Surfactant Replacement Therapy in Extremely Low Gestational Age Newborns

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There is a growing body of evidence over the last years suggesting continuous positive airway pressure (CPAP) ventilation being the first choice of ventilatory support in newborns with extremely low gestational age, and early rescue surfactant treatment being as effective as prophylactic therapy. The Intubation Surfactant Extubation procedure is discussed as an alternative procedure that may have the potential to combine the positive effects of surfactant and early CPAP. A further mode of surfactant administration, administration via a thin endotracheal catheter during spontaneous breathing with CPAP, has recently come into clinical use. This less invasive surfactant administration technique shows some short-term benefits but still cannot be recommended for general use in this vulnerable population. Long-term follow-up studies are needed to allow new recommendations on surfactant therapy in this high-risk population.

Keywords: Low birth weight, Prematurity, Respiratory distress syndrome.

Many trials have been carried out to establish the relative efficacy of various surfactant products in improving clinical outcome in preterm infants with respiratory distress syndrome (RDS). Meta-analyses of trials comparing natural and synthetic surfactants showed a clear reduction in air leaks and suggested improved survival with natural surfactants [1]. In 2000, Ainsworth, *et al*. [2] reported a higher mortality rate in infants receiving a synthetic surfactant compared with the natural surfactant. A Cochrane review of eleven trials demonstrated a significant reduction in the risk of pneumothorax and mortality rate by use of natural surfactant [3]. Both natural surfactant extracts and synthetic surfactant extracts were effective in the treatment and prevention of RDS but natural surfactant treatment was associated with greater early improvement in the requirement for ventilatory support.

Prophylactic surfactant administration to infants judged to be at risk of developing RDS (intubated infants less than 30-32 weeks gestation) demonstrated a decreased incidence of pneumothorax, pulmonary interstitial emphysema and mortality [4]. Results suggested that there would be two less cases of pneumothorax and five less deaths per 100 infants treated with prophylactic surfactant compared to rescue treatment when surfactant was given within 15 minutes of birth. This regimen was shown to be as effective as treatment before the first breath [5].

In contrast, no difference between early and late surfactant therapy was observed in a controlled clinical study having a high rate of antenatal steroid treatment in the study population [6]. In most of the earlier trials, the rate of antenatal steroid use was low. The latest Cochrane review of trials comparing early selective treatment of RDS (within the first two hours of life) to late selective treatment found evidence of the benefit of early therapy [7].

RECENT TRIALS

Some recent trials focussed on continuous positive airway pressure (CPAP) treatment and optimal surfactant timing in extremely low gestational age newborns [8-11]. The Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial assigned 610 infants who were born at 25-28 weeks of gestational age to CPAP or intubation and ventilation at 5 minutes after birth [8]. At 28 days, there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group (OR 0.63; 95% CI 0.46 to 0.88; *P*=0.006). At 36 weeks of gestational age, 33.9% of 307 infants who were assigned to receive CPAP had died or had bronchopulmonary dysplasia (BPD), as compared with 38.9% of 303 infants who were assigned to receive intubation (OR favoring CPAP 0.80; 95% CI, 0.58 to 1.12; *P*=0.19). There was little difference in overall mortality. In the CPAP group, 46% of infants were intubated during the first 5 days, and the use of surfactant was halved. The incidence of pneumothorax was significantly increased with 9% in the CPAP as compared

with 3% in the intubation group ($P<0.001$), but there were no other serious adverse events. The CPAP group had fewer days of ventilation. Results showed that primary CPAP treatment with surfactant administration, only if ventilation is required, was comparable to intubation and immediate surfactant replacement therapy.

The Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) by the NICHD Neonatal Research Network included infants between 24 and 27 week of gestational age, who were assigned to intubation and surfactant treatment within 1 hour after birth or to CPAP treatment, including the possibility of surfactant administration if intubation criteria were met [9]. Overall, death or BPD was not significantly different between the study groups. A significantly lower mortality rate was found in infants who were born between 24 and 25 weeks and treated with CPAP compared to the same age group treated with intubation and surfactant therapy (death during hospitalization: 23.9% *vs.* 32.1%, $P=0.03$; death at 36 weeks: 20.0% *vs*. 29.3%, $P=.01$). This study demonstrated that CPAP with subsequent surfactant therapy (if needed) is an equivalent alternative to intubation and primary surfactant treatment. The Breathing Outcomes Study, a prospective secondary study to the SUPPORT trial, assessed respiratory morbidity at 6-month intervals from hospital discharge to 18-22 months corrected age [10]. Treatment with early CPAP rather than intubation/surfactant was associated with less respiratory morbidity defined as wheezing more than twice per week during the worst 2-week period or cough longer than 3 days without a cold.

A multicentre randomized trial by the Vermont Oxford Network DRM study group [11] compared three approaches to the initial respiratory management of preterm neonates born at 26 to 29 weeks of gestational age: prophylactic surfactant followed by a period of mechanical ventilation (prophylactic surfactant); prophylactic surfactant with rapid extubation to bubble nasal CPAP (intubate-surfactant-extubate) or initial management with bubble CPAP and selective surfactant treatment (nCPAP). The primary composite outcome of death or BPD at corrected 36 weeks of gestational age in 648 infants enrolled at 27 centres did not differ between the groups. In the nCPAP group, 48% were managed without intubation and ventilation, and 54% without surfactant treatment. The authors concluded that initial CPAP was a possible and less invasive and probably even less expensive alternative to surfactant prophylaxis.

Prophylactic surfactant followed by nCPAP, and nCPAP with early selective surfactant therapy were compared in the CURPAP trial [12]. Of 208 inborn infants born at 25 to 28 weeks of gestational age, who were not intubated at birth, 105 were randomly assigned to prophylactic surfactant or nCPAP within 30 minutes of birth. Thirty-three (31.4%) infants in the prophylactic surfactant group (n=103), needed mechanical ventilation in the first 5 days of life compared with 34 (33.0%) in the nCPAP group (RR 0.95, 95% CI0.64-1.41; P=0.80). Death and type of survival at 28 days of life and at corrected 36 weeks of gestational age, and incidence of main morbidities of prematurity (secondary outcomes) were similar between groups. A total of 78.1% of infants in the prophylactic surfactant group and 78.6% in the nCPAP group survived in room air at corrected 36 weeks of gestational age [12]. In summary, prophylactic surfactant was not superior to nCPAP and early selective surfactant in decreasing the need for mechanical ventilation and the other morbidities of prematurity in spontaneously breathing very preterm infants on nCPAP.

Taking these results together, primary nCPAP treatment and early surfactant therapy after establishment of respiratory distress syndrome signs seem to be appropriate for clinical practice in extremely low gestational age infants.

The Intubation Surfactant Extubation (INSURE) procedure is discussed as an alternative procedure that may have the potential to combine the positive effects of surfactant and early CPAP [13]. Another mode of surfactant administration, via a thin endotracheal catheter during spontaneous breathing with CPAP, has recently come into clinical use [14-16]. Results of a multicentre German study showed that the application of surfactant to spontaneously breathing preterm infants was feasible, and it reduced the need for subsequent mechanical ventilation [17]. This effect was even more pronounced in the subgroup of infants who were stabilized with CPAP after birth. The intervention group had significantly fewer median days on mechanical ventilation, and a lower need for oxygen therapy at 28 days compared with the standard treatment group. The authors recorded no differences in mortality or serious adverse events between the groups. The main limitations of the new method were the need for expertise, and a risk of trauma [18]. This minimally invasive surfactant therapy (MIST) was also successfully evaluated in eleven preterm infants (25 to 28 weeks of gestational age) in Australia [19]. The subsequent initiated Collaborative Paired Trials Investigating Minimally-Invasive Surfactant Therapy (OPTIMIST) trial is planned to enroll a total of 606 infants from more than 30 centres worldwide, and is expected to be completed by end-2017 [20].

Klebermass, *et al*. [21] used this less invasive surfactant administration (LISA) technique in a

prospective cohort of 224 preterm infants (23 to 27 weeks of gestational age), and compared the results with a historical control group [21]. LISA was well tolerated by 94% of all infants, and 68% of infants stayed on CPAP on day 3. The rate of mechanical ventilation was 35% within the first week and 59% during the entire hospital stay. Compared to historical controls, significantly higher survival rates and significantly less intraventricular hemorrhage and cystic periventricular leukomalacia, but higher rates of patent ductus arteriosus and retinopathy of prematurity were documented. Experience with the MIST technique used in 44 preterm infants was recently compared to the INSURE procedure of a historical control group of 31 infants. It resulted neither in any difference regarding the rate of intubation and mechanical ventilation during the first 72 hours, nor secondary respiratory outcomes and relevant morbidities between the groups [22]. Interestingly, significantly more babies in the MIST group (35%) compared to the INSURE group (6.5%) needed a second dose of surfactant.

A meta-narrative review of the efficacy and safety of minimally invasive surfactant administration using a thin catheter, aerosolization, a laryngeal mask airway, and pharyngeal administration in preterm infants with or at risk for respiratory distress syndrome recently reported on 10 studies (6 randomized and 4 observational), including 3081 neonates [23]. None of the studies reported any significant harm with any of the techniques. No statistically significant reduction in BPD but a potential reduction in the need for mechanical ventilation within 72 hours of birth when compared with standard care was observed in eligible studies. The authors concluded that surfactant administration via a thin catheter might be an efficacious and potentially safe method.

GUIDELINES AND RECOMMENDATIONS

Updated guidelines of the European Association of Perinatal Medicine [24] recommend the early use of CPAP of at least 5-6 cm H_2O in spontaneously breathing babies via mask or nasal prongs. Babies with or at high risk of RDS should be given a natural surfactant preparation and prophylaxis (within 15 min of birth) should be given to almost all babies below 26 weeks of gestational age. These guidelines also recommend prophylaxis for all preterm babies with RDS who require intubation for stabilization. Early rescue surfactant is recommended for previously untreated babies if there is evidence of RDS. Immediate (or early) extubation to non-invasive respiratory support following surfactant administration should be considered provided the baby is otherwise stable. Up to three doses of surfactant are recommended if there is ongoing evidence of RDS such as a persistent oxygen requirement and need for mechanical ventilation.

The latest guidelines of the American Academy of Pediatrics Committee on Fetus and Newborn [25] implicate the following for the use of surfactant in case of RDS. Preterm infants born at <30 weeks gestation who need mechanical ventilation because of severe RDS should be given surfactant after initial stabilization. Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency. Preterm and term neonates who are receiving surfactant should be managed by nursery and transport personnel with the technical and clinical expertise to administer surfactant safely, and unexperienced personnel should wait for the transport team to arrive.

The Committee on Fetus and Newborn recently recommended the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants resulting in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy [26]. Early CPAP is likely to result in a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy. Additionally the Expert committee states the necessity of individualized patient care that is provided in a variety of care-settings, and thus the capabilities of the health care team need to be considered as well. Finally the committee recommends that the use of 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, and 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.

CONCLUSIONS

There is a growing body of evidence in recent years suggesting CPAP ventilation being the first choice of ventilatory support in extremely low gestational age newborns, and early rescue surfactant treatment being as effective as prophylactic therapy. The new minimal or less- invasive surfactant administration technique shows some short-term benefits but still cannot be recommended for general use in this vulnerable population of preterm infants. It is highly encouraging to observe all those new studies being in search for the optimal clinical management of RDS in extremely low gestational age newborns. Long-term follow-up studies are needed to formulate recommendations on surfactant therapy in this high-risk population.

REFERENCES

1. Halliday HL. Natural vs. synthetic surfactants in neonatal respiratory distress syndrome. Drugs. 1996;51:226-37.
2. Ainsworth SB, Beresford MW, Milligan DWA, Shaw NJ, Fenton AC, Ward P. Pumactant and poractant alfa for treatment of respiratory distress syndrome in neonates born at 25–29 weeks' gestation: A randomised trial. Lancet. 2000;355:1387-92.
3. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2001:CD000144.
4. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001:CD000510.
5. Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, Guillet C, *et al.* Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics. 1998;101:1006-12.
6. Gortner L, Wauer RR, Hammer H, Stock GJ, Heitmann F, Reiter HL, *et al*. Early versus late surfactant treatment in preterm infants of 27 to 32 weeks' gestational age: A multicenter controlled clinical trial. Pediatrics. 1998;102:1153-60.
7. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012:CD001456.
8. Morley CJ, David PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358:700-8.
9. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, *et al*. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362:1970-9.
10. Stevens TP, Finer NN, Carlo WA, Szilagyi PG, Phelps DL, Walsh MC, *et al*., SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). J Pediatr. 2014;165:240-9.
11. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, *et al.* Vermont Oxford Network DRM Study Group. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128:e1069-76.
12. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, *et al*. CURPAP Study Group. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics. 2010;125:e1402-9.
13. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrøm K, *et al.* Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med. 1994;331:1051-5.
14. Kribs A, Pillekamp F, Hünseler C, Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: Feasibility and outcome in extremely premature infants (postmenstrual age d"27 weeks). Paediatr Anaesth. 2007;17:364-9.
15. Kribs A, Vierzig A, Hünseler C, Eifinger F, Welzing L, Stützer H, *et al.* Early surfactant in spontaneously breathing with nCPAP in ELBW infants — a single centre four year experience. Acta Paediatr. 2008;97:293-8.
16. Kribs A, Härtel C, Kattner E, Vochem M, Küster H, Möller J, *et al.* Surfactant without intubation in preterm infants with respiratory distress: First multi-center data. Klin Padiatr. 2010;222:13-7.
17. Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, *et al*. German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378:1627-34.
18. Kribs A. How best to administer surfactant to VLBW infants? Arch Dis Child Fetal Neonatal Ed. 2011;96:F238-40.
19. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed. 2011;96:F243-8.
20. Dargaville PA, Kamlin CO, De Paoli AG, Carlin JB, Orsini F, Soll RF, *et al.* The OPTIMIST-A trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25-28 weeks gestation. BMC Pediatr. 2014;14:213.
21. Klebermass-Schrehof K, Wald M, Schwindt J, Grill A, Prusa AR, Haiden N, *et al*. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. Neonatology. 2013;103:252-8.
22. Aguar M, Cernada M, Brugada M, Gimeno A, Gutierrez A, Vento M. Minimally invasive surfactant therapy with a gastric tube is as effective as the intubation, surfactant, and extubation technique in preterm babies. Acta Paediatr. 2014;103:e229-33.
23. More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: A meta-narrative review. JAMA Pediatr. 2014;168:901-8.
24. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, *et al*. European Association of Perinatal Medicine. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 update. Neonatology. 2010;97:402-17.
25. Polin RA, Carlo WA; Committee on Fetus and Newborn; American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. Pediatrics. 2014;133:156-63.
26. Committee on Fetus and Newborn; American Academy of Pediatrics. Respiratory support in preterm infants at birth. Pediatrics. 2014;133:171-4.