Surfactant and Noninvasive Ventilation

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Key Words
Pulmonary surfactant · Preterm infants · Respiratory distress syndrome · Continuous positive airway pressure

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 noninvasive ventilation approach with a strategy for surfactant administration is important to ensure optimal outcome, but questions remain about the optimal timing, mode of delivery and value of predictive tests for surfactant deficiency. Key findings in this review include the following: (1) a noninvasive ventilation strategy with CPAP from birth has a similar outcome to routine intubation in the delivery room; (2) prophylactic surfactant treatment has no advantage over early CPAP with selective surfactant administration; (3) surfactant during CPAP can be safely administered by rapid intubation-extubation (the INSURE method or via tracheal placement of a thin catheter), and (4) predictive tests for surfactant deficiency are being developed and might in future aid in directing surfactant treatment to infants at risk of developing severe RDS. A strategy for surfactant administration should be part of a noninvasive ventilation approach for preterm infants at risk of developing significant RDS. The different methods for surfactant administration during CPAP are reviewed here.

Introduction

The preterm lung is usually not injured at birth but can easily be harmed. To promote healthy lung development, research over recent years has focused on identifying respiratory strategies that are as noninvasive and lung protective as possible. A deficiency of pulmonary surfactant is the most important factor contributing to the development of respiratory distress syndrome (RDS) [1] and also makes the lung susceptible to ventilator-induced injury. Despite mounting evidence that a noninvasive ventilation strategy immediately after birth is feasible, many extremely preterm infants will still be intubated in the delivery room (DR) [2]. Intubation is often performed as part of a clinical routine, frequently with the aim of administering surfactant as early as possible rather than reflecting a clear need for assisted ventilation. There is evidence suggesting the opposite – two thirds of a population of extremely preterm infants were recently reported as establishing spontaneous breathing immediately after birth [3]. However, in immature lungs the surfactant pool size is small [4], leading to elevated surface tension, alveolar collapse at end expiration and increased work of breathing. If untreated, this will result in RDS and respiratory failure. With continuous positive airway pressure (CPAP) the loss of lung volume can be prevented and functional residual capacity established – even a small surfactant pool might be enough to support initial spontaneous breathing [5]. Recent trials have demonstrated that even extremely preterm infants can be safely stabi-
lized on CPAP after delivery and then selectively treated with surfactant for RDS. This initially less invasive care strategy has the advantage of reducing the need for mechanical ventilation (MV) and thereby also the risk of lung injury. Two recent meta-analyses of the available studies show a reduction in the risk of death or broncho-pulmonary dysplasia (BPD) at 36 weeks of postmenstrual age [6, 7].

The European guidelines for the management of RDS currently recommend rescue surfactant as the standard approach and advise that surfactant should be given early in the course of the disease, particularly for the most immature infants below 26 weeks of gestation [8]. However, the optimal timing and method of surfactant administration remain to be determined.

A Short History of Surfactant Research

The story of surfactant research began in 1929 with the publication by the Swiss physiologist Kurt von Neergaard [9] showing that lowering the surface tension of the air-liquid interface stabilizes the alveoli. von Neergaard also stated that surface tension might be of importance for the first breath of a newborn infant. However, this observation remained unpursued for several years. In the late 1940s and 1950s, hyaline membrane disease was recognized as the most common cause of death in preterm infants. The hallmark of the disease, the histological finding of hyaline membranes, was not seen at birth but was formed soon after as a result of atelectasis and lung injury. Peter Gruenwald [10], a pathologist in New York, took the findings of von Neergaard a step further when he first proposed the linkage between elevated surface tension and hyaline membrane formation in 1947. A few years later, the pediatrician Mary Ellen Avery took an interest in lung physiology when she was recovering from tuberculosis, and the work of John Clements caught her eye. Clements et al. [11] had demonstrated that compression of surface films from animal lung extracts lowered surface tension and he was the first to define surface-active material from the lung as ‘surfactant’. Together with her mentor Jere Mead at Harvard University in Boston, Avery set out to investigate autopsy material from infants dying soon after birth and in a seminal publication from 1959 they confirmed that lung extract from preterm infants dying of hyaline membrane disease was unable to lower surface tension and that this was associated with a deficiency of surface-active material [1].

Although the cause of hyaline membrane disease (or respiratory distress syndrome, RDS, as it is called today) was now established, progress in developing a specific treatment was slow. However, in 1963 something happened that came to be of great importance for surfactant research – Patrick Bouvier Kennedy, the son of President John F. Kennedy, was born prematurely and died at 2 days of age from RDS. This increased public awareness of the disease and stimulated research into finding a cure. Soon after the death of Patrick Kennedy, two studies of nebulized synthetic surfactant to treat RDS were published but the results were disappointing [12, 13]. The reason for the lack of effect was discovered during the 1970s by Swedish perinatal pathologist Bengt Robertson, obstetrician Goran Enhörning and, later, clinical chemist Tore Curstedt. They performed the ground-breaking experimental work of surfactant replacement in animal models showing that, with direct tracheal instillation of a natural surfactant preparation containing surfactant proteins, normal lung expansion and survival of the animals could be achieved [14]. This led to the first successful clinical trial of surfactant administration in preterm infants with RDS, which was published in 1980 by Fujiwara et al. [15]. The efficacy and safety of surfactant therapy was then further established by several multicenter trials and proven to dramatically decrease neonatal mortality and serious pulmonary air leak syndromes [16, 17]. In 1990 the American Food and Drug Administration first approved the clinical use of an exogenous surfactant and since then surfactant treatment has become one of the cornerstones in the care of preterm infants with RDS.

A Question of Timing

Surfactant treatment is defined as prophylactic when administered in the DR, usually within 15 min from birth. Theoretically, it would be desirable to give prophylactic surfactant prior to the first breath for optimal protection, although that is rarely feasible in clinical practice. The term rescue or selective administration is used to describe later surfactant treatment to infants with progressive signs of RDS. However, the criteria for selective surfactant treatment vary a lot between studies. Recently, a Cochrane review of prophylactic versus selective use of surfactant has been updated [18]. The meta-analysis now includes a comparison of earlier studies conducted prior to the routine application of CPAP and more recent large trials, reflecting the current practice of greater antenatal steroid use and DR stabilization on CPAP. While the ear-
lier studies demonstrated a decreased risk of air leaks and neonatal morbidity with prophylactic surfactant, this is no longer supported by the more recent trials. Furthermore, the subgroup analysis of studies with routine application of CPAP showed that the risk of chronic lung disease or death was lower in those stabilized on CPAP and given selective surfactant treatment if needed compared to prophylactic treatment. This implies that routine prophylactic surfactant can no longer be recommended as it does not improve clinical outcome and may even lead to an increased risk of lung injury in comparison to an approach of early stabilization on CPAP.

If DR intubation can be avoided and the infant stabilized on CPAP, some will be able to continue on CPAP alone but many, particularly the most extremely preterm infants, will still develop progressive respiratory distress and need surfactant. Hence, with regard to the timing of surfactant treatment, maybe we should be asking ourselves – how early is early enough? This question has not been fully addressed to date in randomized controlled trials (RCTs). Instead, the issue of DR management and surfactant administration has been approached from slightly different angles. The following three trials compared primary DR intubation followed by MV to primary CPAP treatment: (1) the COIN trial (CPAP or Intubation at birth) [19], (2) the SUPPORT trial (Surfactant Positive Pressure and Oxygen Randomized Trial) [20] and (3) the VON DRM trial (Vermont Oxford Network Delivery Room Management) [21]. None of these studies had specific criteria for surfactant administration for infants in the CPAP arm, but the CPAP failure criteria, and thereby also the intubation criteria, often, but not always, coincided with surfactant being administered (table 1). The indications for surfactant treatment in the comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestational age of infants, weeks</th>
<th>CPAP arm, n</th>
<th>Criteria for intubation</th>
<th>Criteria for surfactant treatment</th>
<th>Infants intubated in CPAP arm</th>
<th>Infants treated with surfactant in CPAP arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>COIN</td>
<td>25–28</td>
<td>307</td>
<td>FiO₂ &gt;0.60</td>
<td>Local guidelines</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>SUPPORT</td>
<td>24–27</td>
<td>663</td>
<td>Hemodynamic instability, acidosis or FiO₂ &gt;0.50</td>
<td>When intubated surfactant given if age &lt;48 h</td>
<td>83%</td>
<td>67%</td>
</tr>
<tr>
<td>VON DRM</td>
<td>26–29</td>
<td>223</td>
<td>Repeated apneas, hypercapnia &gt;65 mm Hg, FiO₂ &gt;0.40 discretionary/≥0.60 mandatory</td>
<td>When intubated surfactant given if supplemental oxygen required</td>
<td>45%</td>
<td>45%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestational age of infants, weeks</th>
<th>CPAP arm, n</th>
<th>CPAP + surfactant, n</th>
<th>Criteria for failure</th>
<th>Treatment when failure of CPAP arm</th>
<th>Criteria to start MV</th>
<th>MV rate (CPAP vs. CPAP + surfactant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VON DRM</td>
<td>26–29</td>
<td>223</td>
<td>219</td>
<td>≥12 apneas/6 h or &gt;1 apnea/6 h requiring ventilation, hypercapnia &gt;65 mm Hg, FiO₂ &gt;0.40 discretionary/≥0.60 mandatory</td>
<td>Intubation and mechanical ventilation; surfactant if supplemental oxygen</td>
<td>Same as criteria for failure regardless of which arm</td>
<td>52 vs. 59%</td>
</tr>
<tr>
<td>CNRN</td>
<td>27–31</td>
<td>138</td>
<td>141</td>
<td>FiO₂ &gt;0.75, desaturation not responding to suctioning + PPV, hypercapnia &gt;65 mm Hg/pH &lt;7.22</td>
<td>Intubation followed by MV in both arms; surfactant given up to a maximum of 4 doses before 72 h of age</td>
<td>Same as criteria for failure regardless of which arm</td>
<td>39 vs. 26%</td>
</tr>
<tr>
<td>CURPAP</td>
<td>25–28</td>
<td>103</td>
<td>105</td>
<td>FiO₂ &gt;0.40, &gt;4 apneas/h or &gt;2 apneas/h if requiring ventilation, hypercapnia 65 mm Hg, pH &lt;7.2</td>
<td>Surfactant given followed by rapid extubation (INSURE)</td>
<td>Same as criteria for failure; in CPAP arm after 1 dose of surfactant during brief intubation</td>
<td>33 vs. 31%</td>
</tr>
</tbody>
</table>
group of infants randomized to MV differed between the trials – from prophylactic in the VON DRM trial to within 1 h from birth in the SUPPORT trial and unspecified in the COIN trial.

Two other trials, together with the VON DRM trial, compared a strategy of primary CPAP versus prophylactic or very early surfactant treatment followed by rapid extubation to CPAP: (4) the CNRN trial (Columbian Neonatal Research Network) [22] and (5) the CURPAP trial [23] (table 2). In the CURPAP trial it was also specified that the infants in the primary CPAP group were to receive surfactant followed by rapid extubation if meeting CPAP failure criteria, making CURPAP the only study to date attempting to evaluate the timing of surfactant treatment during noninvasive ventilation. Simplified, this could be described as a comparison of prophylactic versus selective INSURE (Intubation-Surfactant-Extubation).

None of the individual studies has been able to show any differences in terms of primary outcomes, mortality and/or BPD. For secondary outcomes, primary CPAP compared to DR intubation resulted in fewer days on MV in both the COIN and SUPPORT trials, regardless of the fact that between 46 and 83% of these infants required intubation at some point (table 1). A concern in the COIN trial was the significantly higher incidence of air leaks in the CPAP group and the late timing of surfactant treatment for many of these extremely preterm, and probably surfactant-deficient, infants may have contributed. When early rescue surfactant treatment at a fraction of inspired oxygen (FiO₂) of 0.40 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 lower in the CPAP group [24]. Of the studies including infants receiving prophylactic or very early surfactant treatment followed by rapid extubation, only one, the CNRN trial, showed a reduction in MV rates, reduced air leaks and a trend toward less BPD. However, it must be kept in mind that in this study the strategy for intubation and surfactant treatment in the comparison group with primary CPAP alone would be considered as very late rescue – at FiO₂ reaching 0.75. Neither the CURPAP trial nor the VON DRM trial were able to demonstrate any significant differences among groups. In summary, all of these studies show that intubation can be avoided by primary CPAP in about half of the cases and that rescue surfactant is just as good as prophylactic or very early surfactant administration followed by rapid extubation, as long as one does not wait too long.

To further evaluate the effects of trying to avoid endotracheal intubation and MV in preterm infants, two systematic reviews have recently been published. The meta-analyses compared noninvasive respiratory support to routine intubation at birth and the effect on the need for supplemental oxygen at 36 weeks of postmenstrual age. The meta-analysis performed by Schmölzer et al. [6] included three of the above-mentioned studies (COIN, VON DRM and CURPAP) – a total of 2,782 infants – and found a significant reduction in the combined incidence of BPD or death (relative risk 0.91; 95% CI 0.84–0.99) and a number needed to treat of 25. In addition to the five studies reviewed here, the meta-analysis conducted by Fischer and Bührer [7] also included two recent RCTs of surfactant treatment with a thin catheter technique and in the 3,289 infants studied they found a similar reduction in the risk of death or BPD, with an odds ratio of 0.83 (95% CI 0.71–0.96) and a number needed to treat of 35.

A Question of Tube or Catheter

A dilemma in a noninvasive ventilator approach is that intubation is generally needed for surfactant administration. Some different strategies for surfactant treatment during CPAP are available. The Scandinavian model, the so-called INSURE procedure, has now been used for more than two decades and has proven effective in reducing the need for MV [22, 25–29].

The INSURE procedure for spontaneously breathing infants was first reported by a Swedish neonatologist working in Kuwait [30] and then further developed in conjunction with CPAP in Denmark, resulting in the first RCT in 1994 [25]. In this study 68 infants with a gestational age of 25–35 weeks and moderate-to-severe RDS were randomly assigned to either nasal CPAP and surfactant or nasal CPAP alone at an oxygenation index corresponding to approximately FiO₂ of 0.40. A single dose of surfactant reduced the need for MV by half – from 85 to 43%. The effect was even more pronounced if surfactant was given as early rescue treatment, at FiO₂ of 0.30–0.35, which was reported in a subsequent randomized study of 60 infants with a gestational age of <30 weeks [26]. 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 [22, 27–29]. Although a second surfactant dose is less frequently needed after INSURE compared to surfactant followed by MV [27, 28], the overall use of surfactant increased in Stockholm in the 5-year period after the introduction of INSURE compared to the 5-year period previously (from 42 to 65% in infants of 27–34 weeks of...
gestation with RDS) [27]. This is consistent with the Cochrane meta-analysis comparing early surfactant administration with brief MV to later, selective surfactant treatment followed by continued MV [31]. The meta-analysis showed significantly reduced rates of BPD and fewer air leaks after early surfactant and rapid extubation within 1 h of treatment, a result that was even more pronounced in a sub-analysis using a low threshold for surfactant treatment of FiO$_2$ <0.45. The INSURE procedure is a method of providing 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 MV rates.

The INSURE method inevitably requires positive pressure ventilation, even if only for a brief period. Concern has been raised that this might induce injury to the immature and fragile lung of the extremely preterm surfactant-deficient infant. An alternative to INSURE has therefore been developed with the aim of treating spontaneously breathing infants on CPAP with surfactant after inserting a thin feeding catheter into the trachea under direct laryngoscopy. First reported by the German group led by Angela Kribs [32], the method called LISA (Less Invasive Surfactant Treatment) was studied in a multicenter RCT, the AMV trial (Avoid Mechanical Ventilation) [33]. The LISA method is reported to be well tolerated in extremely preterm infants but less easy to perform in more mature infants of ≥29 weeks [34]. This is in contrast to INSURE, for which a birth weight <750 g has been identified as an independent risk factor for failure [35]. However, in the recently published randomized multicenter trial of infants with a gestational age between 26 and 28 weeks the first attempt at surfactant replacement with the catheter technique was unsuccessful in only 5% of the cases and the approach significantly reduced the need for MV [33]. Hence, LISA has been shown to be an alternative to the INSURE strategy.

The two methods, INSURE and a slightly modified LISA technique, were compared in the Take Care trial in which 100 infants with a gestational age of <32 weeks were randomized to receive surfactant by one of the two techniques [36]. Despite a strikingly similar need for pressure support and supplemental oxygen in the first 24 h following treatment, the primary outcome, the need for MV during the first 72 h of life, was significantly lower in infants treated by the modified LISA technique. This is a somewhat surprising finding as failure after INSURE due to progressive RDS usually occurs within a fairly short time after treatment. Also, in spite of the rather small number of infants studied and allowance for recruiting infants with gestation of >30 weeks, the authors reported a significant reduction in BPD at a corrected age of 36 weeks in favor of the Take Care technique [36].

Yet another alternative for surfactant administration is the use of a semi-rigid vascular catheter that allows insertion into the trachea without using a Magill forceps. This technique has been named MIST (Minimally Invasive Surfactant Treatment) and was demonstrated to be a promising approach in a feasibility trial [37]. The same group reported a reduction in the need for intubation during the first 3 days in infants of 25–28 weeks of gestation in a recent two-center study [38]. A large multicenter RCT study of the MIST technique (OPTIMIST-A) is currently recruiting patients [39]. To date, only one experimental study has assessed the LISA approach and demonstrated that, in preterm lambs, oxygenation following surfactant administration by the LISA technique was better than CPAP alone and similar to surfactant followed by MV, but that the LISA technique resulted in less homogenous distribution of surfactant and there was a trend towards poorer lung compliance compared to surfactant followed by MV [40]. Further studies, both experimental and clinical, are needed to determine the place for and importance of less invasive methods of surfactant administration, both with regard to the timing of treatment and the ability to reduce the triggering of inflammatory responses by avoiding even short periods of positive pressure ventilation.

**A Question of Whom to Treat**

As outlined above, with early CPAP, intubation can be avoided in more than half of the infants at risk. Therefore, early assessment of lung maturity and identification of those infants that will go on to require surfactant might allow this approach to be even more effective.

Lamellar body count (LBC) in gastric aspirate obtained close to birth is a test for lung maturity that has recently been reported to be a promising tool [41, 42]. It is based on the presence of lamellar bodies, a storage form of surfactant, in amniotic fluid and the fact that lamellar bodies are similar in size to platelets. Samples can easily be run in an automatic blood counter to yield an 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 cutoff value. Before implemented in clinical routine, the usefulness of LBC has to be proven in larger clinical studies. Another method to

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assess lung maturity is by using a captive bubble surfac
tometer to estimate the surface tension in lung fluid aspi-
rated during resuscitation [43].

**Conclusion**

Current evidence indicates the following:

- Just as safe – a strategy of early CPAP with later rescue surfactant is as safe as routine DR intubation and MV in very preterm infants at risk of RDS.
- You have time – with a strategy of early CPAP, pro-
phyllactic surfactant is not superior to later selective
treatment, indicating that there is room for stabiliza-
tion using noninvasive respiratory support during the
first vulnerable hours of life.
- Plan for surfactant – compared to early CPAP alone,
there is an advantage for the INSURE strategy, irre-
respective of whether treatment is given early or late,
shown mainly in a reduction in the need for MV.
- Prophylactic surfactant no longer gives any clear ben-
efits over selective treatment, but with a practice of early
CPAP a strategy for surfactant administration is impera-
tive and, if needed, surfactant should be given early in the
course of RDS. Predicting which infants will fail CPAP
and the determination of the optimal time and mode for
surfactant administration are important future goals.

**Disclosure Statement**

The authors declare no conflicts of interest.

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