Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

01 May 2010

Preterm infants who received early surfactant treatment needed less mechanical ventilation and were at a lower risk for pulmonary air leak and bronchopulmonary dysplasia, although more surfactant was administered to infants in the early treatment group compared with those in the selective treatment group. The availability of surfactant, infant ventilators, and capacity to deliver nasal continuous positive airway pressure will determine whether this intervention can be applied in under-resourced settings.

RHL Commentary by Leonard DT and Schelonka RL

1. INTRODUCTION

Preterm birth continues to be an important public health problem globally and is a leading cause of perinatal death and disability worldwide. (1, 2) Respiratory distress syndrome (RDS) is the most important contributor of morbidity and mortality in preterm infants, particularly in under-resourced settings that lack neonatal health-care facilities and access to expensive interventions such as surfactant therapy and mechanical ventilation (3). Treatment options for RDS include supplemental oxygen, continuous positive airway pressure (CPAP), mechanical ventilation, and surfactant replacement (2). This review focuses (4) on the timing of surfactant replacement therapy for preterm infants with RDS.

2. METHODS OF THE REVIEW

The Cochrane review team, evaluating early surfactant administration versus the more conventional practice of “selective” surfactant for preterm infants with RDS, searched English-language databases as well as conference proceedings for related clinical trials. “Early surfactant” was defined as surfactant administration followed by rapid extubation (less than 1 hour of mechanical ventilation) to nasal continuous positive airway pressure (NCPAP). “Selective surfactant” was defined as surfactant administration when the infant met predetermined ventilator settings and supplemental oxygen thresholds; mechanical ventilation was continued, and the settings were reduced based on the infant’s response to surfactant and progression of respiratory disease. Infants were extubated when they reached specified, low, ventilator settings and needed little or no further supplemental oxygen support. For inclusion in the review, studies had to be randomized controlled trials with one or more of the following outcome measures: need for mechanical ventilation, bronchopulmonary dysplasia (BPD), death, and other common neonatal morbidities.
3. RESULTS OF THE REVIEW

Six randomized controlled trials involving 664 infants met the inclusion criteria. Two of the trials included newborn infants at a postmenstrual (gestational) age of 25–35 weeks, and the remaining studies had enrolled larger babies with a lower birth-weight cut-off of 1250 or 1500 grams. The infants who had received early surfactant had a lower risk for subsequently receiving mechanical ventilation [relative risk (RR) 0.67; 95% (confidence interval) CI 0.57–0.79], for developing pulmonary air leak (RR 0.52 95%; CI 0.28–0.96] and for developing BPD (RR 0.51; 95% CI 0.26–0.99). More infants in the early surfactant group received surfactant than those in the selective surfactant group (RR 1.62; 95% CI 1.41–1.81). Infants in the early surfactant group also received a greater number of surfactant doses than those in the selective surfactant group (weighted mean difference 0.57 does per patient; 95% CI 0.44–0.69). There was no difference in mortality with either treatment strategy. A stratified analysis was done measuring FiO2 (fraction of inspired oxygen from air) at study entry. A lower treatment threshold of oxygen FiO2 < 0.45 showed a lower risk for pulmonary air leak (RR 0.46; 95% CI 0.23–0.93) and BPD (RR 0.43; 95% CI 0.2–0.92). Surfactant treatment with a higher oxygen FiO2 treatment threshold of >0.45 was associated with increased incidence of patent ductus arteriosus needing treatment (RR 2.15; 95% CI 1.09–4.13).

4. DISCUSSION

4.1 Applicability of the results

Although the combined analysis of the included trials showed that preterm infants who had received early surfactant treatment needed less mechanical ventilation and were at a lower risk for pulmonary air leak and BPD, more surfactant was administered to infants in the early treatment than in the selective treatment group. It is important to note that the trials included in the review were conducted in well-resourced settings where surfactant and ventilators were readily available.

The cost of intensive care for newborn infants is higher the younger the infant in terms of gestational age (5). The availability of surfactant, infant ventilators, and capacity to deliver NCPAP will determine whether this intervention can be applied in an under-resourced setting. In nurseries with moderate but limited resources, it is important to assess the potential cost and benefit of mechanical ventilation versus those of additional surfactant in a context of improved neonatal outcomes. Surfactant is an expensive therapy and surfactant medication needs to be refrigerated at all times prior to administration. Infant ventilators, and the expertise needed to operate them, may also be scarce resources in many settings. In situations where surfactant supplies are limited, and mechanical ventilation is more readily available than surfactant, it may be more prudent to use a selective approach to surfactant replacement. For many nurseries, whether to give early surfactant or to use a selective strategy may be based on which therapeutic approach best utilizes their limited resources.

4.2 Implementation of the intervention

For nurseries with capacity to administer surfactant and provide even brief ventilator support, the bulk of evidence would suggest that early surfactant administration with rapid extubation to NCPAP reduces the need for mechanical ventilation and lowers the risk for important morbidities such as air leak and subsequent development of BPD and may also reduce the incidence of sepsis, which is an important killer in under resourced countries. The key to successful implementation of an early surfactant administration strategy is care of the infant after surfactant is administered – i.e. expert administration of NCPAP. Infants receiving early surfactant therapy require continued close observation as some of them may later need reintubation and mechanical ventilation.

A relatively recent advance in assisted ventilation for infants is “bubble NCPAP” (BCPAP), which has a
number of advantages over other delivery systems. When tested in a resource-limited region of India, BCPAP was shown to be a simple, inexpensive and effective therapy that could be applied by nurses (6). In a head-to-head comparison of BCPAP and ventilator CPAP, BCPAP was found to be a promising method of continuous positive airway pressure delivery for preterm neonates with moderate respiratory distress (7). It has recently been called a potentially better modality for CPAP delivery overall (8).

For nurseries with extremely limited resources – i.e. without the capability to provide mechanical ventilation – the choice of early versus selective surfactant administration would not apply. It is tempting to speculate whether preterm infants with RDS given early surfactant and followed immediately with BCPAP would have improved outcomes. Available randomized controlled trials do not address this question as all of the studies included in the review involved at least a brief period (less than 1 hour) of mechanical ventilation after surfactant administration. Case series from two separate groups in Kuwait and Romania reported the experience of giving surfactant to preterm infants at a time when they had no access to infant ventilators. Collectively, these groups showed that surfactant followed immediately by CPAP improved short-term, mostly physiological outcomes; however, there were insufficient data to comment on improvements in mortality and morbidity associated with such an approach in under-resourced settings (9, 10).

4.3 Implications for research

Previously, a group in Pakistan had examined neonatal care practices in an under-resourced region of the country and found that it was possible to provide successful respiratory support at an average cost per infant of US $1391 (3). In addition, because of ease of use, low cost, and growing availability of BCPAP worldwide, there are many new opportunities for the care of preterm infants with RDS. Carefully designed studies are needed to determine if early surfactant and BCPAP, without mechanical ventilation, reduce mortality without increasing morbidity. Because the availability of exogenous surfactant may limit the feasibility of an early treatment strategy, it is also important to determine which selective surfactant treatment with an immediate return to BCPAP improves outcomes for preterm infants with RDS.

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This document should be cited as: Leonard DT, Schelonka RL. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome: RHL commentary (last revised: 1 May 2010). *The WHO Reproductive Health Library*; Geneva: World Health Organization.

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