To intubate or not—that is the question: continuous positive airway pressure versus surfactant and extremely low birthweight infants

N Finer

Perspective on the paper by Booth *et al* (see page 398)

There is currently a great dilemma regarding the early management of extremely low birthweight (ELBW) infants, which involves the use of continuous positive airway pressure (CPAP) after delivery compared with the use of prophylactic or early surfactant. Although there is good evidence that prophylactic and early surfactants reduce mortality and respiratory morbidity,^{1–4} few of these studies had large numbers of the smallest babies who are the longest-term residents of our neonatal intensive care units; also, none of the studies randomised infants in the placebo or control group to treatment with early CPAP. In addition, surfactant treatment may be associated with a lowered rate of milder disabilities at 1 year of age.⁵ The use of mechanical ventilation, especially in the first few days of life, seems to considerably increase the risk for bronchopulmonary dysplasia as defined by the need for oxygen at 36 weeks,^{6–7} and the incidence of bronchopulmonary disease (BPD) may be increasing in the most premature infants^{8–9} with a lesser incidence of the most severe forms of this disorder.¹⁰ There is an established association between the occurrence and severity of BPD and later neurodevelopmental disabilities.^{11–15} In our current quandary, is it better to avoid mechanical ventilation in the most vulnerable of preterm infants to circumvent the effects of intubation and baro-volutrauma and not administer early surfactants by using early CPAP, or do the benefits of intubation with the administration of early surfactant outweigh any subsequent morbidities seen with the use of CPAP?

Gregory *et al*¹⁶ showed that CPAP improved oxygenation in the presurfactant era for infants with respiratory distress and that CPAP was able to help in the establishment and maintenance of functional residual capacity. Subsequent studies, mostly in the presurfactant era, showed that the early use

of CPAP decreased the use of subsequent positive pressure ventilation.¹⁷ Previous studies have shown that nasal CPAP is effective in preventing failure of extubation in preterm infants after a period of endotracheal intubation and intermittent positive pressure ventilation.¹⁸ There are, however, no studies evaluating the effectiveness of prophylactic nasal CPAP in ELBW infants.¹⁹ Of the two prospective trials that have been completed, one was in the presurfactant era,²⁰ whereas the other reported outcomes for infants of 28–31 weeks gestation.²¹ For these studies CPAP started within 2 h of life was not associated with any improvement in clinical outcomes. So far, there are no prospective randomised controlled trials comparing the use of CPAP initiated at delivery with early surfactant administration in a population of infants <27 weeks gestation.

The stimulus to use CPAP from birth onwards as a mode of support for very low birthweight and ELBW infants came from a report by Avery comparing outcomes in eight neonatal units in the US.²² Avery reported that one unit (Columbia) had a lower rate of chronic lung disease and had a much greater use of CPAP compared with early intubation mechanical ventilation. In a subsequent report comparing two hospitals in Boston with Columbia, Van Marter *et al*⁶ looked at the outcomes in these three institutions relative to their initial forms of support. This retrospective review showed that 75% of the infants at the Boston centres were initially treated with mechanical ventilation compared with only 29% at Columbia, whereas the corresponding figures for initial CPAP as the form of support for Boston versus Columbia were 11% versus 63%. An intriguing observation from this paper was that Columbia used markedly less surfactants (10% *v* 45%) and yet Columbia was able to maintain a low rate of chronic lung disease (CLD) compared with the other centres. This study also

found that the use of mechanical ventilation on day 1 increased the odds of developing CLD 13-fold, with a decreasing odds ratio associated with initiation of mechanical ventilation later in the first week of life.

If we now fast forward to the present, we can see that there has been a trend towards the use of early CPAP as noted by Booth *et al*,²³ (see p 398) with most published studies representing cohort evaluations, suggesting that introduction of early CPAP has led to a decrease in the use of mechanical ventilation. The approach, taken by Booth *et al*, of early intubation to provide surfactant followed by extubation in essence mimics the studies by Verder *et al*, albeit for a more immature population.^{24–25} Verder *et al* published two trials in which infants of ≥25 weeks were randomised to receive a surfactant after intubation with a brief period of ventilation of 5 min and then extubation if stable, compared with continuing CPAP. Both studies were stopped after interim analysis and showed a statistically significant reduction in the need for ventilation or death for the surfactant-treated infants within 7 days (from 63% to 21%) in their later trial. Thomson *et al*²⁶ have presented their results of the multicentre trial of infants between 27 and 29 weeks who were randomised to early nasal CPAP and prophylactic surfactants, early nasal CPAP and rescue surfactants, early intermittent positive pressure ventilation with prophylactic surfactants, and conventional management. They reported that CPAP was initiated within 6 h of birth and that the CPAP-treated infants had a shorter duration of mechanical ventilation; they did not find any differences in the rates of CLD or other complications. This study did not require the use of CPAP in the delivery room and has not yet been published in its full form. To date, there are no results from randomised controlled trials comparing the use of CPAP initiated in the delivery room with the use of prophylactic or early surfactant.

The recent experience of Columbia has been presented in more depth by Ammari *et al*,²⁷ who reviewed 261 infants of <1240 g, reflecting treatment from June 1999 to July 2002. The authors noted that of the 87 infants of 23–25 weeks, 69% were treated with initial CPAP and, overall, 31% of these 87 infants could be maintained on CPAP. Of the group of infants between 26 and 28 weeks, 95% were started with CPAP in the delivery room and 78% were successful in requiring only CPAP as their treatment. Of the infants <699 g at birth, 73% were started on CPAP, with an overall success of CPAP

alone of 33%. They reported that there were fewer pneumothoraces for infants who were started on CPAP than for the infants who were CPAP failures or for those who were initially intubated in the delivery room. Notably, only 51% of the infants who were CPAP failures and 53% of the infants ventilated from birth received surfactant. These observations shed further light on the need for the comparison of the most evidence-based intervention, prophylactic or early surfactant, with early CPAP. Infants weighing <700 g seem to be at the greatest risk of CPAP failure. This is certainly consistent with other retrospective and prospective observations suggesting that infants of 23 weeks are unlikely to be successfully resuscitated without intubation in the delivery room.^{28, 29}

Thus, while there is good evidence for the use of prophylactic and early surfactants currently, it could be argued that many of those studies did not include large numbers of infants of 23–25 weeks gestation. Early CPAP has been shown to be effective in reducing the need for subsequent mechanical ventilation, but most of these studies were from the presurfactant and antenatal steroid era.³⁰ CPAP is useful in preventing extubation failure in preterm infants,¹⁸ and the use of synchronous non-invasive nasal ventilation is even more effective in these situations.³¹ To date, however, there have been no prospective studies comparing the use of CPAP beginning at delivery with an appropriate control group of infants who received a prophylactic or early surfactant. Although there are several reports describing individual unit experiences with early CPAP in the ELBW infant, the use and timing of surfactant administration in such infants either before the use of CPAP or for infants who fail CPAP has not been consistently reported. These issues make it difficult, if not impossible, to evaluate the overall benefit of such an approach in that the withholding of surfactant from infants who were initially intubated and ventilated or were later CPAP failures may have compromised their ultimate outcomes.

There are three prospective trials currently under way, one of which has completed enrolment, which are attempting to evaluate and compare the use of CPAP initiated immediately after delivery with the early administration of surfactant, generally within the first hour of life, for the ELBW infant. The Coin trial, which has now completed enrolment, studied infants of 25 weeks–28 weeks and 6 days gestational age at birth, who showed spontaneous breathing in the delivery room after stabilisation, with evidence of

respiratory distress. Infants were then randomised to nasal CPAP or to intubation with surfactant administration (<http://www.bapm.org/trials/view-trial.php?RecordID=19>). The Vermont Oxford Network is now enrolling infants in a three-arm trial in which infants are randomised to (a) intubation, early prophylactic surfactant with subsequent stabilisation on ventilator support; (b) intubation, early prophylactic surfactant with rapid extubation to CPAP; and (c) early stabilisation with nasal CPAP, with selective intubation and surfactant administration for clinical indications (<http://www.vtoxford.org/home.aspx?p=research/drm/index.htm>). Infants eligible to be enrolled in this trial are 26 weeks to 29 weeks and 6 days gestational age at birth. The SUPPORT trial is currently enrolling infants of 24 weeks to 27 weeks and 6 days gestational age, and these infants are randomised to either CPAP beginning in the delivery room with criteria for subsequent intubation, or intubation with surfactant treatment within 1 h of birth with continuing ventilation, with criteria for extubation (<http://www.clinicaltrials.gov/ct/show/NCT00233324?order=13>). Although the specific criteria for intubating an infant assigned to CPAP in these trials are not identical, they are remarkably similar, and include a PaCO₂ (partial pressure of alveolar carbon dioxide) >60–65 mm Hg, or an FiO₂ (fractions of inspired oxygen) requirement of >0.4–0.6 or significant apnoea. As can be seen, therefore, the answer to the question of which approach is best when started at delivery may be available within the next 2–3 years for infants of age ≥24 weeks gestational age. None of the above trials is enrolling infants of 23 weeks gestational age, a very high-risk group with a high mortality and a very high need for early intubation in the delivery room.²⁹

Booth *et al* have shown that with appropriate attention a high proportion of their very preterm infants could be successfully extubated in the first few days of life, and that infants managed on continuing CPAP have a decreased mortality and incidence of CLD. They used CPAP of 6–7 cm H₂O and increased CPAP to as high as 9 cm H₂O. Although there may be a physiological basis for such increases,³² the sustained use of these levels of CPAP for ELBW infants has not been evaluated, and the authors have not presented their data on air leaks or other possible related morbidities. Indeed, there are no published prospective clinical trials comparing different levels of CPAP used for sustained durations for ELBW infants.

Clearly, we do not have unequivocal answers at this time, and there are an

increasing number of observational cohort descriptions that suggest that the avoidance of intubation and early surfactants can be associated with acceptable short-term outcomes as defined by the occurrence of BPD or other major morbidities. For the more mature infants aged ≥26 weeks, early CPAP started at delivery with intubation and surfactant administration for those infants who show a significant oxygen requirement and immediate extubation to CPAP for infants with an adequate respiratory effort, appears reasonable. For infants of <26 weeks the path is less clear. Recent reports suggest that the success of CPAP alone increases with increasing gestational age, and that CPAP alone is unlikely to be successful for more than a minority of infants weighing <600 g or of <24 weeks gestational age. These percentages will certainly increase as the individual units gain more experience with such infants and the interfaces required to deliver CPAP. Until the results of the current trials are available, my own preference, in the absence of participation in a current randomised trial, is to intubate infants of ≤26 weeks gestational age and administer surfactant within the first 30 min of life, followed by aggressive attempts to extubate the infant to CPAP or, preferably, nasal synchronous intermittent ventilation within the next 24–48 h. Further studies that include longer-term neurodevelopmental follow-up are required to determine the safety and effectiveness of the earlier use of CPAP without surfactant, the acceptance of higher PaCO₂ (partial pressure of alveolar carbon dioxide) values and the use of higher levels of CPAP in ELBW infants with respiratory distress.

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Correspondence to: N Finer, Department of Paediatrics/Neonatology, UCSD Medical Centre, 200 West Arbor Drive No 8774, San Diego, CA 92103-8774, USA; nfiner@ucsd.edu

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