United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation

Anne Greenough,[1]* Janet Peacock,[2] Sanja Zivanovic,[1] Mireia Alcazar-Paris,[1] Jessica Lo,[2] Neil Marlow[3] and Sandy Calvert[4]

[1]Division of Asthma, Allergy and Lung Biology, Medical Research Council (MRC) Centre for Allergic Mechanisms in Asthma, King's College London, London, UK
[2]Division of Health and Social Care Research, King's College London, London, UK
[3]Institute for Women's Health, University College London, London, UK
[4]Department of Child Health, St George's Hospital, University of London, London, UK

*Corresponding author

Declared competing interests of authors: Anne Greenough has held grants from various ventilator manufacturers and received honoraria for giving lectures and advising various ventilator manufacturers.

Published June 2014
DOI: 10.3310/hta18410

Scientific summary

United Kingdom Oscillation Study: long-term outcomes
Health Technology Assessment 2014; Vol. 18: No. 41
DOI: 10.3310/hta18410

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

One in 200 infants in the UK is born extremely prematurely, that is before 29 weeks of gestation. Advances in neonatal care have meant that 75% of such babies survive, but many have long-term respiratory and/or functional problems; for example, up to 40% develop bronchopulmonary dysplasia (BPD). Infants with BPD have frequent hospital admissions in the first 2 years after birth, particularly for respiratory infections. Supplementary oxygen at home may be required for many months. BPD infants who require home oxygen compared with those who do not have greater health-care utilisation with an associated doubling of their cost of care throughout the preschool years; the families' quality of life has also been reported to be poorer. At preschool and school age, troublesome recurrent respiratory symptoms are common. In one cohort of children who had BPD, 28% coughed more than once per week and 7% wheezed more than once per week in the preschool years, and in a cohort of 7- to 8-year-olds, whereas only 7% of term controls were wheezing, 30% of BPD children and 24% of prematurely born children without BPD were also affected. Troublesome symptoms and lung function abnormalities are even seen in young adults who had BPD. Nine per cent of very prematurely born infants have serious disability at 2 years of age. At school age, BPD is associated with poor cognitive and academic achievement, which is the predominant problem leading to educational special needs support. This poor cognitive and academic achievement, together with motor, attention and behavioural problems, contributes to functional deficits that may persist to adult life.

Infants born extremely prematurely usually require respiratory support which, although often life-saving, is frequently associated with lung damage which leads to the long-term respiratory problems described above. The United Kingdom Oscillation Study (UKOS) was a multicentre, randomised trial undertaken to determine whether use of high-frequency oscillation (HFO) or conventional ventilation (CV) from within 1 hour of birth would reduce mortality and the incidence of BPD. A total of 797 infants born before 29 weeks of gestation were randomised from 25 centres.

The aim of this follow-up study was to determine the long-term outcomes of children at 11–14 years of age who had been recruited into UKOS and, in particular, to test the hypothesis that use of HFO in the newborn period would be associated with superior small airway function at school age. In addition, we wished to assess the effects of HFO compared with CV on a broad range of respiratory health and educational outcomes as the results of those follow-up assessments of children from the randomised trial would robustly inform the true risk–benefit ratio of the use of HFO in very prematurely born infants. A null (no difference) finding would be as clinically important as any difference that might be observed, as it would resolve the uncertainty surrounding the long-term effects of HFO and CV and determine whether or not HFO could be safely used to support very prematurely born infants. A subsidiary aim was to track the lung function in the subset of children previously assessed at 1 year, as those results would highlight whether or not changes in lung function over time differed according to ventilation mode.

Study design

Comprehensive lung function and cardiac assessments were undertaken when the children were 11–14 years of age at King's College Hospital (KCH) NHS Foundation Trust, London, UK. All assessments were made by a research fellow and research nurse blind to the child's randomised mode of ventilation. Respiratory, health-related quality of life and functional assessment questionnaires were completed. Parents and their children who were unable to attend the London centre completed the questionnaires only.

Sample size

The primary outcome was small airway function. A sample size of 320 allowed a difference of 0.36 standard deviations (SDs) in the mean lung function results to be detected with 90% power at the 5% significance level. Differences in lung function of equal to 1.0 SD have been demonstrated in children with and without adverse respiratory outcomes; thus, our sample size allowed detection of a clinically important difference in lung function. Secondary outcomes were other aspects of respiratory health and symptoms, multiattribute health status as assessed by Health Utilities Index version 3 (HUI-3), the Strengths and Difficulties Questionnaire (SDQ), special educational needs (SEN) support and subject-specific educational attainment.

Results

Three hundred and nineteen children (160 received HFO) were recruited into this follow-up study (planned sample size 320): 59 took part by completing the detailed questionnaires only, four completed the assessment only and 256 completed both the questionnaires and assessment at KCH.

Comparison of the baseline characteristics of those who were and were not recruited demonstrated significant differences with regard to only the mother's ethnic group. Children who were recruited were more likely to have a Caucasian mother (90% vs. 73%), and were less likely to have a mother who smoked during pregnancy (24% vs. 38%). Differences in the birthweight *z*-score was of borderline significance; recruited children had, on average, a lower *z*-score than those not recruited (mean –0.59 vs. –0.41).

There were four maternal and neonatal characteristics factors that differed significantly between the two ventilation groups: the CV group had a higher mean birthweight (923 g vs. 867 g), and were born at a slightly later gestational age (mean gestational age 27.0 weeks vs. 26.7 weeks), a greater proportion were born at 26–28 weeks of gestation rather than a lower gestational age (81% vs. 68%) and a greater proportion had received surfactant (99% vs. 95%).

There were no significant differences between the two groups in their characteristics when they were assessed at 11–14 years of age. There was a statistically significant difference in the primary outcome of small airway function [forced expiratory flow at 75% vital capacity (FEF_{75})]; the *z*-score was higher in the HFO group (mean FEF_{75} *z*-score was –1.19 vs. –0.97). This difference was significant both in the unadjusted model that allowed for multiple births, but did not include any covariates, and in the fully adjusted model which additionally adjusted for the baseline neonatal factors that had shown imbalance between the groups. The adjusted difference in mean *z*-scores was 0.23 [95% confidence interval (CI) 0.02 to 0.45]. There were a greater percentage of children with lung function results below the tenth centile in the CV group (46%) than in the HFO group (37%). There were similar mean differences between the groups for both forced expiratory flow at 50% vital capacity (FEF_{50}) and forced expiratory flow at 25% vital capacity (FEF_{25}). There were also significant differences between the ventilation groups with regard to a number of the other lung function results: forced expiratory volume at 1 minute (FEV_1), peak expiratory flow rate (PEF), diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$), maximum vital capacity (VC_{MAX}), respiratory resistance at 5 Hz and the FEV_1 : forced vital capacity (FVC) ratio. The results were all worse in the CV group. There were no significant differences with regard to airway hyper-reactivity and exhaled nitric oxide between the two groups. Sensitivity analyses were performed on the lung function measurement results; pubertal stage and cotinine levels were added to the fully adjusted model. This further analysis demonstrated findings consistent with those of the previous analysis, with significant differences in the primary outcome and the above secondary outcomes with similar effect sizes. Multiple imputation was used to allow for incomplete lung function data for some tests, which certain children were unable to do. Those analyses gave results that were unchanged from those reported above. Further

analyses adjusting for factors, such as Index of Multiple Deprivation score, that differed between those recruited and those not recruited did not change the findings.

Analysis of the lung function results of 42 children who had been assessed at 1 year of age and at age 11–14 years showed that their small airway function had deteriorated, as demonstrated by an increase in gas trapping.

There were no significant differences between the two ventilation groups with regard to the echocardiographic results.

There were no significant differences between ventilation groups with regard to respiratory morbidity in the last 12 months or health problems as documented by the parent-completed questionnaire. The HUI-3 was completed separately by the child and their parent(s); there were no significant differences by ventilation group. The SDQ was completed by the child, their parent and their teacher; there were no significant differences between the ventilation groups. When the SDQ scores were dichotomised, the only significant difference between the two groups was for the children's report of emotional symptoms, with a higher proportion in the HFO group [odds ratio (OR) 2.50 (95% CI 1.13 to 5.56)], but this was not confirmed by parental or teacher reports.

Two hundred and twenty-four teachers completed questionnaires regarding the children's educational attainment and provision, and returned them directly to the researchers. There were statistically significant differences in attainment in three subjects – art and design, information technology (IT) and design and technology; the attainment was better in the HFO group. There was a trend towards a smaller proportion of the HFO children receiving SEN support compared with the CV children [41% vs. 53%; OR 0.56 (95% CI 0.32 to 1.00)]. The results of the teacher rating scale for attention deficit hyperactivity disorder did not differ significantly by ventilation group.

Conclusions

We have demonstrated that school children born extremely prematurely who were supported by HFO in the neonatal period had significantly better lung function than those who were supported by CV. The HFO group had significantly better small airway function (FEF_{75}), as we had hypothesised. In addition, they also had superior large airway function and those results are particularly compelling as there were similar findings from different assessments of large airway function (FEV_1, FEF_{50}, FEF_{25}) including from the non-volitional test impulse oscillometry. In addition, the HFO group had better $D_{L,CO}$ results, suggesting a greater lung surface area for gas exchange. There were significant differences in the baseline characteristics of the two groups who were successfully followed up, all of which favoured the CV children. They were born at a significantly higher birthweight and gestational age, and a greater proportion had received surfactant. The differences between the two groups, with respect to the above lung function test results, remained significant after adjusting for those differences in baseline characteristics. The difference in the mean FEF_{75} results between the two groups was due to a shift in the entire CV group's distribution downwards, rather than an effect on only certain children. Thus, the use of HFO would potentially benefit all extremely prematurely born infants. The differences in lung function, although statistically significant, were relatively small, on average approximately 0.30 *z*-scores. Those differences were not associated with increased respiratory morbidity as documented by symptom status and need for medication on the parent-completed questionnaires or greater number of hospital admissions, but only three of the whole cohort had required admission to hospital for chest problems. Nevertheless, there was a difference of almost nine percentage points with regard to lung function results below the tenth centile in favour of the HFO group. Respiratory reserve in childhood may explain why there was no increase in respiratory morbidity in the CV group as documented by parent reports, but the CV group's poorer lung function may make them more vulnerable to lung function insults such as smoking.

The results of our subset, who were also measured at 1 year of age, suggest that their small airway function has deteriorated, as they had greater evidence of gas trapping when assessed at 11–14 years of age than when they were assessed at 1 year corrected age. Those results are in keeping with the decline in small airway function seen in the first year after birth in moderately prematurely born infants and extremely prematurely born infants initially supported by CV. Thus, it will be very important to reassess all of the children to determine whether or not their lung function deteriorates further with increasing age and they become symptomatic.

We were concerned that any respiratory benefit associated with use of HFO might have been associated with adverse neurodevelopmental outcomes as, in some trials, HFO has been associated with increases in severe intracranial haemorrhage and periventricular leukomalacia. Those adverse outcomes could be the result of lung overdistension compromising cardiac output and cerebral perfusion and/or hypocarbia. However, no significant differences between the groups were seen regarding the majority of assessments of functional outcomes. A significantly greater proportion of the HFO children recorded that they had emotional symptoms on the SDQ questionnaire, but this difference was not found by the parents or teachers. There were significant differences between the two groups in educational attainment with regard to art and design, IT, and design and technology, all favouring the HFO children. In addition, a borderline significantly greater proportion of the CV children were receiving SEN support at school.

Our results emphasise the importance of the long-term follow-up of children born very prematurely entered into randomised trials if the full impact of interventions delivered in infancy is to be robustly determined. Furthermore, a lack of a positive result in infancy may not mean the intervention had no effect, but rather it may become manifest later and hence it is not possible to predict whether that effect could be adverse or beneficial on the results of short-term outcomes. It is essential that very prematurely born children entered into randomised trials are repeatedly assessed so that any changes with increasing age can be determined and appropriate treatment given. The results of this long-term follow-up should encourage neonatologists to use prophylactic HFO in extremely prematurely born infants.

Trial registration

This trial is registered as ISRCTN98436149.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 18, No. 41. See the NIHR Journals Library website for further project information.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: www.hta.ac.uk/

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/116/10. The contractual start date was in March 2011. The draft report began editorial review in May 2013 and was accepted for publication in January 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland www.prepress-projects.co.uk).