Surfactant, mechanical ventilation or CPAP for respiratory management of preterm infants?

Adaptation from *in utero* to extra-uterine life involves changes in physiology of every organ system. It is a complex process, but most babies born at term gestation have a smooth transition. However, babies born prematurely are different and are at a disadvantage because the changes required for extra-uterine adaptation puts extra demand on them which they may not be able to cope with. Of the physiological processes involved, cardio-respiratory adaptation is the most important and it can be detrimental if the changes after birth do not proceed according to plan. The factors which predispose to cardiopulmonary maladaptation in preterm infants include immaturity of respiratory drive, compliant chest wall and the surfactant deficiency resulting from immature lung development.

Samir Gupta

Consultant Neonatologist, University Hospital of North Tees, Stockton

Sunil K Sinha

Professor of Neonatal Medicine, The James Cook University Hospital, Middlesbrough sunil.sinha@stees.nhs.uk

Keywords

continuous positive airway pressure; respiratory distress syndrome; ventilation; surfactant; non-invasive support

Key points

Gupta S., Sinha S.K. Surfactant, mechanical ventilation or CPAP for respiratory management of preterm Infants? *Infant* 2010; 6(6): 191-94.

- 1. A proportion of preterm babies can be managed on CPAP.
- Others requiring intubation and mechanical ventilation should be recognised early after birth and offered prophylactic surfactant.
- Use of CPAP after extubation is beneficial and should be used routinely.
- 4. Different forms of non-invasive respiratory support such as bilevel positive airway pressure (BiPAP) and high flow nasal canula (HFNC) are also available for use in newborns, but their efficacy and safety require further validation.

t present, exogenous surfactant Areplacement therapy and mechanical ventilation (MV) remain the 'Standard of Care' while treating such infants. However, this requires endotracheal intubation - an invasive procedure associated with complications¹. Moreover, the skills required to intubate very small babies are not universally available and may vary among the healthcare professionals even in developed countries. A combination of these factors have now motivated professionals caring for such babies to use non-invasive forms of respiratory support which do not require placement of an endotracheal tube. Although appearing to be simple to use, scientific evidence for the efficacy and safety of individual techniques may not yet be fully established and users should be aware of their limitations.

These non-invasive respiratory support methods include:

- Continuous positive airway pressure (CPAP)
- Nasal intermittent positive pressure ventilation (IPPV)
- High flow nasal cannula (HFNC).

Clinical studies of CPAP for respiratory distress syndrome

CPAP works by delivery of a continuous distending pressure using an air-oxygen mixture and a device to generate pressure.

The application of CPAP helps keep the upper airway open during both inspiration and expiration, and improves the functional residual capacity (FRC). Its use in the management of respiratory distress syndrome (RDS) has been extensively studied, both in observational studies and randomised controlled trials.

The clinical studies of the use of nasal CPAP for respiratory care in newborns falls under three categories:

- early use of CPAP alone
- early use of CPAP with surfactant replacement therapy
- later use of CPAP to facilitate extubation.

Early use of CPAP without surfactant

In the pre-surfactant era, the first study of the use of CPAP in preterm babies by Gregory et al reported that CPAP facilitated oxygenation in babies with respiratory distress through establishment and maintenance of FRC2. After the initial report of CPAP use in 1971, the practice of CPAP declined because of the high rate of complications. However, further interest in the use of CPAP at birth was generated following a report from Avery et al, comparing outcomes of preterm babies in eight neonatal units in the United States, which used either CPAP or MV as the first line of action in treating babies with respiratory distress3. They reported

RESPIRATION

that the centre using CPAP had a much lower incidence of chronic lung disease compared with the early intubation and MV as practised in other units. As this observational study was from the presurfactant era, data were revisited in the post-surfactant era by Van Marter et al⁴. This study also found that the use of MV on day 1 increased the odds of an infant developing chronic lung disease.

These two observational studies, in the pre- and post-surfactant eras, had the limitation of a single centre experience of CPAP use, a pooled data of the study population, and no data as regards to long-term outcomes. From further reports^{5,6} it became clear that the feasibility of the use of nasal CPAP and its success are dependent on a number of factors including the gestational age of the infant and the severity of lung disease. There are also a number of other questions which cannot be answered from these observational studies and required confirmation in large clinical trials.

Two large randomised controlled trials, comparing early use of CPAP without surfactant with standard care of MV with prophylactic surfactant have now been completed and their findings made public. In the CPAP or Intubation (COIN) trial, 610 infants were randomised to receive either early CPAP or intubation and ventilation immediately after birth7. In this multi-centre randomised clinical trial, infants were stratified by centre and gestational age (25-28 weeks). At 28 days' postnatal age, the CPAP group showed fewer deaths or oxygen requirement but this advantage was lost when data were analysed at 36 weeks' post menstrual age (PMA). Moreover, a significant number of babies in the CPAP group eventually needed intubation and ventilation during the first five days (46%). There was no difference in the duration of respiratory support, but there was a significant increase in the rate of pneumothorax in the CPAP group (9% versus 3%)7. Another trial recently published, Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT trial), randomised 1316 infants born between 24-27 weeks' gestation to early CPAP initiated in the delivery room without administering surfactant (CPAP group), and intubation and surfactant treatment within one hour after birth (ventilation group). The primary outcome of death or chronic lung disease (CLD) at 36 weeks

did not differ between the two study groups (47.8% in CPAP vs. 51.0% in ventilation group). However infants in the CPAP group less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia (p<0.001), and had fewer days of MV (p=0.03). There was no difference in the incidence of pneumothorax between the two study groups and significantly more infants were alive at seven days and not requiring MV (p=0.01)⁸.

These two trials have recruited 1926 infants with almost half of them successfully managed on early CPAP for at least 5-7 days. This reassures clinicians that a subgroup of extreme premature infants with adequate respiratory drive can be managed on CPAP from birth without any adverse short-term outcomes. The differences in the rates of pneumothoraces could be attributed to the higher level of CPAP used in the COIN trial (8cmH₂O) as compared to the SUPPORT trial (5cmH₂O).

Early use of CPAP with surfactant replacement therapy

There are limited data on the combined use of CPAP and surfactant immediately after birth. The advantages of surfactant administration followed by brief ventilation and extubation (Intubation-SURfactant-Extubation - INSURE) were proven in the randomised trial of Verder et al compared to the provision of nasal CPAP alone⁹. Based on this study, the INSURE approach has been evaluated for management of RDS. In a retrospective, descriptive bi-centre study from Sweden, the investigators compared two five-year time periods before and after the introduction of INSURE-strategy in babies 27 to 34 weeks' gestation. The authors reported a 50% reduction in the number of infants requiring MV after the introduction of INSURE-strategy without any adverse effects¹⁰.

In a small prospective study, Dani et al randomised 27 preterm infants of <30 weeks' gestation, to nasal CPAP and surfactant administration followed by immediate extubation and nasal CPAP application (SURF-nasal CPAP group); and MV after surfactant administration (SURF-MV group). The primary end point was the need for MV during the first seven days of life. At seven days of life there were six patients (43%) in the SURF-MV

group still undergoing MV but none in the SURF-nasal CPAP group. The duration of oxygen therapy, nasal CPAP, and MV, the need for a second dose of surfactant, and the length of stay in the intensive care unit were all significantly greater in the SURF-MV group¹¹. Results of another large randomised controlled trial (VON trial) are now available in abstract form though this trial was stopped early. In this trial 648 infants between 26-29 weeks' gestation were randomised into three groups: prophylactic surfactant and MV; INSURE; and CPAP with selective intubation. This trial reported no difference in death or CLD at 36 weeks between the three study groups. There was also no difference in the rates of pneumothorax between the three groups¹². These results do provide conflicting results and raise the question, should infants with RDS be devoid of surfactant while managed with non-invasive respiratory support?

The results from a recent study report no difference in need for mechanical ventilation, BPD or pneumothorax among infants born at 25-28 weeks' gestation and randomised to receive prophylactic or early selective surfactant with nasal CPAP, suggesting early rescue surfactant is as good as prophylactic surfactant¹³.

CPAP to facilitate extubation

In contrast to its use for early respiratory management, CPAP is an established mode of providing respiratory support after extubation from MV. It has been observed to reduce the incidence of respiratory failure compared to head box oxygen. This may be because of maintenance of FRC and reduction in the work of breathing associated with CPAP. However, in this meta-analysis, post-extubation CPAP was shown to be effective only at pressures of 5cmH₂O or more, and only among babies ventilated for less than two weeks¹⁴.

There is a variety of CPAP devices available based on the flow characteristics; they can be broadly grouped into 'variable' flow and 'continuous' flow devices. Infant flow driver® CPAP (IFD CPAP) and Benveniste® gas jet valve CPAP are prototypes of 'variable' flow device, and ventilator CPAP and Bubble® CPAP are continuous flow devices.

A large study by Stefanescu et al compared IFD CPAP and ventilator CPAP after extubation and did not show any difference in extubation failure rate between the two CPAP groups¹⁵. In a recently published study, Gupta et al compared IFD CPAP and Bubble CPAP to facilitate successful extubation and found a significant reduction in extubation failure among babies ventilated for less than two weeks, who were managed on Bubble CPAP as compared to IFD CPAP. Babies on Bubble CPAP also required significantly shorter duration of CPAP support¹⁶. Further trials comparing long-term outcomes and evaluation of most appropriate CPAP devices at birth is now under investigation.

Uncertainties about CPAP

Despite short-term successes with CPAP in treatment of respiratory distress in newborns, there are still many unanswered questions about CPAP, such as what pressure to use, how to give and how to wean. Various physiological studies suggest improved respiratory mechanics by increasing CPAP pressures from 0 to 88cmH₂O. How high is high enough without any significant side effects for specific CPAP devices is yet to be determined, as the complex interaction between the cardiac haemodynamics and pulmonary function would require welldesigned trials to suggest the optimal CPAP pressures in vivo.

Similarly, there is a choice of nasal interfaces available for use. The in vitro studies clearly demonstrate the advantages of short and wide prongs as the drop in pressure between the proximal and distal end is minimum with increasing width and decreasing length of prongs (reducing resistance). The clinical trials by Davis et al also confirmed these findings and short bi-nasal prongs are now routinely used with CPAP devices¹⁷. There is however an unanswered question regarding the use of nasal masks as compared to prongs and the appropriateness in delivering the set CPAP pressures. The need to close the mouth using a chin strap or pacifier is also debated. How to wean babies from CPAP is another vexing issue. The two widely used weaning methods are 'time off' and 'weaning pressure'. Only one trial attempted to compare these two methods of weaning, but because of methodological flaws, it was difficult to deduce conclusions¹⁸. Until further data is available, the individualised approaches of weaning on CPAP continue to be based on local preference and practice.

Other non-invasive support techniques

Nasal ventilation is an intriguing concept that has gained acceptance in some units without much evidence for its efficacy. It can be given either as synchronised nasal intermittent positive pressure ventilation (NIPPV) or synchronised bilevel CPAP (SiPAP). The studies reported on synchronised NIPPV have been with Infant Star® ventilator which has now been discontinued. The other modality, non invasive SiPAP, is a variable flow nasal CPAP device which provides a bi-level CPAP. The bi-level nasal CPAP is provided for the spontaneously breathing infant through delivery of sighs above a baseline nasal CPAP pressure.

The initial studies on nasal ventilation compared nasal CPAP with NIPPV after extubation, and reported significantly less extubation failures with NIPPV. The Cochrane review comparing NIPPV and nasal CPAP post-extubation included 159 babies from the three trials and reported a clinically important difference in the reduction in extubation failure with NIPPV¹⁹.

The use of NIPPV at birth for treatment of RDS has been reported in two studies. In a recent randomised trial, Kugelman et al²⁰ compared NIPPV and nasal CPAP for treatment of RDS in preterm babies below 35 weeks' gestation. They reported a reduction in the need for endotracheal intubation and ventilation in babies treated with NIPPV as compared to nasal CPAP (31% versus 65%, p=0.05), and decreased incidence of CLD at 36 weeks' PMA (2% versus 15%, p=0.09). In an observational study by the Neonatal Research Network of NICHD, Bhandari et al²¹ reported a reduction in broncho-pulmonary dysplasia (BPD)/death with use of nasal ventilation in the sub-group of infants 500-750g (61% versus 71%, p<0.03), but no difference in the sub-groups of 751-1000g and an increase in BPD/death in the 1001-1500g subgroup.

The study by Kugelman et al was small and included relatively larger preterm babies who normally may not need any respiratory support, whereas the study of Bhandari et al is only an observational study with its attendant methodological flaws. Thus, non-invasive positive pressure ventilation as a respiratory support modality should still be considered only experimental, particularly in premature babies below 28 weeks' gestational age until more convincing data becomes available.

Humidified high flow nasal cannula (HFNC) has been introduced into neonatal respiratory care as a means of providing positive distending pressure to the baby with respiratory distress. HFNC has the advantage of providing heated, humidified gas flow through a standard nasal cannula. It is thought to provide positive distending pressure by using high gas flow (>1 litre per minute). Babies seem to tolerate this therapy well but there are many unknowns and the limited data on its safety and efficacy precludes its routine use as a suitable alternative to the established CPAP therapy²². With the limited studies on the use of HFNC and the uncertainty of the delivered pressures at different flow rates, definitive conclusions about its safety and efficacy for use in premature babies at all gestations cannot be drawn until more data are available.

Conclusions

It is thus clear that a subgroup of premature infants who are spontaneously breathing at birth can be managed on early CPAP alone. However, half of the premature infants who are extremely premature with severe RDS, or are not spontaneously breathing, should be offered standard care of MV with prophylactic surfactant replacement therapy.

CPAP is proven to be effective in facilitating extubation and weaning babies off the MV. Though current evidence on use of non-invasive respiratory support is intuitively appealing, there are a number of issues relating to efficacy and safety which need clarification in on-going clinical trials, including the long-term effect on respiratory and neurological outcomes.

References

- Donn S.M., Sinha S.K. Minimising ventilator induced lung injury in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; 91(3): F226-30.
- Gregory G.A., Kitterman J.A., Phibbs R.H. et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N Engl J Med* 1971; 284(24): 1333-40.
- Avery M.E., Tooley W.H., Keller J.B. et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987; 79(1): 26-30.
- Van Marter L.J., Allred E.N., Pagano M. et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000; **105**(6): 1194-201.

RESPIRATION

- Ammari A., Suri M., Milisavljevic V. et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr* 2005; 147(3): 341-47.
- Aly H., Milner J.D., Patel K. et al. Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? *Pediatrics* 2004; 114(3): 697-702.
- Morley C.J., Doyle L.W., Brion L.P. et al. for COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008; **358**(14): 700-08.
- SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010; 362: 1970-79.
- Verder H., Robertson B., Greisen G. 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(16): 1051-55.
- 10. Bohin K., Gudmundsdottir T., Katz-Salamon M. et al. Implementation of surfactant treatment during continuous positive airway pressure. *J Perinatol* 2007; **27**: 422-27.
- 11. Dani C., Bertini G., Pezzati M. et al. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress

syndrome among preterm infants <30 weeks' gestation. *Pediatrics* 2004; **113**(6): e560.

- Dunn M., Kaempf J., de Klerk A. et al. Delivery Room Management of Preterm Infants at Risk for Respiratory Distress Syndrome (RDS). *E-PAS* 2010: 1670.2
- 13. Sandri F, Plavka R, Simeoni U, et al. The CURPAP Study: An international randomized controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants. *Neonatology* 2008; **94**: 60-62.
- 14. Davis P.G., Henderson-Smart D.J. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev* 2000(3): CD000143.
- 15. Stefanescu B.M., Murphy W.P., Hansell B.J. et al. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. *Pediatrics* 2003; **112**(5): 1031-38.
- 16. Gupta S., Sinha S.K., Tin W., Donn S.M. A randomised controlled trial of post-extubation bubble continuous positive airway pressure versus infant flow driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr 2009; 154(5): 645-50.
- 17. Davis P., Davies M., Faber B. A randomised

controlled trial of two methods of delivering nasal continuous positive airway pressure after extubation to infants weighing less than 1000g: binasal Hudson versus single nasal prongs. *Arch Dis Child Fetal Neonatal Ed* 2001; **85**(2): F82-85.

- 18. Singh S.D., Bowe L., Smith J. et al. Nasal CPAP weaning of VLBW infants: Is decreasing CPAP pressure or increasing time off the better strategy? Results of a randomised controlled trial. *E-PAS* 2006:59:2635.4, 2006.
- Davis P.G., Lemyre B., de Paoli A.G. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev* 2001(3):CD003212.
- 20. Kugelman A., Feferkorn I., Riskin A. et al. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. J Pediatr 2007; 150(5): 521-26, 526 e1.
- Bhandari V., Finer N.N., Ehrenkranz R.A. Use of nasal ventilation (NV) is associated with significantly decreased bronchopulmonary dyplasia (BPD) and/or death in babies of 500-750 grams birth weight (BW). *E-PAS* 2007:61:8225.8, 2007.
- 22. Lampland A.L., Plumm B., Meyers P.A. et al. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. J Pediatr 2009; 154(2): 177-82.



The 1st Global Congress for Consensus in Pediatrics & Child Health

17-20 February 2011

Paris Marriott Rive Gauche Hotel, France

The first in its kind, this international Pediatrics Congress will bring together primary care and community pediatricians, hospital doctors, neonatologists, nurses, family doctors, researchers, policy makers and child care professionals from all over the world to discuss all the issues that need consensus in the most acute and daily problems related to children health. The CIP congress will launch the opening of the global initiative for Consensus in Pediatrics.

Further information is available at: www.cipediatrics.org

Secretariat - Paragon Conventions Tel: +41-22-5330-948, Email: cip@cipediatrics.org