Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome

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Aim: To evaluate whether very preterm babies can be extubated successfully to nasal continuous positive airway pressure (nCPAP) within one hour of birth after receiving one dose of surfactant in the treatment of respiratory distress syndrome (RDS).

Methods: Forty-two infants of 25 to 28 \( \frac{6}{35} \) wk of gestation were intubated at birth and given one dose of surfactant. They were then randomized within one hour of birth to either continue with conventional ventilation or to be extubated to nCPAP.

Results: Eight out of 21 (38%) babies randomized to nCPAP did not require subsequent reintubation. (Ventilation rates of 62% vs 100%, \( p = 0.0034 \). The smallest baby successfully extubated weighed 745 g. There were also significantly fewer infants intubated in the nCPAP group at 72 h of age (47% vs 81%, \( p = 0.025 \). There was no significant difference between the two groups in the number of babies that died, developed chronic lung disease or severe intraventricular haemorrhage.

Conclusion: A significant number of very preterm babies with RDS can be extubated to nCPAP after receiving one dose of surfactant. nCPAP is a potentially useful modality of respiratory support even in very premature infants.

Key words: Chronic lung disease, CPAP, preterm, respiratory distress syndrome

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Pulmonary disease continues to be the major cause of morbidity and mortality in very low-birthweight infants (1), and although conventional mechanical ventilation has reduced mortality, pulmonary morbidity remains high (2–4). This morbidity consists initially of an acute idiopathic respiratory distress syndrome (RDS) which may be followed by a chronic structural lung injury known as chronic lung disease (CLD), also known as bronchopulmonary dysplasia (BPD) (5). Antenatal steroids and postnatal surfactant have decreased morbidity from RDS but the incidence of CLD remains high. CLD complicates the outcome of 30–60% of very low-birthweight infants treated for RDS (3, 6–8), causing both long-term morbidity and late mortality. The aetiology of CLD is poorly understood, but ventilator-induced barotrauma may be an important factor in the pathogenesis (9, 10).

The ventilation strategy of an extremely preterm infant with RDS in the majority of neonatal intensive care units is reliant on the use of intubation and conventional mechanical ventilation. (Over a 3-y period in the study centre 98 infants were born between 25 and 28 \( \frac{6}{35} \) wk of gestation, 98.8% had been intubated, and 97.6% had required conventional ventilation for the first 24 h of life (pers. commun. Peter Crowle). However, the Scandinavian management of this group of babies is quite different and centres on the early use of continuous positive airway pressure (CPAP), with very low reliance on conventional ventilation. One group reported using CPAP alone in 98% of babies aged less than 28 wk, with a failure rate of only 30%, and none of the infants developed chronic lung disease (11).

In another study of babies with more severe RDS, a single dose of surfactant followed by nCPAP (nasal CPAP) reduced the need for subsequent mechanical ventilation from 85% to 40% (12). Despite these reports, the use of nCPAP in the acute management of RDS in this group of patients has not been practised in the majority of units around the world.

The aim of this study was to determine whether nCPAP could be used as a safe alternative to conventional ventilation in very preterm babies with acute lung disease in the UK. The hypothesis of the study was that the need for conventional ventilation in very preterm infants could be reduced by 33% with the early use of nCPAP following a prophylactic dose of surfactant.
Subjects and methods
All babies born between 25 and 28⁺⁻⁶ wk gestational age born at the study centre were eligible for entry. Exclusion criteria were infants without respiratory disease, those with severe congenital malformations, pulmonary hypoplasia, pneumothorax or Apgar scores of less than 3 at 5 min. The Norfolk and Norwich Healthcare Trust Ethics Review Committee approved the study and informed consent was given by the parents of all the infants in the study.

All babies were electively intubated at delivery and a dose of surfactant (Pumactant 100 mg) was given as soon as practicably possible (within 20 min), umbilical arterial access was then gained, chest X-ray performed and each infant then randomized to either conventional or novel management with nCPAP. Randomization was done by computer-generated random number sequence stored in sealed opaque envelopes. Randomization was stratified into infants of 25–26 wk gestation and infants of 27–28 wk gestation.

Infants randomized to novel therapy were loaded with caffeine base (25 mg/kg) and extubated within one hour of birth to nCPAP. The CPAP was delivered using the infant flow-driver device (EME Ltd., Brighton, Sussex, UK), with an initial pressure of 5 cm H₂O, increasing up to a maximum of 9 cm H₂O if necessary (criteria for increasing CPAP pressure included increasing oxygen requirement (1 infant) and recurrent apnoea (1 infant). The CPAP was continued unless any of the failure criteria were met (FiO₂ >70%, pH <7.2, PaO₂ <6 kPa, significant apnoea).

Infants randomized to conventional ventilation continued with time cycled pressure limited ventilation (unless it was clinically not indicated to do so, i.e. had reached extubation criteria as described below). The mode of conventional ventilation was either patient triggered ventilation (PTV) or synchronized intermittent mandatory ventilation (SIMV) using the SLE 2000 Ventilator (Specialized Laboratory Equipment, Surrey, UK) with initial settings of inspiratory time 0.4 s, rate 60 bpm, peak inspiratory pressure (PIP) 16 cm H₂O and PEEP 4 cm H₂O. Ventilation and weaning strategies were managed according to unit guidelines. These guidelines did not include the routine use of paralysing agents, but did involve the use of morphine (5–20 mcg kg⁻¹ h⁻¹) as an analgesic to infants that were not being weaned off the ventilator. In this study, if there had been no progress in weaning an infant off the ventilator by 4 h of age an infusion of morphine was commenced. Weaning strategies for conventional ventilation involved the manipulation of PIP, FiO₂ and ventilatory rate to maintain blood gas values of pH >7.25, PaCO₂ between 4.5 and 6 kPa and PaO₂ between 6 and 10 kPa. The order of preference for weaning was to achieve a PIP ≤18 cm H₂O before reductions in rate were considered and once rates were down to 40 BPM, caffeine was given (25 mg kg⁻¹), morphine weaned off and the ventilator mode changed to SIMV.

The primary outcome in this study was the need for continuing conventional ventilation from one hour of birth (however, to avoid bias owing to the design of the study, we allowed infants in the conventional group that could be extubated within the first 6 h of life to be classified as successful extubations). Data were collected prospectively and included at one hour, arterial blood pH, PaO₂, PaCO₂ and ventilator settings of FiO₂, PIP and mean airway pressure from which the oxygenation index (OI) was calculated (FiO₂ [%] × mean airway pressure [cm H₂O]/PaO₂ [mmHg]). Other outcome data included number of days spent in oxygen, oxygen requirement at 28 d, requirement for home oxygen, and the occurrence of death, pulmonary interstitial emphysema (PIME), pneumothorax and worst cranial ultrasound abnormalities (scored as 0: no haemorrhage; I: localized subependymal haemorrhage; II: intraventricular haemorrhage; III: intraventricular haemorrhage with ventricular dilatation; IV: parenchymal haemorrhagic lesions) and parenchymal cysts (scored as 0: no cysts; I: porencephalic cyst; II: cystic leucomalacia).

Statistical analysis
To enable detection of a 33% reduction in the need for conventional ventilation with 80% power at the 5% significance level, we needed to include 21 infants in each treatment group. Data were stored and analysed using Excel computer software (Microsoft Corporation) with the statistical package “Analyse-it” (Analyse-it software, Ltd.). Analysis was by intention to treat. Fisher’s exact test was used to compare categorical variables, and the Mann–Whitney U-test was used for non-parametric or discrete variables. A probability (p) value of less than 0.05 was considered significant.

Results
A total of 58 infants were identified during the study period, from October 1997 to November 1999; 16 of these infants were not randomized (4 parents refused to give consent, 4 met CPAP failure criteria prior to trial entry and 8 were not enrolled owing to lack of study staff). Of the 42 infants randomized, 21 were assigned to treatment with CPAP and 21 continued with conventional ventilation. There were no significant differences in the group demographics between the infants randomized to CPAP and those randomized to conventional ventilation (Table 1). Arterial blood pH, PIP and OI measures of respiratory severity were also very similar in both groups.

Of the 21 babies randomized to receive nCPAP, 8 (38%) did not require reintubation as part of their management. However 4 (19%) of the babies in the
Table 1. Comparison of the clinical characteristics* of 42 infants randomized to either nCPAP or conventional ventilation at entry to the study. Figures are expressed as median (range) except where otherwise stated.

<table>
<thead>
<tr>
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<th>nCPAP group (n = 21)</th>
<th>Conventional group (n = 21)</th>
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<tr>
<td>Male:Female ratio</td>
<td>57%:43%</td>
<td>47%:53%</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>27 + 1 (25–28 + 4)</td>
<td>27 + 2 (25–28 + 6)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>885 (700–1280)</td>
<td>910 (550–1360)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>Apgar at 1 min</td>
<td>6 (1–9)</td>
<td>5 (1–9)</td>
</tr>
<tr>
<td>Apgar at 5 min</td>
<td>9 (3–10)</td>
<td>8 (5–10)</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cm H2O)</td>
<td>18 (16–28)</td>
<td>20 (15–31)</td>
</tr>
<tr>
<td>Oxygenation index at 1 h</td>
<td>7.7 (2.6–28.2)</td>
<td>7.9 (3.3–26.6)</td>
</tr>
<tr>
<td>Arterial blood pH at 1 h</td>
<td>7.33 (7.2–7.46)</td>
<td>7.32 (6.98–7.44)</td>
</tr>
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</table>

*The differences between groups were not significant.

nCPAP: Nasal continuous positive airway pressure.

Fig. 1. Survival plot showing the number of infants remaining intubated in both groups over the first 72 h of the study. A significantly lower number of infants in the nasal continuous positive airway pressure (nCPAP) group were intubated at 72 h of age (p = 0.025).

CPAP group were not extubated at all during the study period (three babies because of a high oxygen requirement, FiO2 >70%, and one baby with no arterial access). Therefore, of the 17 babies that were extubated, 8 (47%) never required re-ventilation. Two infants were also extubated and required re-ventilation more than 48 h later, (one infant with a pneumothorax at 8 d and one with a persistent metabolic acidosis at 5 d). Three children required reintubation between 24 and 48 h and four of the babies required reintubation within the first 24 h (three within 30 min for recurrent apnoea and desaturation, and one at 11 h with a pH of less than 7.20). None of the 21 babies in the conventional group was extubated (or in a condition to be extubated, i.e. low pressure, low rate ventilatory support) within 6 h of birth. The first infant in the conventional group was extubated at 30 h of age.

Extubation to nCPAP at 1 h of age was successful in 8/21 (38%) children. The need for continuing intubation and ventilation was therefore reduced by 38% in the CPAP group versus the conventional group (ventilation rates of 62% vs 100%, p = 0.0034). This difference in ventilation requirement was also significantly different at 72 h of age when 81% of the conventional group and 47% of the CPAP group (p = 0.025) remained intubated and ventilated for their respiratory management (Fig. 1).

There were no significant differences between the

Table 2. Secondary outcome measures in the nCPAP and conventional groups. Figures are expressed as median (range) or absolute number (percentage).

<table>
<thead>
<tr>
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<th>CPAP group (n = 21)</th>
<th>Conventional group (n = 21)</th>
<th>p-value</th>
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<tr>
<td>Days of nasal CPAP as primary therapy</td>
<td>2 (1–15)</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>Days ventilated</td>
<td>3 (0–13)</td>
<td>7 (2–20)</td>
<td>0.01</td>
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<tr>
<td>Days in oxygen</td>
<td>13 (0–70)</td>
<td>16 (1–103)</td>
<td>0.19</td>
</tr>
<tr>
<td>Oxygen requirement at 28 d</td>
<td>10 (48%)</td>
<td>12 (57%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Oxygen requirement at 36 wk post-conceptional age</td>
<td>1 (5%)</td>
<td>4 (19%)</td>
<td>–</td>
</tr>
<tr>
<td>Home oxygen requirement</td>
<td>0 (20%)</td>
<td>2 (10%)</td>
<td>–</td>
</tr>
<tr>
<td>Air leak (PIE/pneumothorax)</td>
<td>7 (33%)</td>
<td>7 (33%)</td>
<td>–</td>
</tr>
<tr>
<td>Death</td>
<td>4 (19%)</td>
<td>4 (19%)</td>
<td>–</td>
</tr>
<tr>
<td>Any abnormality of head scan (including Grade I–IV/cysts)</td>
<td>5 (24%)</td>
<td>12 (57%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Abnormal head scan (including Grade III–IV/cysts)</td>
<td>2 (10%)</td>
<td>5 (24%)</td>
<td>0.41</td>
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</table>

nCPAP: Nasal continuous positive airway pressure; PIE: pulmonary interstitial emphysema.
two groups for the outcome of death, oxygen requirement at 28 d, oxygen requirement at 36 wk postconceptional age or severe cranial ultrasound scan abnormality (grade III–IV/cysts) (Table 2). There was a slight increase in grade I or II IVH in the conventional therapy group (p = 0.04).

The results of the 21 infants randomized to CPAP are presented in Table 3 and have been displayed to show any difference between those infants that were not extubated in the first hour of life against those that were extubated and either tolerated extubation well (i.e. survived >48 h) versus those that required reintubation within 48 h. Infants that were successfully extubated had a significantly higher gestational age at birth, and better oxygenation index at the point of extubation. Any difference in birthweight did not reach statistical significance. There were no differences between these two groups in 1- and 5-min Apgar scores and the use of antenatal steroids.

### Discussion

In this study we have shown that a significant number of very preterm babies with RDS can be extubated to nCPAP after receiving only one dose of prophylactic surfactant at birth. We have confirmed that nCPAP is a potentially useful modality of respiratory support even in very preterm infants. Although the important outcome measures of death, CLD and severe cranial ultrasound abnormalities were similar in both groups, we found that the total number of cranial ultrasound abnormalities were more common in infants managed with conventional ventilation.

CPAP is the application of positive pressure to the airways of the spontaneously breathing patient throughout the respiratory cycle. CPAP increases lung functional residual capacity (FRC) (13) through the recruitment of collapsed alveoli, and also by increasing the volume of patent alveoli. Reviews of neonatal practice have suggested that the highest survival figures and lowest incidences of CLD are associated with a respiratory support policy of early nCPAP, tolerance of high PCO₂ values and avoidance of muscle relaxants (14–17). It is well established that conventional mechanical ventilation of premature monkeys (18) and rabbits (19) causes epithelial injury within minutes, and that these lesions progress to hyaline membrane formation. The sequence of lung injury leading to CLD appears to be damage to the alveolar capillary membrane by conventional mechanical ventilation, followed by granulocyte sequestration and activation which amplifies the lung damage leading to chronic structural lung injury (20). Methods of ventilation that prevent large phasic pressure–volume excursions in surfactant-deficient models do prevent or greatly reduce the formation of hyaline membranes (21). CPAP is a method of ventilation that prevents large phasic pressure–volume excursions, and new devices dedicated to CPAP delivery, such as the infant flow nasal CPAP driver, are reported to reduce the work of breathing compared to other CPAP devices (22, 23).

In this study we have shown that very small infants with RDS can be successfully managed with CPAP after a dose of prophylactic surfactant. This reported success rate could be improved further if the definition for successful extubation was revised to managing 48 h without the need for intubation, in which case 10/17 (59%) babies that were extubated were “successfully extubated”. We have also shown that the number of infants remaining intubated and ventilated still remained significantly lower at 72 h of age in the nCPAP group.

Since completion of the study, the Licence for Pumactant (ALEC) has been withdrawn and there is a potential for different results using natural surfactants. One criticism that we have of the study is that the clinicians involved in the care of the baby in the first hour were not blinded to the assigned treatment modality and there was a tendency to reduce ventilatory support more rapidly if a baby had been randomized to CPAP. In retrospect, it would have been wise to blind...
clinicians up until the point of extubation (although this would have been difficult, as a dose of caffeine would have to be given promptly if the baby was to be extubated at 1 h of age).

One other conclusion that might be drawn from our results is that infants ventilated in a conventional fashion in our study centre were perhaps kept intubated longer than necessary and that could account for the improved results in the CPAP group. However, results from 1995 and 1996 (the two years preceding this study) confirm that infants of less than 28 wk gestation were ventilated for a mean of 8.6 d in 1995 and 8.8 d in 1996 (pers. comm. Peter Crowle), which compares with a figure of 7.8 d from the conventional arm in this study. Again, the conclusion could be drawn that infants in the study unit were “inappropriately ventilated”, although the study unit guidelines on weaning infants were not dissimilar to many other units in the UK (personal observation).

It is important to notice that the results demonstrated in our study are in the context of a dose of prophylactic surfactant at birth and we can draw no conclusion on the benefits of nCPAP after a dose of surfactant as rescue therapy in infants of this gestational age.

The fact that we found no difference in the incidence of secondary outcome measures may be a real effect but is almost certainly influenced by the simple design of this study, which was not powered to detect any significant differences in these outcomes. Despite the small numbers in the study the finding of a higher incidence of cranial ultrasound abnormalities in the conventional group was a surprising result. Cranial US scans were performed in a non-blinded fashion by either the resident medical staff or by a consultant radiologist. The scans were not performed prior to randomisation, thus making it difficult to comment on the timing of these findings.

We believe we have established that it is possible to use this therapy in the acute management of extremely preterm infants, although we are not in a position to recommend it as first-line therapy (partly because of the limitations of the study, as described above). Of note is that the results from this study are still quite different from the Scandinavian experience. The results of a large multicentre study are needed to provide more information on the role that nCPAP has to play in extremely preterm infants. The results of a larger study may also confirm whether secondary outcome measures, such as the incidence of CLD and or cerebral ultrasound changes are altered by its use.

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