

## REVIEW ARTICLE

## RDS – CPAP or surfactant or both

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**Keywords**

Continuous positive airway pressure, newborn, pulmonary surfactant, respiratory distress syndrome

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DOI:10.1111/j.1651-2227.2011.02543.x

**ABSTRACT**

There is mounting evidence that early continuous positive airway pressure (CPAP) from birth is feasible and safe even in very preterm infants. However, many infants will develop respiratory distress syndrome (RDS) and require surfactant treatment. Combining a non-invasive ventilation approach with a strategy for surfactant administration is important, but questions remain about the optimal timing, mode of delivery and the value of predictive tests for surfactant deficiency.

**Conclusion:** Early CPAP in very preterm infants is as safe as routine intubation in the delivery room. However, a strategy for surfactant administration should be part of a non-invasive ventilation approach for those infants at risk of developing significant RDS.'

**INTRODUCTION**

Deficiency of pulmonary surfactant is one of the most important factors contributing to the development of respiratory distress syndrome (RDS) (1). In immature lungs, the elevated surface tension resulting from surfactant deficiency leads to alveolar collapse at the end of expiration, atelectasis, uneven inflation and regional alveolar overdistension. If untreated, this will result in epithelial injury and pulmonary

oedema which further interfere with surfactant function, producing the clinical picture of RDS. Superimposed lung injury from mechanical ventilation and high concentrations of inspired oxygen trigger the release of pro-inflammatory cytokines, which further impair surfactant function and predispose to the development bronchopulmonary dysplasia (BPD) (2).

The introduction of surfactant replacement treatment significantly reduced mortality in infants with RDS (3), and in the United States, surfactant was identified as the single most important factor for the decrease in overall neonatal mortality rate in the early 1990s (4). Despite the effectiveness of surfactant treatment in the acute phase of RDS, BPD remains an important adverse outcome in preterm infants and its incidence has been correlated with use of mechanical ventilation (5).

Continuous positive airway pressure (CPAP) is a non-invasive respiratory support option and a means to avoid harmful effects of positive pressure ventilation. Infants with mild RDS can often be managed on CPAP alone, without exogenous surfactant treatment (6,7). Extremely preterm infants are at risk of severe RDS, and their immature lungs are highly vulnerable to ventilator

**Key notes**

- A non-invasive ventilation strategy with CPAP from birth has similar outcome as routine intubation in the delivery room.
- Prophylactic surfactant treatment has no advantage over early continuous positive airway pressure (CPAP) with selective surfactant administration.
- Surfactant can be safely administered during CPAP with the INSURE approach.
- Predictive tests for surfactant deficiency are under way and might in the future aid in directing surfactant treatment to infants at risk of developing severe RDS.

induced injury. The European guidelines for treatment of RDS recommend intubation and prophylactic surfactant within 15 min from birth to all infants below 26 weeks of gestation (8), but with the use of early CPAP stabilization in the DR, the optimal timing and delivery mode of surfactant treatment remain uncertain. This review will focus on the evidence base for non-invasive respiratory support in combination with surfactant treatment in RDS.

### **SURFACTANT IN THE DELIVERY ROOM OR LATER?**

Timing of surfactant treatment is defined as prophylactic when administered in the DR, usually within 15 min from birth. To protect the immature, surfactant-deficient lung from injury and facilitate establishment of functional residual capacity (FRC), it might be desirable to give surfactant prior to the first breath, however that is rarely feasible in clinical practice. The term rescue administration is used to describe later, selective surfactant treatment to infants with progressive signs of RDS; however, the criteria for selective surfactant treatment vary a lot between studies. When the aim is to avoid intubation in the DR by stabilizing spontaneously breathing infants on CPAP, some will be able to continue on CPAP alone, but many extremely preterm infants will still need surfactant and the question might rather be how early is early enough?

The Cochrane review of prophylactic (within 15 min from birth) versus selective (in established clinical RDS 6–24 h from birth) surfactant use includes eight studies, all performed between 1991 and 1997, and shows that in infants <30 weeks prophylactic surfactant significantly reduce the risk of mortality (RR 0.62), the combined outcome of mortality and BPD (RR 0.78) (9). However, antenatal steroid use was not reported in two studies, and the overall use was 14–50%. This should be kept in mind as antenatal steroids will reduce the severity of RDS, and it is therefore unclear whether these results hold true today in a setting of high antenatal steroid use.

In reviewing early versus delayed selective surfactant treatment, four studies performed between 1992 and 1998 are included in the Cochrane database (10). Early surfactant treatment was defined as within 2 h from birth, and the timing for selective treatment varies between studies (3–18 h). The results showed reduced risk of air leaks (RR 0.70), mortality (RR 0.77) and BPD (RR 0.70) with early surfactant. Again, the data are difficult to apply on current care practice as immediate postnatal CPAP was not generally practised, antenatal steroid use was low or information was lacking and two studies used synthetic surfactant, which we know is inferior to natural.

For the extremely preterm infants below 27 weeks of gestation, the rates of intubation in the DR remain high, reflecting a need for initial resuscitation, an intention to give surfactant prophylactically or a care practice of DR intubation irrespective of the infant's status. In the Vermont Oxford Network, 81% of infants with birth weight below 750 g were intubated in the DR and in Sweden, with a very

strong CPAP tradition, 61% in a national 3-year cohort of infants with a gestational age below 27 weeks were subjected to DR intubation (11). Recent randomized trials, COIN and SUPPORT (12,13), show that with early CPAP, stabilization without intubation in the DR is feasible, but CPAP failure is frequent, particularly in the most immature infant <26 weeks where 46–83% required later intubation. Both trials had a design with late rescue surfactant treatment in the CPAP groups, at FiO<sub>2</sub> levels of 0.6 and 0.5, respectively. There are no good predictors of early CPAP failure, but selective surfactant treatment at lower threshold of inspired oxygen appears to be beneficial and does not increase intubation rate compared to higher thresholds (14).

### **EARLY CPAP OR MECHANICAL VENTILATION?**

Providing positive end expiratory pressure, as with CPAP, will help stabilize the lung, reduce airway resistance and increase functional residual capacity, which may prevent lung injury and RDS development even in surfactant-deficient lungs (15). This is illustrated by the fact that in preterm lambs receiving CPAP from birth, an endogenous surfactant pool of 4 mg/kg (compared to the estimated surfactant pool size of 100 mg/kg in full term infants) was sufficient to prevent severe respiratory failure (16). Mechanical ventilation of the surfactant-deficient lung on the other hand will rapidly result in lung injury and trigger the release of pro-inflammatory cytokines, which further impairs surfactant function and may predispose to the development of chronic lung injury (2). Animal data suggest that CPAP elicits an attenuated inflammatory response and less morphologic lung injury compared to mechanical ventilation (17).

In addition, respiratory distress in preterm infants is associated with delayed absorption of foetal lung water owing to defective sodium transport mechanism (18). CPAP enhances lung expansion and fluid clearance, and if applied early, CPAP will aid in the transition phase and improve oxygenation (19). It is the positive end expiratory pressure that will help form and maintain FRC. Starting CPAP immediately after birth in spontaneously breathing extremely preterm infants is crucial because the non-compliant lung will otherwise collapse and positive pressure is more likely to be required to open the lung with the subsequent risk of injuring the lung. Hence at birth, before established FRC, is probably the least safe time to use positive pressure ventilation in preterm infants.

This is reflected in several surveys of centres showing that a practice of early CPAP is linked to a favourable outcome and the rates of MV strongly are associated with pulmonary morbidity and BPD (5,20,21).

### **Randomized trials of early CPAP**

Three recent randomized trials address the issue of early CPAP or delivery room intubation.

1. The CPAP or Intubation at Birth (COIN) trial enrolled 610 preterm infants born at 25 and 0/7 to 28 and 6/7 weeks

and randomized spontaneously breathing infants at 5 min of age to either CPAP alone or intubation and MV (12). Infants were mask-ventilated for the first minutes of life if needed and CPAP pressure was set to 8 cm H<sub>2</sub>O, which is in the highest usual range. Intubation criteria in the CPAP group were severe apnoea, acidosis or oxygen requirement of >60%. Surprisingly, there was no protocol for surfactant treatment, which was administered according to local guidelines. In the CPAP group, 46% required intubation during the first 5 days.

At 28-day gestation, the unadjusted odds ratio for death or BPD was in favour of the CPAP group, but the primary outcome of death or BPD at 36-week gestation did not differ between the groups. The secondary outcomes revealed less days intubated and in need of MV in the CPAP group, and fewer infants in the CPAP group received surfactant (38% vs. 77%,  $p < 0.001$ ). Moreover, the CPAP group exhibited a significantly higher rate of pneumothorax (9.1% vs. 3.0%,  $p < 0.001$ ). The high CPAP pressure, the low use of surfactant and the late timing of surfactant treatment are factors likely to have contributed to the high incidence of air leaks. When early rescue surfactant treatment at FiO<sub>2</sub> 0.4 was used in a retrospective report from the Netherlands regarding change of care practices from elective DR intubation to early CPAP, the incidence of pneumothorax was instead lower in the CPAP group (22).

2. The Surfactant Positive Pressure and Oxygen Randomized Trial (SUPPORT) enrolled 1316 infants born at 24 and 0/7–27 and 6/7 weeks and randomized to DR CPAP 5 cm H<sub>2</sub>O or DR intubation with surfactant treatment within 1 h (13). Intubation criteria for the CPAP group were hemodynamic instability, acidosis or oxygen requirements of >50% to reach O<sub>2</sub> saturations of >88%. All infants in the CPAP group who were intubated within the first 48 h received surfactant.

In the CPAP group, 67% received surfactant and 83% were intubated for any reason. Rates of death or BPD were similar for the two strategies (48% in the CPAP group vs. 51% in the intubation/surfactant group, RR0.95). CPAP infants had fewer days on MV, had less use of postnatal corticosteroids for BPD and were more likely to be alive and off MV by day 7 of life ( $p = 0.01$ ).

3. The CURPAP trial aimed to evaluate the efficacy of combining prophylactic surfactant and early nasal CPAP in very preterm infants and enrolled 208 infants born at 25 and 0/7–28 and 6/7 weeks (23). Infants were managed with CPAP from birth and randomized at 30 min of age to either prophylactic surfactant followed by immediate extubation back to CPAP or CPAP alone. In the latter group, surfactant was administered as early rescue if oxygen requirements were >40% to maintain saturations of 85–92%. The need for MV in the first 5 days of life was similar in both groups (31.4% vs. 33.0%). Mortality, BPD and the incidence of air leaks did not differ.

The trials do not provide substantial evidence of superiority but clearly show that early CPAP is as efficient in the DR as routine intubation in extremely preterm infants. In addition, they indicate no advantage of prophylactic

surfactant but suggest early rescue surfactant is important. Yet another recent randomized trial from Columbia addresses that issue and shows that in slightly more mature infants, 27 and 0/7–31 and 6/7 weeks, on early CPAP after birth randomized to either surfactant followed by immediate extubation to CPAP within the first hour or continued CPAP alone, the need for MV, as well as the incidence of air leaks, was significantly reduced in the early surfactant group and there was a trend towards a lower incidence of BPD (24).

The Vermont Oxford Network reports that in comparing DR intubation with prophylactic surfactant and continued MV to DR intubation with rapid extubation to CPAP and early CPAP with rescue surfactant when FiO<sub>2</sub> exceeded 0.6, the outcome was similar, but approximately half of the early CPAP infants required MV and received late rescue surfactant treatment, suggesting both that with early CPAP intubation can be avoided in many infants and that early identification of those infants that will need surfactant remains elusive (25).

### SURFACTANT TREATMENT DURING CPAP?

To date, surfactant needs to be administered as a tracheal instillation to be effective. This poses a dilemma in a non-invasive ventilator approach as intubation is generally needed for surfactant administration. Some different strategies for surfactant treatment during CPAP are available. The Scandinavian model, the so-called INSURE (INTubation SURfactant Extubation) procedure, has now been used for almost two decades and has proven to reduce the need for MV (24,26–30).

INSURE in spontaneously breathing infants was first reported by a Swedish neonatologist working in Kuwait (31) and then further developed in conjunction with CPAP in Denmark, resulting in the first randomized controlled trial in 1994 (26). In this study, 68 infants with a gestational age 25–35 weeks and moderate-to-severe RDS were randomly assigned to either nCPAP and surfactant or nCPAP alone at an oxygenation index (a/A ratio of 0.22) corresponding to FiO<sub>2</sub> 0.4 approximately. The results showed that a single dose of surfactant reduced the need for mechanical ventilation by half, from 85 to 43%. The effect was even more pronounced if surfactant was given as early rescue treatment, at FiO<sub>2</sub> 0.3–0.35 (a/A ratio 0.35), which was reported in a subsequent randomized study of 60 infants with gestational age <30 weeks (27). Several studies have followed, all confirming a significantly reduced need for MV with the INSURE strategy, both compared to CPAP alone and to primary intubation and surfactant (24,28–30). Although a second surfactant dose is more seldom needed after INSURE compared to surfactant followed by mechanical ventilation (28,29), the overall use of surfactant increased in Stockholm in the 5-year period after the introduction of INSURE compared to the 5-year period before (from 42 to 65% in infants with RDS, 27–34 weeks of gestation) (28). This is consistent with the Cochrane meta-analysis comparing early surfactant administration with

brief mechanical ventilation to later, selective surfactant treatment followed by continued mechanical ventilation (32) that also shows significantly reduced rates of BPD and less air leaks after early surfactant and rapid extubation within 1 h, which is even further pronounced in a sub-analysis using a low threshold for surfactant treatment of  $\text{FiO}_2 < 0.45$ . The INSURE procedure is a means to provide surfactant for a selected population of surfactant-deficient infants. Making surfactant treatment available to more infants is thereby to be regarded as a desirable effect associated with INSURE, and the major factor for reducing in MV rates.

An alternative to the INSURE procedure is to treat spontaneously breathing infants on CPAP with surfactant by inserting a thin catheter into the trachea. The technique is labelled minimally invasive and generally performed without analgesia, but it still requires direct laryngoscopy. It is reported to be well tolerated in extremely preterm infants (33,34), but more difficult in infants with more advanced gestational age, >28 weeks (35). This is in contrast to INSURE for which a birth weight <750 g has been identified as an independent risk factor for failure (36). However, in the recently published randomized multicenter trial of infants with gestational age between 26 and 28 weeks, it was shown that the first attempt of surfactant replacement with the catheter technique was unsuccessful in only 5% of the cases and that the approach significantly reduced the need for mechanical ventilation (37), hence it has been proven to be an alternative to the INSURE strategy.

#### CAN WE PREDICT WHO WILL NEED SURFACTANT?

To allow for early and correct surfactant treatment of infants at risk, a test for lung maturity predicting the development of severe BPD would be helpful. Lamellar body count (LBC) in gastric aspirate obtained close to birth is such a test that has recently been reported to be a promising tool (37,38). It is based on the presence of lamellar bodies, a storage form of surfactant, in amniotic fluid and the fact that lamellar bodies are of the same size as platelets. Samples can easily be run in an automatic blood counter to yield a LBC within minutes. Moderate-to-severe RDS can be predicted by LBC with a sensitivity and specificity of 73–92% depending on the choice of cut-off value. Before implemented in clinical routine, the usefulness of LBC has to be proven in larger clinical studies. A randomized trial is under way in which LBC is used to guide selective surfactant administration in preterm infants.

#### CONCLUSION

Current evidence indicates that a strategy of early CPAP in very preterm infants is as safe as routine intubation in the DR. There appears to be no serious side effects and a tendency towards improved outcome, at least in the short term. Prophylactic surfactant no longer gives any clear benefits over selective treatment, but surfactant should be given early in the course of RDS and a strategy for surfactant administration is imperative for a practice of early CPAP.

Predicting which infants will fail CPAP and deciding the optimal time and mode for surfactant administration are important future goals.

In a situation of equipoise, the least invasive approach should be chosen. Thus, early CPAP could now be considered as the recommended ventilation support preterm infants, leaving the burden of proving superiority to those still advocating primary intubation.

#### CONFLICTS OF INTEREST

The author has declared no potential conflicts.

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