Pediatric RESEARCH

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COMMENT

Why, when, and how to give surfactant

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Pediatric Research (2019) 86:15–16; https://doi.org/10.1038/s41390-019-0372-1

Surfactant treatments together with antenatal corticosteroid treatments are uniformly viewed as the most important pharmacological interventions to improve outcomes of preterm infants. Both therapies are old as antenatal corticosteroids became standard of care and was widely used after 1994. Surfactants were first approved by the Food and Drug Administration (FDA) in 1990 and also became standard of care for treating respiratory distress syndrome (RDS). The clinical applications of these old therapies have evolved to be most critical for pregnancies at risk of very preterm deliveries and for the very premature infants. *Pediatric Research* is publishing this month a consensus statement to promote uniform approaches for surfactant treatment in the United Kingdom.[1] This is a thoughtful approach to treatment based on large clinical and research experiences world-wide, but especially in Europe.[2] I have some comments that may help the reader better assess these recommendations and how they may evolve in the future.

The first recommendation that all neonatal units should have an agreed upon policy for the management of RDS and specifically surfactant treatment just makes sense. The quality improvement literature supports that uniformity of care improves outcomes as do protocols for treating asthma, for example.

The consensus recommendation is for initial stabilization of very preterm infants with continuous positive airway pressure (CPAP) rather than with routine intubation and surfactant treatment immediately after delivery. This approach avoids intubation and positive pressure ventilation, which will not be necessary for many infants and can cause early lung injury. The selection of a CPAP strategy over a prophylactic surfactant treatment is supported by randomized controlled trials and meta-analysis.[3] As an aside, I much prefer the wording—treatment to prevent RDS rather than prophylactic treatment. However, the details of how the transition to air breathing can be best accomplished are the subject of ongoing research and remain controversial. Compelling animal-based research demonstrates more rapid lung aeration with CPAP coupled with several long inspiratory breaths or a long sustained inflation of 5–15 s.[4] However, a meta-analysis of clinical experiences found sustained inflation to not be beneficial.[5] A multinational trial using sustained inflation was stopped for increased mortality in the sustained inflation group relative to routine CPAP and ventilation as needed at birth and as recommended by the Neonatal Resuscitation Program. The recent identification of glottic closure after birth that prevents ventilation remains an unsolved problem.[6] A recent study from Tingay and colleagues[7] demonstrated more uniform aeration and less injury using a gradual aeration strategy rather than by sustained inflation. Thus how respiratory transition should best be performed remains to be determined in practice.

The approach of delivery room treatment with surfactant remains a recommendation for very preterm infants who must be intubated for lack of respiratory effort, stabilization, and high oxygen requirements. The recommendation that surfactant always should be available in the delivery suite is cumbersome as the drugs must be kept refrigerated and will be infrequently used except for very high volume delivery services. If the Neonatal Intensive Care Unit is located adjacent to the delivery unit, complete neonatal care and surfactant treatment can be given quickly and efficiently. I certainly support avoidance of intubation at delivery of breathing infants who can transition with CPAP and some low pressure-assisted breaths if needed.

The next recommendation is about the decision of when to treat infants with progression of RDS with rescue surfactant. The assessment of an infant clinically at perhaps 2 h of age for progression of RDS assumes that a diagnosis of RDS can be reliably made. In reality, a distinction between surfactant-deficiency RDS, lung inflammation/infection from chorioamnionitis, some degree of pulmonary hypoglycemia, or other lung problems is seldom made.[8] The goal to prevent CPAP failure with a surfactant treatment assumes that these infants are receiving effective CPAP and that the oxygen requirement is increasing.[9] For the very preterm infant, an oxygen need of >30% in association with a clinical assessment of the breathing effort should trigger a surfactant treatment, a reasonable recommendation. However, what is effective CPAP? The different CPAP devices, patient interfaces, and pressure levels may not perform equivalently. There also are CPAP variants now being used for the management of all stages of RDS that include noninvasive mechanical ventilation and high flow nasal cannula.[10] Some guidance of what is an adequate trial of CPAP would be helpful. However, I suspect that a consensus on what is an adequate trail of CPAP will be contentious. The elements of an adequate CPAP trial will certainly depend on the size, gestational age, and respiratory effort of the infant. I think that all infants who are presumed to have significant RDS should be treated with surfactant—we have a remarkably effective therapy and being a CPAP cowboy simply puts the infant at risk.

The choice of surfactant depends on the options available within each country. Synthetic surfactants are not generally available but continue to be developed and tested.[11] The animal source surfactants are uniformly effective and have stood the test of time. The recommendation by this consensus committee is that poractant at the 200 mg/kg dose may be the best choice for an initial surfactant treatment is reasonable.[1] However, other animal lung source surfactants are effective at lower doses. In low resource care environments where cost is paramount, surfactant dose and choice may differ without much compromise to efficacy. Initial dosing and re-dosing should be based on infant weight as specified for each drug. Infants who do not respond to surfactant

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Received: 15 February 2019 Accepted: 18 February 2019
Published online: 12 March 2019

with improved lung function should be re-evaluated to consider diagnoses other than RDS.

How to treat with surfactant is the hot issue of the day. The only option evaluated during development of surfactants for RDS was intubation, surfactant treatment, and ventilatory support. The option of intubation–surfactant–extubation (INSURE) has been effectively used for many years for surfactant treatments. The goal of the extubation arm of the procedure is to transition the infant quickly back to CPAP when stable, which can be minutes to hours. An advantage of the procedure is control of the airway. Sedation and pain treatment often accompany the procedure and their effect on respiratory effort may delay extubation.[12] With efforts to decrease stress and avoid any mechanical ventilation, variant procedures called less invasive surfactant administration (LISA) and minimally invasive surfactant treatment (MIST) are being evaluated and used in many NICUs.[13] These related approaches require laryngoscopy to place a fine catheter in the trachea with subsequent surfactant treatment while the infant is breathing spontaneously. The MIST procedure includes catheter placement in the trachea while maintaining CPAP. All therapies require laryngoscopy, which likely is the most stressful component of the treatment for the infant. Sedation and pain management also may be used with caution for these techniques that do not include intubation with endotracheal tubes.

Surfactant treatment by intra-tracheal instillation is a high-skill procedure. Comparisons of INSURE, LISA, and MIST may reflect the skills of the operator and the assistance required to optimize the procedures more than the procedures themselves. Their real benefit may result from the emphasis on the patient comfort and procedural consistency. In a recent report, Taylor and colleagues[14] note that the majority of surfactant treatments are off-label from the package inserts approved by the FDA and other regulatory agencies. Surfactant were approved for delivery room treatment of intubated infants at risk of RDS or intubated and ventilated infants with RDS in the 1990s. The requirements for studies for the FDA to relabel for treatment procedures for surfactants are unrealistic. Approaches to non-invasive support that avoids intubation and positive pressure ventilation represent progress in the efforts to improve treatment procedures.

ADDITIONAL INFORMATION

Competing interests: I have no conflict of interest relevant to the content of the clinical use of surfactant. Chiesi has supported a grant for sheep model research on steroids and surfactant performed in Western Australia.

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