The prevention of bronchopulmonary dysplasia. Is there synergy between early nasal CPAP and surfactant?

Extremely preterm babies still develop bronchopulmonary dysplasia (BPD) however, evidence is accumulating that the use of early nasal continuous positive airway pressure (nCPAP) may reduce the risk. This article explores whether combining early nCPAP with surfactant could reduce the risk of BPD still further by drawing on the research evidence base and personal clinical practice.

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Key points

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- 1. nCPAP may reduce the risk of BPD.
- 2. In experienced hands many extremely preterm babies will breathe spontaneously if placed on nCPAP at birth.
- 3. Prophylactic surfactant may improve the chance of successfully maintaining ELBW babies on nCPAP.
- 4. The randomised controlled trials currently in progress may provide further evidence regarding the role of nCPAP and surfactant in reducing BPD.

n the early 1990s there was great hope that antenatal steroids combined with surfactant and either low tidal volume, low peak pressure ventilation or high frequency oscillatory ventilation (HFOV), would not only improve the survival of extremely preterm infants but also bring about a reduction in the incidence of BPD. As evidence began to mount in the late 1990s that a reduction in BPD was occurring, many institutions worldwide decided to revisit their standard practices in an effort to reduce long term respiratory morbidity. This review of practice is a continual evolving process and has two essential elements; research and practice-based evidence.

The research-based evidence

To identify the most applicable evidence one must first understand that this 'new BPD' differs from that originally described by Northway¹. It affects predominantly infants born between 24 and 28 weeks' gestation with birthweights less than 1000 grams, many of whom have received antenatal glucocorticoids, minimal 'gentle ventilation', and exogenous surfactant therapy². A variety of factors including surfactant deficiency, volutrauma, oxygen exposure, antenatal exposure to proinflammatory cytokines, postnatal infection, patent ductus arteriosus and inadequate postnatal nutrition, are thought to play a role in the pathogenesis of BPD (FIGURE 1). The single greatest predictor for BPD is the initiation of mechanical ventilation in the very low birthweight infant³⁻⁵.

Ventilatory strategies such as HFOV⁶, patient trigger⁷ and volume techniques have not been associated with a reduction in the incidence of BPD in extremely preterm babies. Long term animal studies

demonstrate that HFOV reduces the severity of lung injury but does not prevent the arrest in alveolarisation and vascular development which underlies new BPD⁸⁻¹⁰. This failure may be due to the fact that all respiratory support strategies which involve endotracheal intubation for any length of time expose the susceptible lungs of the preterm infant to both ventilatory induced injury (baro and volu-trauma) and low grade infection of the lung parenchyma. The associated inflammation then contributes to the development of BPD. When developing ventilation and oxygen exposure strategies to minimise lung injury and improve outcome it must be remembered that preterm infants who fail to achieve a functional residual capacity (FRC) are more likely to develop hyaline membrane disease¹¹. The best way to avoid mechanical ventilation could be to use nCPAP whenever possible, thereby minimising volutrauma, yet intervening to prevent atelectasis and the cycle of events that lead to acute lung injury, inflammation and increased risk of BPD (FIGURE 2). Avoidance of intubation would prevent the reduction of mucociliary flow, mucosal injury and secondary infection.

nCPAP's mechanism of action is complex and only partial understood. It is believed to work by improving oxygenation without increasing PaCO₂, through the stabilisation and then recruitment of collapsed alveoli. The FRC is increased resulting in an increased alveolar surface area for gas exchange and a decrease in intrapulmonary shunt. Endogenous surfactant is conserved. The breathing pattern regularises with stabilisation of the rib cage, reduced recession and increased efficiency of the diaphragm¹².







FIGURE 2 Surfactant deficiency and acute lung injury.

What is the evidence to support the use of early nCPAP? Retrospective evidence

In 1987, Avery⁴ suggested that the lower rate of chronic lung disease seen in certain units might be due to a combination of factors including the use of early CPAP and permissive hypercapnia. Few randomised controlled trials have evaluated the role of CPAP; most were in the pre surfactant and antenatal steroid era (1970s to 1980s) using a variety of methods. Small trials have compared CPAP vs. no CPAP, and early vs. late CPAP for the treatment of respiratory distress syndrome (RDS). A review published by The Cochrane Library of prophylactic CPAP¹³ concluded that these few small trials provided insufficient information to make recommendations for clinical practice.

There was therefore little evidence to support the routine use of CPAP in infants with or at risk of developing RDS. During the early 1990s uncontrolled retrospective studies from Denmark reported favourable survival outcomes with low BPD rates when preterm infants were treated with early nCPAP¹⁴⁻¹⁶. Similar retrospective studies have now been published by many centres worldwide^{17,18} reporting lower rates of BPD in units that avoid intubation and ventilation of preterm infants, however none had undertaken formal randomised control trials.

The use of early nCPAP was not uniform in these retrospective studies; many differences exist including the age treatment was commenced, gestational age of infants included and the methods used to administer nCPAP. Given the paucity of data, what other evidence exists to support the current view that the use of early nCPAP in extremely preterm infants will have a beneficial effect on pulmonary outcome?

Animal evidence

Until very recently preterm animal models of RDS treated with early nCPAP had proved impossible to develop, primarily due to poor respiratory drive. However, recent studies have proved more successful and encouraging data has been published. In a two hour study Jobe¹⁹ documented that conventionally ventilated preterm lambs demonstrate significantly more initial acute lung injury than those lambs treated with CPAP. A longer term study in preterm baboons delivered at the equivalence of 25 weeks' gestational age has shown that early nCPAP combined with prophylactic surfactant enables lung development to continue at a very similar rate to that *in utero*²⁰.

Do extremely preterm infants breathe if placed on nCPAP at birth?

Anecdotal reports from neonatal units experienced in the technique of early nCPAP administered at birth suggest these infants can breathe spontaneously. In two retrospective studies, involving extremely low birthweight (ELBW) infants, a reduction in the need for intubation in the delivery room was demonstrated when practices were changed. In these studies the introduction of early nCPAP reduced the needed for intubation from 84% to $40\%^{21}$ and 89% to 33%²². However published work suggests there is a learning curve for practitioners²² and success is gestational age dependent. Almost all babies born at 24 weeks' gestation or less required intubation in the delivery room, however by 28 weeks the majority did not²¹. These small retrospective studies also suggest a reduction in surfactant usage, number of days ventilated, BPD and length of stay. Some infants will require subsequent ventilation following initial nCPAP for worsening respiratory failure. Two recent retrospective studies^{23,24} have reported an increase in death, pneumothorax, BPD, IVH (grade III - IV) and NEC in these infants who failed early nCPAP treatment started at birth, when compared to those who were successful maintained on nCPAP. However this increase was still less than that observed in the group who required mechanical ventilation from birth.

Retrospective studies cannot fully answer safety and efficacy issues. A recent five centre feasibility study has been published²⁵ in which 104 ELBW infants were randomised to receive either resuscitation with CPAP in the delivery room or if intubation was required PPV (positive pressure ventilation) +PEEP (positive end expiratory pressure); or PPV without PEEP only if intubation was required. Once

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admitted to the neonatal unit all could receive nCPAP. Similar numbers required intubation in the delivery room (49% vs 41%). The authors state the overall rate of 45% requiring intubation was better than the 71% for infants <28 weeks' gestation reported by the NICHD Neonatal Research Network for 2002. Gestational age and birth weight were both shown to determine the likelihood of intubation at delivery with 100% at 23 weeks, 53% at 24 weeks, 38% at 25 weeks, and 18% at 27 weeks. Nine out of the 14 babies below 600g required intubation at delivery. An additional 35% of all infants required intubation within the first seven days. The administration of CPAP/PEEP in the delivery room did not affect the need for intubation and ventilation either at delivery or in the first seven days of life. In all only 20% of ELBW infants were managed just on nCPAP during their first seven days of life. The study contains no data on safety or long term outcomes; the results have however been used to help in the design of the protocol for the SUPPORT trial which will compare the use of early nCPAP from birth with early surfactant followed by conventional ventilation in infants 24 to 27⁺⁶ weeks gestation. The results of this prospective randomised trial together with those from the COIN trial, and the Vermont Oxford Network nCPAP trial will help clarify the role early nCPAP has in the respiratory management of extremely preterm infants and the prevention of BPD.

Prophylactic nCPAP in the more mature infant

As already discussed most published nCPAP studies have been retrospective in nature, however Sandri et al²⁶ have recently published a prospective randomised trial evaluating the benefits and risks of prophylactic nCPAP in infants of 28-31 weeks' gestation. Infants were randomised to commence nCPAP either within 30 minutes of birth or if FiO_2 exceeded 0.4. There was no difference in the need for surfactant or subsequent mechanical ventilation in the two groups and the authors conclude there is no benefit from commencing nCPAP prophylactically in these more mature infants.

The administration of surfactant in combination with nCPAP

None of the nCPAP studies cited so far have used prophylactic surfactant. Failure

of early nCPAP can result from surfactant deficiency. When nCPAP alone is unable to establish a FRC, respiratory failure develops and ventilation with surfactant treatment is required. It is difficult to assess the surfactant pool required to enable an extremely preterm infant to establish stable respiration on nCPAP however, such studies can be preformed in animals. Mulrooney et al²⁷ reported that in preterm lambs nCPAP failure is primarily due to low surfactant pool size and that increased nCPAP pressure did not prevent failure. The administration of surfactant prophylactically may therefore be beneficial, increasing the likelihood of successful management on early nCPAP.

In 1994 Verder²⁸ reported in a randomised control trial that a single dose of surfactant (Curosurf[™] 200mg/kg) given during a brief intubation significantly reduced the need for mechanical ventilation and improved oxygenation in infants with moderate to severe RDS who had been treated with early nCPAP. No significant differences were noted in the incidence of death, intraventricular haemorrhage, pneumothorax, or oxygen requirement at 28 days. This study was criticised as babies above 30 weeks' gestation were included, and surfactant treatment was given late, median age of randomisation being 12 hours. In a subsequent controlled trial²⁹ confined to infants <30 weeks' gestation the combined use of early nCPAP with the earlier administration of CurosurfTM (200mg/kg) resulted in a significant improvement in oxygenation and a further reduction in the need for mechanical ventilation. Again, there were no differences for death or BPD.

- nCPAP device
- surfactant use
- early management in delivery room and on admission to neonatal unit
- gentle ventilation with PEEP
- sedation
- extubation and reintubation criteria
- oxygen saturation limits
- permissive hypercapnia
- minimal handling and positioning
- reduction of infection
- early nutrition
- high quality basic nursing and medical care

TABLE 1 Key factors for successful earlynCPAP.

Both of these studies recruited only those babies managed on nCPAP from soon after birth. They do not answer the question – is early nCPAP plus prophylactic surfactant, with the addition of rescue ventilation if respiratory failure develops, better than modern elective ventilation?

Two randomised controlled trials have attempted to answer this question. The first aimed to establish if early nCPAP with prophylactic surfactant was an effective and safe way to manage infants with or at risk of developing RDS³⁰. Two hundred and thirty seven infants, 27-29 weeks old, were randomised before birth to one of four treatment arms:

- early nCPAP with prophylactic surfactant
- early nCPAP +/- rescue surfactant
- early intermittent positive pressure ventilation (IPPV) with prophylactic surfactant
- conventional management, (IPPV+/rescue surfactant).

Seventy eight per cent of infants in the nCPAP groups were established on nCPAP by six hours of age (p < 0.001), the majority by two hours of age. Increasing gestational age increased the probability of success (p<0.001). The early nCPAP groups had a reduced need for ventilation in the first five days of life, however no treatment strategy reduced total duration of respiratory support or oxygen dependency at 28 days or 36 weeks. The need for further doses of surfactant was least in the early nCPAP with prophylactic surfactant group (18%). There were no differences in the rates of respiratory, ultrasound and other neonatal complications.

The second study³¹ randomised 42 infants 25-28 weeks of age to either prophylactic surfactant and early extubation to nCPAP or prophylactic surfactant and continued ventilation. Eight of the 21 infants (38%) randomised to nCPAP following surfactant did not require subsequent ventilation. Fewer babies in the nCPAP group were ventilated at 72 hours (47% vs. 81% p=0.003) and they required less total days of ventilation (3days vs.7days p=0.01). No differences in mortality, BPD and IVH were noted.

Personal practice

To move from a primarily ventilator dependent strategy for respiratory support to one where nCPAP is first choice presents many challenges. Those wishing to introduce the technique of early nCPAP to



FIGURE 3 Total number of days of respiratory support by type for all admissions over the four year period since nCPAP was introdued.





their neonatal unit should recognise that although the device is simple, the 'learning curve' can be challenging. Achieving success requires changes to the way many aspects of care are delivered by the multidisciplinary neonatal team. Much can be learnt by observing the practices in centres around the world where early nCPAP has proven to be successful. **TABLE 1** summaries the key areas that require a consistent guideline or approach to be followed by all senior members of the nursing and medical teams. In the limited space available all of these factors cannot be discussed in detail, however this should not detract from their importance.

Delivery of nCPAP

There are many ways to deliver nCPAP; three of the most popular are the Benveniste³² system used mainly in Scandinavia; the Infant Flow Driver[™] used widely in the UK, Europe and USA; and the bubble device variation used in the USA, Australia and New Zealand and in some units in the UK. The device used is not critical to success, however some important points to note when choosing a device include variable flow³³, work of breathing³⁴, length and width of the prongs³⁵, ease of fixation, effective humidification of gases, the ability to delivery a variable pressure and the presence of safety features such as pressure monitoring with relief values and oxygen concentration monitoring.

Probably the most important factor is staff training; this is simplified if only one type of device is used within an individual neonatal unit. Staff training must pay particular attention to prong fixation. All nCPAP prongs can produce nasal trauma, this can be minimised by correct application. Lesions can be minor, producing redness of the nose, or severe enough to cause erosion of the nasal septum which may require later corrective plastic surgery³⁸.

Surfactant use

In the author's unit prophylactic Curosurf[™] has been used routinely for all babies born at less than 30 weeks gestation since 1996. This means all extremely preterm infants are intubated within a few minutes of delivery, given a standard dose of 120mg CurosurfTM and then transported to the neonatal unit intubated. The aim is to extubate as soon as possible with many babies placed directly on nCPAP. A single standard dose of surfactant means that the individual baby does not have to be weighed to calculate the dose nor do staff have to remember an estimated dose for each gestational age, simplifying the whole process.

In addition to deciding whether to give surfactant as prophylaxis or rescue treatment, one must also decide the criteria upon which rescue treatment will be administered and whether this will be by the INSURE technique (intubation, surfactant, extubation) or to continue ventilation in the conventional way. INSURE was first described in 1994 by Verder²⁸ and has since become a popular method to administer rescue surfactant to babies managed on nCPAP from birth. However, it must be remembered that nCPAP can mask the severity of surfactant deficiency by virtue of its prime action which is to maintain the FRC. If choosing to administer surfactant as rescue treatment, earlier treatment with an initial high dose of surfactant (200mg/kg) is more effective and enables INSURE to be successful²⁹.

In our practice, the majority (85%) of extremely preterm babies require only one

dose of prophylactic surfactant. Those requiring further doses often have very severe lung disease from birth; this is commonly associated with perinatal sepsis or severe hypoxia before birth due to antepartum haemorrhage etc. Further doses of surfactant should be given as soon as the severity of lung disease is established, at a dose of at least 100mg/kg. A number of babies who fail extubation to nCPAP will require a rescue dose of surfactant to overcome atelectasis.

nCPAP plus prophylactic surfactant

In 2000, the unit adopted the practice of combining early nCPAP and prophylactic surfactant. **FIGURES 3 AND 4** show the impact of this treatment on the type of respiratory support extremely preterm babies require and the total duration of intubated ventilation. As staff have become more experienced even babies less than 26 weeks' gestational age have been found to be successfully managed on nCPAP without adverse outcome.

Conclusions

Early nCPAP offers the potential to reduce BPD in extremely preterm infants. Those infants that fail nCPAP have a higher rate of complication. Prophylactic surfactant treatment may offer a way to improve outcome by reducing the nCPAP failure rate and thereby reducing the risk of complications. Evidence to support its widespread application is limited but encouraging. Many questions remain unanswered including:

- Which infants will breathe spontaneously soon after birth and are therefore candidates for early nCPAP?
- Will the early administration of surfactant, either prophylactically or as early rescue, increase the likelihood of success?
- Will early nCPAP reduce BPD within the setting of a randomised control trial? The randomised controlled trials

currently in progress should provide further data to clarify the role nCPAP and rescue surfactant will have in the prevention of lung injury, however none have been designed to assess the role of prophylactic surfactant.

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