ORIGINAL ARTICLE

Respiratory outcome in late childhood after neonatal continuous negative pressure ventilation

K Telford, L Waters, H Vyas, B N Manktelow, E S Draper, N Marlow

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See end of article for
authors' affiliations

Correspondence to:
Professor N Marlow,
Academic Division of Child
Health, School of Human
Development, Queen's
Medical Centre, Nottingham
NG7 2UH, UK; neil.
marlow@nottingham.ac.uk

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Background: The outcome in late childhood for children entered into a randomised trial of continuous negative extrathoracic pressure (CNEP) versus standard respiratory management for the treatment of neonatal respiratory distress was studied. In the original trial, there were advantages in the duration of oxygen and the prevalence of chronic lung disease for those assigned to receive CNEP.

Aim: To determine whether the above differences had persisted into childhood.

Methods: Outpatient evaluation of children by a paediatrician using Spirometry (Vitalograph Spirometer 2120, Ennis, Ireland) and MicroRint (Micro Medical, Rochester, Kent, UK) techniques independently of the original trial. Parents completed questionnaires about their child's respiratory history and social-demographic information.

Results: 133 (65%) survivors were evaluated at 9.6–14.9 years of age. The group examined were representative of the original cohort and no significant baseline differences were observed between children evaluated who had been allocated to CNEP or standard treatments. We compared Rint (before and after bronchodilator) and forced expiratory flow, volume and vital capacity between the two study groups; none were significant. Children in the standard group had received paediatric intensive care more often ($p=0.19$) and were more likely to be receiving inhaled drugs for asthma ($p=0.19$; all not significant).

Conclusions: No important differences were found at follow-up in late childhood in respiratory outcomes for children treated with neonatal CNEP or standard treatment. Caution should be exercised, as the original trial was not powered to show these differences, but there seems to be no long-term detriment in respiratory outcomes for children treated with CNEP in the neonatal period.

Over the past two decades, survival rates have dramatically increased for very low birthweight and preterm infants. This has been credited to improvements in patient care, especially the greater use of antenatal corticosteroids and the use of exogenous surfactants, and improved strategies for neonatal ventilation. However, exogenous surfactant treatment does not seem to have decreased the rate of chronic neonatal lung disease in very low birthweight infants.^{1,2} Improved survival of these infants has been associated with an increase in later morbidity, in particular, chronic lung disease (CLD); there is a high prevalence of respiratory symptoms and abnormal pulmonary function that persists into childhood.³ The aetiology of CLD of prematurity is multifactorial. The contributing factors include: mechanical injury due to alveolar stretch; oxidative stress; pulmonary oedema and inflammation due to both infectious and non-infectious causes. A variety of strategies have been in use in the neonatal period, with the aim of reducing CLD.

In the early 1990s, Samuels *et al*⁴ carried out a randomised trial of continuous negative extrathoracic pressure ventilation (CNEP) as an additional modality for treating respiratory distress syndrome, compared with standard ventilatory support, which comprised either supplemental oxygen alone or positive pressure ventilation. This was a randomised controlled trial, with a sequential analysis of matched pairs of infants. The study showed benefit for CNEP over standard treatment in terms of an overall composite illness score (the primary outcome). Advantages for the CNEP group were also noted in terms of a mean value of 18 fewer days spent receiving oxygen in the first 2 months and fewer children with chronic lung disease. Owing to the public interest in the outcome of this trial and following the Griffith's report,⁵ we were commissioned to evaluate the long-term outcome for children enrolled in this original study.

In a previous report, we found no difference in terms of death and severe disability at follow-up 9–14 years later.⁶ In the same follow-up study, we assessed respiratory function to investigate whether the differences noted in respiratory outcome at 56 days had clinically relevant effects in late childhood. In this paper, we report the findings of the respiratory evaluations. Our hypothesis was that the earlier reduction in the duration of oxygen therapy by 18 days and the lower prevalence of CLD observed in the CNEP group would produce measurable advantages in lung function parameters and symptoms at follow-up.

METHODS

The overall methods and recruitment to the follow-up study have been described previously⁶: 133 of 205 surviving children were assessed as part of this study; 69 had been allocated to CNEP in the neonatal period and 64 to standard respiratory care. Evaluation of respiratory outcome was carried out by a paediatrician (KT) using parental interview, clinical examination and measurement of lung function.

The core questions from the ISAACS study were used to ascertain the history and severity of respiratory symptoms.^{7,8} To improve the reliability of the interview, the questions also included the diagnosis of asthma by a doctor and the current asthma treatment. Important confounders such as maternal smoking during pregnancy, smoking history of parents and children and family history of atopy were also recorded. Additional information about the number of days of school missed due to illness in the past year, whether the child had

Abbreviations: CLD, chronic lung disease; CNEP, continuous negative extrathoracic pressure; FVC, forced vital capacity; HFOV, high-frequency ventilation oscillatory ventilation; PEEP, positive end-expiratory pressure

been admitted to hospital in the past year and whether the child had ever been admitted to paediatric intensive care was also ascertained.

Clinical examination included subjective assessment of acute signs (presence of recession, use of accessory muscles and auscultation for presence of crackles or wheeze) and measurement of respiratory rate to document the incidence of acute respiratory illness, which could potentially confound the outcome of lung function. Chronic signs (Harrison's sulcus, hyperinflation (clinical evaluation of increased anteroposterior diameter of chest), deviated trachea or other chest deformities) were also assessed by subjective examination. Lung function was measured pre-bronchodilator and 15 min post-bronchodilator (500 µg of salbutamol given via a spacer device) using microRint (resistance interrupter technique) and spirometry.⁹⁻¹¹

Rint is a technique used to measure airway resistance and is an indirect measure of airway obstruction. It requires little cooperation by the patient. The patient breathes normally through a mouthpiece or facemask, and a rapidly occluding valve automatically interrupts the airway for a brief period. When the valve shuts, the airway pressure equilibrates with alveolar pressure and the airway resistance is then computed. It is particularly useful in children, as it overcomes some of the practical difficulties associated with spirometry. A standardised technique was used in this study: the child was seated with elbows resting on a table, holding the microRint mouthpiece with two hands. The paediatrician supported the soft tissue of the child's cheeks and under the chin using both hands. After the procedure had been explained to the child, Rint was measured on random breaths, at peak tidal flow in expiration. Ten measurements each were recorded before salbutamol and after salbutamol treatment.

Spirometry was measured using the standardised technique,¹¹ with the child standing up. Sufficient attempts were allowed to obtain three technically good traces, and the best trace from the three was used.

The study investigators were blind to the neonatal course, including the allocated respiratory care during this period. None of the investigators had been involved in the original study. This study was designed independently of the original trial and was approved by the local research ethics committees at Queen's Medical Centre, Nottingham, North Staffordshire

Hospital and Hammersmith Hospital (The Queen Charlotte and Chelsea Hospital is now closed and incorporated as part of the maternity services at the Hammersmith Hospital). The data were entered twice on to a specifically created MS Access database by KT and LW. Although the original trial had a matched pairs design, the presence of neonatal deaths and unevaluated survivors meant that data on only 38 complete pairs were obtained. Therefore, to include all available data, unpaired analyses were undertaken using all observations.¹² Respiratory outcomes were compared between the treatment groups using linear regression models, adjusting for the matching variables (intubation at 4 h, oxygen requirement at 4 h, gestational age at birth, and treatment centre). The differences between the groups were quantified by adjusted differences in the mean responses, with 95% confidence intervals (CIs). Other outcomes were compared using χ^2 tests, Mann-Whitney U tests or Student's *t* tests as appropriate. SPSS V.11.0 was used for all analyses.

RESULTS

In this study, outcome was investigated only in surviving children. In total, 133 children (65% of surviving children, 69 assigned to receive CNEP, 64 to standard care) were seen for follow-up at a median age of 11.3 (range 9.6–14.9) years. Figure 1 shows the derivation of these children from the original study population.

Small differences were seen only in the median values of variables used for matching in the original trial between the survivors assessed and those not assessed for this paper (table 1). A larger proportion of those evaluated had received surfactants, reflecting the reduced proportion of children evaluated from The Queen Charlotte and Chelsea Hospital, where use of surfactants had not been introduced at the time. Considering the baseline differences between children who had been assigned to each treatment group, matching variables were evenly distributed in each group, as were other important neonatal variables. Differences in total duration of oxygen therapy found in the original study were not significant in this subgroup of patients (CNEP 6 (interquartile range (IQR) 4–22) days *v* standard 7 (IQR 5–29) days; table 2). Infants in the CNEP group tended to be of greater birth weight. They were more likely to have received antenatal steroids, but less likely to

Figure 1 Flow diagram showing derivation of study groups for follow-up analysis.

Table 1 Neonatal variables in all enrolled survivors who were assessed compared with survivors not assessed

	Assessed (n = 133)			Not assessed (n = 72)			p Value*
Matching variables	n	Median	IQR	n	Median	IQR	
Gestational age (years)	133	31	29–33	72	31	28–33	0.50
FiO ₂ at study entry	133	0.52	0.45–0.65	71	0.55	0.40–0.70	0.92
		n	%		n	%	
Intubated at study entry	133	91	68	72	54	75	0.32
Born at QCCH	133	15	11	72	19	26	0.005
Other neonatal variables	n	Median	IQR	n	Median	IQR	
Birth weight	129	1.59	1.17–2.04	69	1.42	1.10–1.89	0.19
Duration of supplemental O ₂ (days)	128	6	4–24	69	6	4–27	0.58
		n	%		n	%	
Male	133	79	59	72	43	60	0.96
Antenatal steroids	129	22	17	69	11	16	0.84
Surfactant treatment	127	41	32	68	15	22	0.13
Postnatal dexamethasone	129	12	9	69	5	7	0.62

* χ^2 test or Mann–Whitney U test.

IQR, interquartile range; QCCH, The Queen Charlotte and Chelsea Hospital.

have received surfactant or postnatal dexamethasone. None of these differences were significant.

Variables that might confound any differences in respiratory outcome at follow-up were considered (table 3): there were no significant differences in age, height, weight, parental smoking or child smoking. More mothers of children who had been assigned standard treatment had smoked during pregnancy; however, this difference was not significant. A smaller proportion of children were from single-parent families in the standard treatment group (not significant), but maternal age, education and socioeconomic status were similarly distributed (table 4). Acute respiratory signs were present in one child and the median respiratory rate was 18 in both groups (standard deviation (SD): CNEP, 3.5; standard, 4.3).

Children in the two groups had missed similar numbers of days at school in the past year (table 5). Admission to hospital in the past year was rare. The number of children who had ever received intensive care in the standard group was double that of the CNEP group; however, the numbers were small and this was not significant. A total of 53 (40%) children were reported to have been diagnosed with asthma. Similar numbers in each group reported a diagnosis of asthma and having had one or more wheezing episode in the past month. More children of the standard group were currently using short-acting bronchodilators and inhaled steroids, and more children assigned to the

CNEP group had one or more signs of chronic respiratory symptoms; neither of these differences were significant.

Analysis of lung function was not carried out in one child because the family had moved abroad; this child only had a neurological and clinical assessment performed by KT. Two children with severe disabilities were unable to perform the manoeuvres necessary for both microRint and spirometry (both these children were in the CNEP group). In six assessments, the parents or the child declined to use the bronchodilator (three in each group). Two parents requested that their child received a smaller dose of salbutamol. One child successfully performed spirometry and microRint testing before bronchodilator use, but after bronchodilator use, was unable to comply with microRint.

Normative data for Rint were not available for 80 (60%) children, as currently available normative data cover children only up to 150 cm in height. Analyses of microRint results therefore use raw data only. Table 6 shows results comparing lung function between the two groups. The only measure with a difference between the two groups that neared significance was in forced vital capacity (FVC) before bronchodilator use. In the CNEP group, FVC was 101% of predicted, and in the standard group, FVC marginally decreased at 96%. A similar trend for higher volumes before bronchodilator use in the CNEP group was seen in other spirometry measures; however, all differences

Table 2 Comparison of neonatal variables for 133 children assessed

	CNEP			Standard			p Value*
Matching variables	n	Median	IQR	n	Median	IQR	
Gestational age	69	31	29–33	64	31	28–33	0.41
FiO ₂ at study entry	69	0.54	0.44–0.65	64	0.50	0.45–0.65	0.70
		n	%		n	%	
Intubated at study entry	69	46	67	64	45	70	0.65
Born at QCCH	69	7	10	64	8	13	0.67
Other neonatal variables	n	Median	IQR	n	Median	IQR	
Birth weight	68	1.61	1.38–2.20	61	1.53	0.98–1.95	0.086
Duration of supplemental O ₂ (days)	68	6	4–22	60	7	5–29	0.23
		n	%		n	%	
Male	69	39	57	64	40	63	0.48
Antenatal steroids	68	13	19	61	9	15	0.51
Surfactant treatment	66	18	27	61	23	38	0.21
Postnatal dexamethasone	68	4	6	61	8	13	0.16
Abnormal cranial ultrasound†	65	5	8	58	3	5	0.57

CNEP, continuous negative extrathoracic pressure; IQR, interquartile range; QCCH, The Queen Charlotte and Chelsea Hospital.

* χ^2 test or Mann–Whitney U test.

†Abnormal cranial ultrasound scan at 56 days or last scan before death. Abnormal includes periventricular leucomalacia, parenchymal haemorrhage, cortical atrophy, porencephalic or subcortical cysts, and hydrocephalus with shunt inserted.

Table 3 Comparison of age, growth indices and parental smoking history

At follow-up	CNEP (n = 69)		Standard (n = 64)		p Value*
	Median	IQR	Median	IQR	
Age (years)	11.5	10.4–12.9	11.3	10.6–12.7	0.84
Height (m)	1.45	1.39–1.56	1.45	1.39–1.54	0.96
Height (z score)	−0.05	−0.94–0.85	0.12	−0.61–0.80	0.69
Weight (kg)	41	31.5–46.5	40	32.5–48.8	0.88
Weight (z score)	0.20	−0.77–0.83	0.37	−0.44–1.02	0.30
Smoking	n	%	n	%	
Maternal smoking in pregnancy	11	16	18	28	0.098
Smoking in household	27	39	21	33	0.994
Child smoking	0	0	2	3	

CNEP, continuous negative extrathoracic pressure; IQR, interquartile range.

* χ^2 test or Student's t test.**Table 4** Comparison of selected demographic variables in the two treatment groups

	CNEP			Standard			p Value*
	n	Median	IQR	n	Median	IQR	
Maternal age (years)	67	39	35–43	61	38	35–43	0.91
Single parent family	69	n	%	61	n	%	
Maternal education ≤ O level/GCSE	67	19	28	61	9	15	0.08
Manual socioeconomic group	67	46	69	61	44	72	0.67
	69	33	48	63	22	35	0.13

CNEP, continuous negative extrathoracic pressure; IQR, interquartile range.

*Student's t test or χ^2 test.**Table 5** Comparison of clinical outcomes

	CNEP (n = 69)		Standard (n = 64)		p Value*
	Median	Range	Median	Range	
School missed owing to illness (days)	4	0–100	2	0–125	0.09
> 4 weeks off school	n	%	n	%	
Hospital admission in past year	2	3	3	5	0.59
Ever admitted to PICU	5	7	6	9	0.66
Asthma	4	6	8	13	0.19
Doctor diagnosis of asthma ever	26	38	27	42	0.60
≥1 wheezing episodes in past month	21	30	18	28	0.77
Current use of short-acting bronchodilators	10	15	15	23	0.19
Current use of steroid inhalers	7	10	13	20	0.10
Chronic respiratory signs	10	15	3	5	0.06

CNEP, continuous negative extrathoracic pressure; PICU, paediatric intensive care unit.

*Mann-Whitney U test or χ^2 test.**Table 6** Comparison of lung function between the standard and continuous negative extrathoracic pressure groups

	Number		Observed mean (SD)		Adjusted effect size for treatment	95% CI	p Value
	CNEP	Standard	CNEP	Standard			
Rint pre (kpa/l/s)	67	63	0.36 (0.14)	0.38 (0.14)	0.026	−0.020 to 0.072	0.27
Rint post (kpa/l/s)	63	59	0.25 (0.09)	0.28 (0.12)	0.026	−0.012 to 0.064	0.18
Rint, % decrease	63	59	28 (21)	27 (20)	1.11	−6.08 to 8.31	0.76
FEF, pre % predicted	67	63	77 (22)	71 (22)	−5.05	−12.75 to 2.66	0.20
FEF, % change	64	60	20 (23)	21 (22)	2.11	−6.07 to 10.23	0.61
FEV, pre % predicted	67	62	87 (12)	84 (13)	−2.66	−7.14 to 1.82	0.24
FEV, % change	64	59	6 (8)	8 (9)	1.57	−1.48 to 4.62	0.31
FVC, pre % predicted	67	63	101 (13)	96 (13)	−4.27	−8.72 to 0.18	0.06
FVC, % change	64	60	2 (6)	3 (6)	1.71	−0.59 to 4.01	0.14

CNEP, continuous negative extrathoracic pressure; FEF, forced expiratory flow; FEV, forced expiratory volume; FVC, forced vital capacity.

Analyses were by linear regression or binary logistic regression with matching criteria as covariates.

were very small. Airway resistance was slightly lower in the CNEP group, again a small and non-significant difference. Lower airway resistance would be expected in children with higher respiratory volumes on spirometry.

DISCUSSION

This study is the first of its kind that evaluates pulmonary function tests in the older child after CNEP in preterm infants with respiratory distress syndrome. We have not been able to support our principal hypothesis that the use of CNEP, associated with reduced measures of CLD in the original trial, would be associated with later improved respiratory outcomes. There may be a variety of reasons why we did not show any significant differences at follow-up in late childhood in respiratory outcomes for children treated with neonatal CNEP. Primarily, the original study⁴ was not designed to evaluate late outcomes, the power calculation being based on neonatal outcomes. Families were not expecting an invitation to join this study; hence, the relatively low follow-up rate may actually hide a significant effect. It should be noted that those neonatal variables significantly different between the two treatment groups in the original trial were not significantly different in those evaluated for this study. Nonetheless, after >10 years for most families, a follow-up rate of 65% was perhaps the best that could be achieved in the absence of interim contact. Despite the relatively low follow-up rate, neonatal and sociodemographic markers were well matched between the two groups. Furthermore, compared with infants who are currently surviving with CLD, this group of infants have higher gestational ages and birth weights and many would not now receive long-term respiratory support owing to the more frequent use of antenatal steroids and earlier use of fast-acting surfactants.

Our choice of outcome measure included microRint, in the expectation that a considerable proportion of children would be too disabled to cooperate with the forced expiratory manoeuvres necessary for spirometry. This was subsequently not found to be the case, and most of the children were able to manage this task.

However, there may be other reasons for the lack of differences between the study groups. Prematurely born infants, both with and without respiratory distress syndrome, have small but significant differences in lung function compared with normal term infants. Parat *et al*¹³ showed reduced lung compliance in preterm infants even in those without bronchopulmonary dysplasia. Others have observed that even in healthy preterm infants, exposure to extrauterine conditions could change lung function, producing higher elastic recoil than in term infants.¹⁴ They suggested that preterm birth by itself may affect alveolarisation and the formation of elastic tissue in the lungs.

Merth *et al*¹⁵ studied the effect of neonatal CLD, hyaline membrane disease and differences in ventilatory support on pulmonary function during the first year of life in 65 infants born prematurely. At 6 and 12 months, infants with CLD either with or without having had hyaline membrane disease at birth had similar pulmonary function tests. Although infants with CLD had lower lung compliance than those without CLD, their functional residual capacities were not significantly different. They concluded that birth weight rather than prior hyaline membrane disease was the major factor in the development of CLD. In another study involving older children, Kennedy *et al*³ also observed that birth weight was a more important prenatal factor than gestational age in determining lung function in late childhood. However, they observed that the addition of supplemental oxygen and a reported history of asthma had a greater effect on the subsequent reduction of expiratory flows

in very preterm babies. In our study, there was no significant difference in the birth weights or reported incidence of asthma in the two groups studied, perhaps explaining the lack of difference in the respiratory outcomes of the two ventilatory groups.

Despite the lack of differences between the two groups, it is notable that both showed low results for forced expiratory volume and forced expiratory flow (1–1.5 SDs below expected). Owing to the small numbers we recruited, we did not explore the neonatal associates of these differences further, but, in so far as this may show the result of neonatal lung injury, it implies a similar degree in both groups despite the differences in neonatal outcome. Release of pro-inflammatory cytokines from lung epithelial cells in response to cellular stretch¹⁶ may contribute to the pathogenesis of CLD, something that would occur with both positive and negative pressure ventilation. Furthermore, in an animal model of CNEP versus positive end-expiratory pressure (PEEP) in piglets, no differences in pulmonary function or haemodynamic parameters between the two groups were found, and the authors concluded that CNEP and PEEP were physiologically equivalent in their model.¹⁷ The same group investigated the effect of CNEP versus PEEP in endotoxin-induced pulmonary hypertension.¹⁸ The increase in PaO₂ was similar in the two groups. No differences were seen in dynamic lung compliance, end-expiratory lung volume, lung resistance or haemodynamic parameters. The transpulmonary pressures and transrespiratory pressure were equal, indicating that CNEP in tandem with intermittent mandatory volume was physiologically equivalent to PEEP and intermittent mandatory volume. The degree of alveolar distension is determined by the pressure gradient across the alveoli, approximated by the transpulmonary pressure. As the two forms of ventilation provided similar levels of transpulmonary pressure, we can only conclude that the two modalities provided similar levels of alveolar distension and possible epithelial protein leaks,¹⁹ resulting in equivalent lung damage.

Other ventilatory modalities have been used to try to reduce short-term and long-term morbidity with similar findings. For example, high-frequency ventilation oscillatory ventilation (HFOV) has been evaluated as a strategy to avoid pulmonary volutrauma and therefore reduce mechanical stress to the alveoli. Although it initially showed promise in reducing pulmonary complications,²⁰ in the most recent Cochrane review of HFOV, an elective mode of early ventilation showed no benefit in reducing respiratory morbidity.²¹ The UK Oscillation Study has been the largest randomised trial comparing two different modalities of ventilation in preterm infants. Neither HFOV nor conventional intermittent positive pressure ventilation as the initial ventilatory modality for babies of of gestation ≤ 28 weeks showed significant short-term improvements,²² differences in pulmonary function tests on a subset of children at 1 year²³ or in respiratory symptoms at 2 years.²⁴ In a 9-year follow-up of a high-frequency ventilation trial in preterm infants, Pianosi and Fisk²⁵ concluded that factors other than the mode of ventilation exerted a greater influence on pulmonary outcome in graduates of neonatal care.

In conclusion, we have produced no evidence that CNEP offers significant pulmonary protection compared with standard treatment for preterm babies with respiratory distress syndrome. In this group of infants, other unidentified factors were probably more important in determining long-term respiratory outcomes.

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What is already known on this topic

- Survivors of prematurity are at risk of later morbidity as a result of chronic lung disease.
- Respiratory symptoms and abnormal pulmonary function are thought to persist into childhood.
- The use of continuous negative extrathoracic pressure in the early 1990s was associated with less neonatal respiratory illness in the preterm compared with standard treatments available at that time.

What this study adds

- At 12 years, pulmonary function and respiratory morbidity were found with similar frequencies in children treated with neonatal continuous negative extrathoracic pressure and in those receiving standard respiratory support for respiratory distress syndrome.

Authors' affiliations

K Telford, L Waters, N Marlow, School of Human Development, University of Nottingham, Nottingham, UK

H Vyas, Children's Services, Queen's Medical Centre, Nottingham, UK

B N Manktelow, E S Draper, Department of Health Sciences, University of Leicester, Leicester, UK

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