlled trials indicate that nasal continuous positive airway pressure (CPAP) may be an effective alternative to prophylactic or early surfactant administration.^{2–8} Respiratory support is being achieved more frequently with CPAP and other less invasive approaches, such as the technique of intubation, surfactant, and extubation (INSURE).⁹

Experimental evidence documents that mechanical ventilation, particularly in the presence of surfactant deficiency, results in lung injury. Early randomized clinical trials demonstrated that surfactant administration in infants with established RDS decreased mortality, bronchopulmonary dysplasia (BPD), and pneumothorax.¹⁰ Subsequent trials indicated that early selective administration of surfactant results in fewer pneumothoraces, less pulmonary interstitial emphysema, less BPD, and lower mortality compared with delayed selective surfactant therapy.¹¹ Trials of prophylactic administration of surfactant demonstrated decreased air leaks and mortality compared with selective surfactant therapy.¹² However, infants enrolled in these trials did not consistently receive early CPAP, an alternative therapy for the maintenance of functional residual capacity. Furthermore, control infants were intubated and mechanically ventilated without exogenous surfactant.

The INSURE strategy also resulted in fewer air leaks and shorter duration of ventilation when compared with later selective surfactant administration with continued ventilation. However, oxygen need and survival at 36 weeks' postmenstrual age or longer-term outcomes were not assessed in these trials.¹³ It is also worth noting that the INSURE studies did not consistently use early CPAP in the control group. In fact, a recent large trial not included in this meta-analysis did not show a benefit of the INSURE strategy when compared with early CPAP.⁷ The INSURE strategy may be more efficacious if an infant can be rapidly extubated. Studies in baboons have demonstrated an increase in the severity of pulmonary injury when extubation to CPAP is delayed, thus reducing the benefits of surfactant administration.¹⁴ Decisions on extubation may have to be individualized, because some critically ill infants may not benefit from rapid extubation. Further research is needed to test the potential benefits of the INSURE strategy on important long-term outcomes. However, rapid extubation after surfactant administration may not be achievable or desirable in the most immature infants, and decisions to extubate should be individualized.

CPAP can be delivered by several noninvasive techniques such as nasal prongs, nasopharyngeal tube, or mask by using a water-bubbling system (bubble CPAP) or a ventilator. Although physician preference for bubble or ventilator CPAP is common, physiologic and clinical studies have been inconclusive. It is feasible to provide noninvasive nasal CPAP starting in the delivery room, even in extremely preterm infants (24–27 weeks' gestation), but the most immature infants had the highest risk of failure.⁶ Noninvasive modes of ventilation, such as nasal intermittent ventilation, do not

appear to provide further benefits compared with CPAP.¹⁵

RANDOMIZED CONTROLLED TRIALS OF NASAL CPAP STARTING AT BIRTH

Recently published large, multicenter randomized controlled trials of prophylactic or early CPAP have enrolled very immature infants, a group that, in previous trials, benefited from surfactant treatment. The COIN (CPAP or INTubation) Trial of the Australasian Trial Network compared the effectiveness of nasal CPAP (8 cm of water pressure) to intubation and mechanical ventilation in preterm infants who were breathing spontaneously at 5 minutes after birth.⁴ There was a trend for a lower rate of death or BPD in infants who received CPAP and used fewer corticosteroids postnatally. The mean duration of ventilation was shorter in the CPAP group (3 days in the CPAP group and 4 days in the ventilator group). However, the CPAP group had a higher rate of pneumothorax than the ventilator group (9% vs 3%; $P < .001$). Although surfactant therapy was not required for intubated infants, three-quarters of the intubation cohort received surfactant. Similarly, 46% of infants in the CPAP group required ventilator support, and 50% received surfactant. Therefore, the comparison was between early CPAP (with 50% of infants ultimately receiving surfactant) and intubation and ventilation, mostly but not always with surfactant administration.

The largest CPAP trial ($N = 1310$), the Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the *Eunice Kennedy Shriver* National Institutes of Health and Human Development Neonatal Research Network investigators, was designed to evaluate nasal CPAP started immediately after birth by

using a limited-ventilation strategy compared with prophylactic surfactant therapy and ventilator support started within 60 minutes after birth by using a limited ventilation strategy in infants born at 24 to 27 weeks' gestation.⁵ This trial used prospectively defined criteria for intubation and extubation. The rate of death or BPD in the CPAP group was 48% compared with 51% in the surfactant group (relative risk [RR]: 0.91; 95% confidence interval [CI]: 0.83–1.01; $P = .07$). Among infants born at 24 and 25 weeks' gestation, the death rate was lower in the CPAP group than in the surfactant group (20% vs 29%; RR: 0.68; 95% CI: 0.5–0.92; $P = .01$). Two-thirds of the infants in the CPAP group ultimately received surfactant. In addition, duration of mechanical ventilation was shorter (25 vs 28 days), and use of postnatal corticosteroid therapy was reduced in the CPAP group (7% vs 13%). The rate of air leaks did not differ between the groups, and there were no adverse effects of the CPAP strategy despite a reduction in the use of surfactant. This trial demonstrated that nasal CPAP started immediately after birth is an effective and safe alternative to prophylactic or early surfactant administration and may be superior. A follow-up study at 18 to 22 months' corrected age showed that death or neurodevelopmental impairment occurred in 28% of the infants in the CPAP group compared with 30% of those in the surfactant/ventilation group (RR: 0.93; 95% CI: 0.78–1.10; $P = .38$).¹⁶ CPAP and the limited-ventilation strategy, rather than intubation and surfactant, resulted in less respiratory morbidity by 18 to 22 months' corrected age.¹⁷

The Vermont Oxford Network Delivery Room Management Trial randomly assigned infants born at 26 to 29 weeks' gestation to 1 of 3 treatment groups: prophylactic surfactant and

continued ventilation, prophylactic surfactant and extubation to CPAP, or CPAP (without surfactant).⁷ There were no statistically significant differences between the 3 groups, but when compared with the prophylactic surfactant group, the RR of BPD or death was 0.83 (95% CI: 0.64–1.09) for the CPAP group and 0.78 (95% CI: 0.59–1.03) for the INSURE group.

Other trials have compared early CPAP with prophylactic or early surfactant administration. The CURPAP² and Colombian Network³ trials did not demonstrate a difference in the rate of BPD between the 2 treatment strategies. Moreover, in the Colombian Network trial,³ infants randomly assigned to prophylactic CPAP had a higher risk of pneumothorax (9%) than infants randomly assigned to INSURE (2%). Infants in the South American Neocosur Network trial were randomly assigned to early CPAP (with rescue using an INSURE strategy) or oxygen hood (with rescue using mechanical ventilation).⁸ The early CPAP strategy (and selective of INSURE, if needed) reduced the need for mechanical ventilation and surfactant.

Standard but diverse CPAP systems have been used in these and other large randomized controlled trials reviewed, including bubble CPAP and ventilator CPAP. A detailed description of the practical aspects of using CPAP systems are beyond the scope of this statement but are available in the published literature.^{18,19}

Preterm infants are frequently born precipitously in hospitals without the capability of CPAP. CPAP can be provided with a bag and mask or other comparable devices in these circumstances. However, special expertise is necessary because CPAP may not be easy to use without specific training. Safe transport before delivery may be preferable depending on clinical circumstances.

Thus, care should be individualized on the basis of the capabilities of health workers in addition to the patient's condition.

A meta-analysis of prophylactic surfactant versus prophylactic stabilization with CPAP and subsequent selective surfactant administration in preterm infants showed that prophylactic administration of surfactant compared with stabilization with CPAP and selective surfactant administration was associated with a higher risk of death or BPD (RR: 1.12; 95% CI: 1.02–1.24; $P < .05$).¹¹ The previously reported benefits of prophylactic surfactant could no longer be demonstrated.

It is notable that infants as immature as 24 weeks' gestational age were enrolled in many of the trials. In a subgroup analysis in the SUPPORT trial, the most immature infants (born at 24 and 25 weeks' gestation) benefited the most from the CPAP strategy. Many extremely preterm infants can be managed with CPAP only; early application of nasal CPAP (without surfactant administration) was successful in 50% of infants weighing ≤ 750 g at birth in 1 retrospective review.²⁰

Surfactant administration can be expensive, particularly in low-resource settings. Additionally, intubation and mechanical ventilation may not be possible or desirable in institutions with limited resources. CPAP provides an alternative for early respiratory support in resource-limited settings. Emerging evidence indicates that early CPAP is an effective strategy for respiratory support in extremely preterm infants, including very immature infants. CPAP appears to be at least as safe and effective as early surfactant therapy with mechanical ventilation.⁹

CONCLUSIONS

1. Based on a meta-analysis of prophylactic surfactant versus CPAP

as well as on other trials of more selective early use of surfactant versus CPAP not included in the meta-analysis, the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy (Level of Evidence: 1).

2. Preterm infants treated with early CPAP alone are not at increased risk of adverse outcomes if treatment with surfactant is delayed or not given (Level of Evidence: 1).
3. Early initiation of CPAP may lead to a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy (Level of Evidence: 1).
4. Infants with RDS may vary markedly in the severity of the respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care. Care for these infants is provided in a variety of care settings, and thus the capabilities of the health care team need to be considered.

RECOMMENDATION

1. Using CPAP immediately after birth with subsequent selective surfactant administration may be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Level of Evidence: 1, Strong Recommendation).²¹ If it is likely that respiratory support with a ventilator will be needed, early administration of surfactant followed by rapid extubation is preferable to prolonged ventilation (Level of Evidence: 1, Strong Recommendation).²¹

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