

ORIGINAL ARTICLE

Sustainable use of continuous positive airway pressure in extremely preterm infants during the first week after delivery

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Background: Early use of nasal continuous positive airway pressure (nCPAP) may reduce lung damage, but it is not clear how many extremely preterm infants can be cared for without mechanical ventilation on the first days after delivery.

Objectives: To describe our experience of nCPAP in infants born at <27 weeks' gestation and to determine the chance of reintubation of this group of extremely preterm infants.

Methods: A retrospective, observational study examined the period from November 2002 to October 2003, when efforts were made to extubate infants to nCPAP at the earliest opportunity. Data were collected on all infants born at <27 weeks' gestation admitted to The Neonatal Intensive Care Unit, Queen Charlotte's and Chelsea Hospital, London, UK. The chance of an individual infant requiring reintubation within 48 h of delivery was estimated, calculating the predictive probability using a Bayesian approach, and oxygen requirements at 36 weeks' postmenstrual age were examined.

Results: 60 infants, 34 inborn and 26 ex utero transfers, were admitted; 7 infants admitted 24 h after birth were excluded and 5 died within 48 h. The mean birth weight was 788 g and the gestational age was 25.3 weeks. Extubation was attempted on day 1 in 21 of 52 infants on ventilators and was successful in 14; and on day 2 in 14 of 35 and successful in 10 of infants extubated within 48 h of delivery survived to discharge. 5 of 23 infants on mechanical ventilation at 48 h of age were on air at 36 weeks postmenstrual age, and 12 of 26 of those were on nCPAP at 48 h of age. The probability of an individual baby remaining on nCPAP was 66% (95% CI 46% to 86%) on day 1 and 80% (95% CI 60% to 99%) on day 2. The smallest infant to be successfully extubated was 660 g and the youngest gestational age was 23.8 weeks.

Conclusions: Extremely preterm infants can be extubated to nCPAP soon after delivery, with a reasonable probability of not requiring immediate reintubation.

Respiratory disease remains a major cause of morbidity and mortality in preterm infants, and both mortality and morbidity from bronchopulmonary dysplasia (BPD) remain high, particularly in extremely preterm infants. Experimental work has suggested that BPD is promoted by mechanical ventilation,¹ and recent studies suggest that treatment soon after delivery with early nasal continuous positive airway pressure (nCPAP) was apparently associated with less lung damage compared with that in controls with intermittent positive pressure ventilation.²⁻³ Early nCPAP might be beneficial for infants, but many of the data are anecdotal and the evidence base is incomplete.⁴⁻⁸

Any treatment that aims to ameliorate BPD will have to be effective in the extremely preterm population, in whom the disease is most common and severe, and probably be suitable for use very soon after birth when many of the major predisposing factors such as chorioamnionitis,⁹ surfactant deficiency¹⁰⁻¹¹ and increased lung water content¹² are present at birth. Variables around the time of birth such as the need for positive pressure ventilation may also help to predict which infants could benefit most from early nCPAP.¹³ However, clinicians may be deterred from instituting nCPAP soon after delivery in very immature infants in the belief that these patients lack the ability to sustain spontaneous ventilation and are likely to need reintubation.

Inadequate information on the ability of very preterm infants to maintain appropriate gas exchange on nCPAP soon after delivery could impede the assessment and implementation of nCPAP as a useful treatment for preterm infants.

Some studies have looked at the ability of preterm infants to sustain nCPAP without undergoing reintubation for further mechanical ventilation,^{4-5 14-16} but none has specifically examined the chance of reintubation in this vulnerable group, where prophylactic surfactant is often given before extubation to nCPAP.

In recent years, like many other institutions, the Neonatal Intensive Care Unit, Queen Charlotte's and Chelsea Hospital London, UK, has developed a culture that aims at early extubation for all preterm infants, and we have gathered information on the natural history and the probability of reintubation for infants born at <27 weeks' gestation who were established on nCPAP in the first week after delivery.

PATIENTS AND METHODS

Data collection

During 2001, we instituted a change in practice whereby we moved from mechanical ventilation being the prime means of respiratory support to nCPAP. We had routinely given prophylactic surfactant to extremely preterm infants since 1996, and this practice was continued. nCPAP after prophylactic surfactant rapidly became an established practice in the neonatal unit. A retrospective, observational study was

Abbreviations: BPD, bronchopulmonary dysplasia; FiO₂, fractions of inspired oxygen; LMP, last menstrual period; nCPAP, nasal continuous positive airway pressure; PaCO₂, partial pressure of alveolar carbon dioxide; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; SpO₂, arterial oxygen saturation

conducted over a period of 1 year between November 2002 and October 2003 to review this method of respiratory support. We examined the clinical records of all infants admitted to the Neonatal Intensive Care Unit, Queen Charlotte's and Chelsea Hospital, at <27 weeks' gestation, as estimated from the date of the mothers last menstrual period (LMP) or by early ultrasound imaging where this date was uncertain.

Standardised data were collected on all infants who were admitted to the neonatal intensive care unit within 24 h of delivery, recording gestational age at birth, birth weight, sex, antenatal corticosteroid and postnatal surfactant treatment, and mode of ventilation on postnatal days 1–7 as well as on day 28 and week 36 of post menstrual age. The timing and reason for all reintubations were noted. Early outcome data were collected on the number of infants receiving increased fraction of inspired oxygen (FiO_2) at 36 weeks' post menstrual age. Postmenstrual age was defined as the age in weeks, starting from the first day of the LMP when the date of LMP was known or by early ultrasound imaging where this date was uncertain.

Early management

All inborn babies were placed in a plastic bag immediately at birth to minimise heat and fluid loss and then electively intubated. Curosurf (Chiesi, Cheadle, UK), as a single bolus dose of 120 mg, was given within 10 min of delivery. Initial ventilation was provided with a Neopuff Infant Resuscitator (Fisher and Paykel, Berkshire, UK) with a positive end expiratory pressure (PEEP) of 5 cm H_2O . We aimed to keep the peak inspiratory pressure (PIP) low at about 16 cm H_2O , or if unable to achieve this, the lowest PIP to maintain appropriate chest movement. An inspiratory time of 0.5 s, rate of 40/min and an initial FiO_2 of 0.3 were advised. Oxygen requirements were monitored by pulse oximetry with arterial oxygen saturation (SpO_2) alarm limits set at 85–92%. All babies were transferred from the delivery room to the neonatal unit on conventional mechanical ventilation, in a transport incubator. They were placed on an open radiant heat cot in a "humidification tent" with convention ventilation continued using the SLE 2000 ventilator. The recommended ventilation criteria were the lowest PIP to maintain adequate but not excessive chest movement, inspiratory time of 0.5 s, FiO_2 to maintain SpO_2 88–90% (alarm limit set at 85–92%) with a PEEP of 5 cm H_2O . The rate was determined after an initial capillary blood gas to maintain the pH >7.2 with partial pressure of alveolar carbon dioxide (Paco_2) between 5.5 and 8 kPa (45–60 mm Hg).

The infants were then assessed for extubation. To be suitable for extubation, the infant had to be haemodynamically stable and should have shown some spontaneous respiration. The PIP pressures had to be relatively low at ≤ 18 cm H_2O and the FiO_2 <0.3 to maintain SpO_2 88–90% (alarm limit set at 85–92%) with a PEEP of 5 cm H_2O . An acceptable capillary blood gas had a pH >7.22 with Paco_2 <8 kPa (60 mm Hg). Those judged clinically suitable for extubation were nursed prone; while they were prone peripheral venous access was obtained and infants then prepared for extubation to nCPAP. Those judged clinically not immediately suitable for extubation had umbilical arterial and venous catheters sited and were reassessed frequently to see whether extubation would be possible. It was not the practice to wean the ventilator rate in those infants judged suitable for extubation postnatally; such infants were extubated from a rate of 30–40 beats/min. For those who required a more prolonged period of ventilation, the rate was reduced to 20–35 beats/min before extubation. The rate was never reduced < 20 beats/min. Around the time of extubation, infants were intravenously given a loading dose of

caffeine citrate (caffeine base 25 mg/kg in two equal doses 1 h apart); a maintenance dose (caffeine base 6 mg/kg once daily) was continued if extubation was successful. Caffeine levels were not monitored during the study period.

All infants received nCPAP via nasal prongs from the Infant Flow Driver (EME, Brighton, UK) with a Fisher and Paykel 850 humidifier, and were nursed while in the prone position, with every effort made to ensure an effective seal and good audible air entry. nCPAP pressure was initially set at 6–7 cm H_2O and quickly increased to a maximum of 9 cm H_2O if chest retractions, increasing tachypnoea or increasing oxygen requirement were observed. FiO_2 was adjusted to maintain SpO_2 88–90% (alarm limit set at 85–92%).

The infants continued on nCPAP as long as there was an adequate respiratory drive, the criteria for which included FiO_2 <0.5, pH >7.20, with no limit set for Paco_2 provided the pH was maintained. Failure of nCPAP requiring reintubation was characterised by recurrent apnoea and bradycardia not responding to stimulation and positioning, respiratory failure with a pH persistently <7.20 or FiO_2 >0.5 to maintain acceptable saturations and, finally, sepsis. Sepsis was defined as a clinical picture with bacterial growth seen on blood culture, change in C reactive protein levels and blood film, or a clinical picture with a change in C reactive protein levels and blood film in the absence of bacterial growth seen on blood culture. The infants were then reintubated and ventilated with the least support to achieve adequate gas exchange and chest inflation, as described earlier.

nCPAP was reduced gradually, with increasing time spent on low-flow nasal cannula oxygen delivered by a low-flow oxygen meter (10–50 cm^3) without humidification if the baby had FiO_2 <0.25 on nCPAP. Additionally, there needed to be a good respiratory effort with no chest retractions, and no apnoea and bradycardia that required active management with positive-pressure T-piece ventilation.

Patent ductus arteriosus was managed conservatively. Routine echocardiography and prophylactic treatment were not undertaken. If a baby repeatedly failed extubation to nCPAP for no reason other than a large duct with bidirectional flow seen on an echocardiogram, then treatment with ibuprofen was considered. Surgical ligation was reserved for cases where the condition of the baby worsened on ventilation and all other causes were excluded.

All infants born outside the Queen Charlotte's and Chelsea Hospital were transferred on conventional ventilation; all had received surfactant within 30 min of birth but not always prophylactically. Once admitted to the neonatal unit in this hospital, they were managed as described earlier.

Statistical analysis

These retrospective observational data were analysed using a bayesian approach to make a point estimate (with 95% confidence limits) of the risk of reintubation for an individual infant.¹⁷

We estimated the probability of successful extubation by calculating the β density according to the simplified function given by Berry¹⁷:

$$\beta(a,b) = p^a(1-p)^b$$

where p , population success proportion; a , number of successful extubations; and b , number of failed extubations.

The population success proportion p is any value between 0 and 1, and represents the possible combinations of success and failure at extubation. If all infants fail extubation, $p = 0$; and if all succeed on CPAP, $p = 1$. If $p = 0.5$, then half the infants extubated succeed in remaining on CPAP.

Evaluating the function creates the β density, which is a model of the probability of success and failure, analogous to

Table 1 Demographic and clinical data on infants studied

	Inborn (n = 34)	Outborn (n = 19)	Total (n = 53)
Birth weight (g)	810.5	749.9	770
Median (range)	(420–1200)	(456–1092)	(420–1200)
Gestational age (weeks)	25.7	25	26.4
Median (range)	(23.1–26.6)	(23.1–26.6)	(23.1–26.6)
Sex (male:female)	19:15	7:12	26:27
Multiples, n(%)	12 (35)	6 (32)	18 (34)
Antenatal steroid treatment, n(%)	29 (85)	16 (84)	45 (85)
Surfactant before extubation, n(%)	34 (100)	19 (100)	53 (100)
Deaths in the first 7 days, n(%)	3 (9)	6 (32)	9 (17)

Weight	Vent D1	Vent D2	Vent D3	Vent D4	Vent D7	Vent D28	Out born	Late death	BPD
420								X	
456							■		
456								X	
542							■		
560									▲
564								X	
580							■	X	
605							■		
610							■		
616								X	
624							■		
660							■	X	
660							■		
666									▲
670							■		▲
670							■		
676								X	
680							■		
682									▲
690							■		
692									▲
712									▲
724						ND			▲
738							■		▲
744									
760									
770									
792									▲
798									▲
822									▲
825						ND	■		▲
830									▲
854									
860									
865						ND			
872									
880						ND			
918								X	
920									
920									
928									
930									
962									
972									
980								X	
1000						ND	■		
1036						ND	■		▲
1036						ND			
1051							■		
1060							■		
1092							■		
1176									▲
1200									

the more familiar model of a linear relationship given by the formula $y = mx + c$. β density curves have several useful properties as models of probability. For large values of a and b , β density curves approximate a gaussian distribution, and thus a mean and 95% confidence limit can be meaningfully calculated. As a and b increase, the curves become progressively narrower and, thus, the confidence limits become narrower. If $a > b$ (the number of successes > the number of failures), the mean value of the curve moves to the right, and the mean value becomes higher.

The mean value of β density calculated using a and b is the predictive probability, which formally estimates the chance that the next time a trial is made it will be successful. In the context of this dataset, predictive probability estimates the probability that the next infant established on CPAP using the practices implemented in this study will escape reintubation.

Estimation of the predictive probability (with the 95% confidence limits for the estimate) has the advantages that it provides a probability estimate that relates directly to an individual case (indeed, the next infant extubated under the same conditions as the dataset was collected) and is of direct relevance to daily clinical practice. A more complete description of this bayesian approach to predicting the outcome of individual cases is given by Berry.¹⁷

This observational study is not randomised and did not set out to test any hypothesis about the effect of early CPAP on respiratory outcome. However, there may be some interest in an exploratory examination of the relationship between extubation at 48 h after delivery and respiratory outcome at 36 weeks of gestation, and we analysed this using Fisher's exact test.

RESULTS

Over this 1-year period, 60 infants born at <27 weeks' gestation were admitted to the neonatal intensive care unit Queen Charlotte's and Chelsea Hospital. Seven infants were excluded from further study as they were admitted 24 h after delivery. Table 1 gives the demographic details of the infants.

The survival rate in infants born at <24 weeks' gestation was 25%, and 50% in those born at 24–24.8 weeks. Of those babies successfully extubated at 48 h, 88% (23/26) survived to discharge. Figure 1 shows the natural history of infants during the first week after delivery; infants receiving mechanical ventilation, those extubated and the cumulative

Figure 1 Ventilation status and selected outcomes for infants in the study. Black blocks, dead; grey blocks, intubated including failed extubation; ND, data not available; white blocks, extubated including continuous positive airway pressure; ▲, requiring supplemental oxygen at 36–40 weeks; ■, ex utero transfer; X, death 7 days after birth.

Table 2 Number of infants extubated in the days after delivery, with the predictive probability that extubation will be followed by establishment of nasal continuous positive airway pressure

Day	Extubation attempted	Successful extubation	Surviving infants on nCPAP	Predictive probability of successful extubation	95% confidence limits for predictive probability
1	21/53 (40)	14 (66)	14/49 (29)	66	46% to 86%
2	15/35 (43)	12 (80)	26/49 (53)	80	60% to 99%
3	7/24 (29)	5 (71)	29/48 (60)	Numbers insufficient	
7	6/17 (35)	4 (67)	30/43 (70)	Numbers insufficient	

Values in parentheses are percentages.

number of deaths are shown for each day. Extubation to nCPAP was attempted in 21 infants on day 1, seven of whom needed reintubation. Table 2 describes the number of extubations in the first 7 days after delivery, with the predictive probability (with 95% confidence limits) of successful establishment of nCPAP during that day. For postnatal days 3 and 7, the numbers are too small to allow calculation of reliable probabilities.

The youngest infant to be sustained on nCPAP after extubation on day 1 was born at 23.8 weeks. In all, 25% of infants born at <24 weeks' gestation were extubated within the first 7 days. No infant with a birth weight <660 g was successfully established on early nCPAP.

Analysis of early outcome data showed that 18 infants were receiving oxygen at 36 weeks' corrected gestational age. Table 3 relates ventilation status at 48 h of age to outcome at 36 weeks' postmenstrual age. Fisher's exact test shows that there is a significant difference between the groups ($p = 0.019$); however, as this study is observational, retrospective and not randomised, this implicit hypothesis testing should be treated with caution.

DISCUSSION

The results of our study over 1 year show that most infants born at <27 weeks' gestation could be treated with nCPAP during the first week of life without requiring reintubation during that time; many for whom this was not possible were extremely unwell and died. By postnatal day 2, more than half the surviving infants were breathing spontaneously on nCPAP.

Only data related to the first week are presented in detail, as this is the period of greatest interest, because any treatment with the potential to reduce BPD must be effective during this time. A review of our records shows that during this period all cases of reintubation were due to failed nCPAP, whereas after 7 days one third were due to other factors, such as sepsis, necrotising enterocolitis or the need for surgery. As these events could have occurred equally in babies receiving mechanical ventilation, the results from the first 7 days give a more meaningful picture of the ability of these infants to sustain themselves with nCPAP support.

This study has limitations. As a retrospective observational study with no randomisation, it reflects a particular practice. Potentially relevant features include a specialist obstetric service experienced in preterm labour and delivery, high incidence of antenatal steroid and prophylactic surfactant

Table 3 Status at 36 weeks' postmenstrual age

	Status at 36 weeks' postmenstrual age		
Ventilation at 48 h	Dead	Oxygen	Air
CMV (23 infants)	11	7	5
CPAP (26 infants)	3	11	12

CMV, cytomegalovirus; CPAP, continuous positive airway pressure.

What is already known about the topic

- Continuous positive airway pressure (CPAP) is a useful form of respiratory support for preterm infants, which might reduce biotrauma and chronic lung disease.
- It is not known whether the most immature infants are able to breathe spontaneously with adequate efficiency to benefit from CPAP.

What this paper adds

- Many infants born at <26 weeks' gestation can be treated effectively with continuous positive airway pressure.

treatment, early use of caffeine, routine early use of parenteral nutrition with early trophic breast milk feeds, skilled nurses experienced in the use of nCPAP soon after delivery, and detailed attention to positioning, with the infant lying prone and at an angle of about 30°. However, the data show that in routine tertiary neonatal practice, it is possible to use nCPAP soon after delivery in a high proportion of very immature infants.

The numbers of infants in the study are too small to make a precise assessment of the chances at different gestational ages or birth weights. However, no baby weighing <660 g sustained nCPAP without requiring reintubation, whereas 25% of infants born at 23 or 24 weeks' gestation were successful in doing so. This suggests that diaphragmatic and intercostal muscle bulk may be more important than the maturity of the respiratory drive in sustaining ventilation on nCPAP, and this possibility deserves further investigation.

In conclusion, early nCPAP treatment seems to be possible and safe in infants between 23 and 27 weeks' gestation. Further studies of the use and value of nCPAP in this age group are justified.

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