Protocolised non-invasive compared with invasive weaning from mechanical ventilation for adults in intensive care: the Breathe RCT

Gavin D Perkins,[1,2]* Dipesh Mistry,[1] Ranjit Lall,[1] Fang Gao-Smith,[2] Catherine Snelson,[3] Nicholas Hart,[4,5] Luigi Camporota,[5] James Varley,[6] Coralie Carle,[7] Elankumaran Paramasivam,[8] Beverly Hoddell,[1] Adam de Paeztron,[1] Sukhdeep Dosanjh,[1] Julia Sampson,[1,2] Laura Blair,[1] Keith Couper,[1,2] Daniel McAuley,[9] J Duncan Young,[10] Tim Walsh,[11] Bronagh Blackwood,[9] Louise Rose,[12] Sarah E Lamb,[1] Melina Dritsaki,[1] Mandy Maredza,[1] Iftekhar Khan,[1,13] Stavros Petrou[1] and Simon Gates[1] on behalf of Breathe collaborators

[1]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
[2]Critical Care Unit, Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[3]Department of Critical Care, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[4]Division of Asthma, Allergy and Lung Biology, King's College London, London, UK
[5]Guy's and St Thomas' Foundation Trust, King's College London, London, UK
[6]Department of Critical Care, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK
[7]Department of Critical Care, Peterborough City Hospital, Peterborough, UK
[8]Department of Critical Care, Leeds Teaching Hospitals, Leeds, UK
[9]School of Medicine, Dentistry and Biomedical Sciences, Centre for Experimental Medicine Institute for Health Sciences, Queen's University Belfast, Belfast, UK
[10]Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK
[11]Anaesthesia, Critical Care and Pain Medicine, Division of Health Sciences, The University of Edinburgh, Edinburgh, UK
[12]Faculty of Nursing, University of Toronto, Toronto, ON, Canada
[13]Population and Patient Health, King's College London, London, UK

*Corresponding author G.D.Perkins@warwick.ac.uk

Declared competing interests of authors: Gavin D Perkins reports grants and non-financial support from the Intensive Care Foundation during the conduct of the study. Daniel McAuley reports personal fees from consultancy for GlaxoSmithKline (London, UK), SOBI (Swedish Orphan Biovitum; Stockholm, Sweden), Peptinnovate Ltd (Stevenage, UK), Boehringer Ingelheim (Ingelheim am Rhein, Germany) and Bayer AG (Leverkusen, Germany). Outside the submitted work, his institution has received funds from grants from the UK National Institute for Health Research (NIHR), the Wellcome Trust and others, and from GlaxoSmithKline for Daniel McAuley undertaking bronchoscopy as part of a clinical trial. In addition, Daniel McAuley is one of four named inventors on a patent US8962032 covering the use of sialic acid-bearing nanoparticles as anti-inflammatory agents issued to his institution, Queen's University Belfast (www.google.com/patents/US8962032). Daniel McAuley is a member of the Health Technology Assessment (HTA) General Board. James Varley reports non-financial support from La Jolla Pharmaceutical Company (San Diego, CA, USA) and personal fees from Emas Pharma (Hitchin, UK) outside the submitted work. Nicholas Hart reports grants from Guy's and St Thomas' Charity during the conduct of the study, grants from Philips Respironics (Murraysville, PA, USA), non-financial support from Philips Respironics RT Meeting (Myotrace), personal fees from Fisher & Paykel Healthcare (Auckland, New Zealand), grants from ResMed (San Diego, CA, USA), grants from B & D Electromedical (Stratford-upon-Avon, UK), grants from Fisher & Paykel Healthcare. In addition, Nicholas Hart has a patent, Myotrace, pending and he is on the Pulmonary Research Advisory Board for Philips. Nicholas Hart's Lane Fox Clinical Respiratory Physiology Research Group has received unrestricted grants (managed by Guy's and St Thomas' Foundation Trust) from Philips Respironics, Philips, ResMed, Fisher & Paykel Healthcare, and B & D Electromedical. Philips Respironics and Philips Research are contributing to the development of the Myotrace technology.

Published September 2019
DOI: 10.3310/hta23480

Scientific summary

The Breathe RCT

Health Technology Assessment 2019; Vol. 23: No. 48
DOI: 10.3310/hta23480

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

Scientific summary

Background

Invasive mechanical ventilation (IMV) is a life-saving medical intervention. Each year in the UK, 110,000 people require IMV. Acute respiratory failure is the most common indication for IMV. Following resolution of the illness that led to the requirement for IMV, clinical focus shifts to the process of weaning the patient from IMV. A key component of this process is the spontaneous breathing trial (SBT). In a SBT, much of the assistance from the mechanical ventilator is removed, in order to assess the patient's readiness to breathe without its support. Patients who pass the SBT proceed to extubation.

In patients who fail a SBT, the traditional approach has been to continue IMV and to administer a further SBT the following day. However, an alternative approach that has been advocated is to extubate the patient to non-invasive ventilation (NIV). The potential benefits of this approach are the avoidance of further ventilator-induced lung injury, a reduced likelihood of ventilator-associated pneumonia (VAP) and increased patient comfort. The key risk is that, if the strategy fails, the patient will require reintubation, which may be associated with increased mortality.

Sixteen small, typically single-centre, trials ($n = 994$) that compared these approaches were meta-analysed in a Cochrane review (Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2013;**12**:CD004127). The review found evidence that the use of NIV in weaning patients from IMV reduced mortality, VAP and duration of mechanical ventilation. However, subgroup analyses found that the beneficial effect was limited to patients with chronic obstructive pulmonary disease (COPD).

In view of the limited generalisability of previous trials to the UK setting and the recognised importance of the clinical issue to the UK critical care community, the National Institute for Health Research (NIHR) Heath Technology Assessment (HTA) programme issued a commissioned call for a study to identify the optimal strategy of liberating patients from IMV.

Objective

The objective of this trial was to determine the clinical effectiveness and cost-effectiveness of NIV as an intermediate step in the protocolised weaning of patients from IMV.

Methods

Design

A pragmatic, open-label, multicentre, randomised controlled trial was conducted to determine if protocolised weaning that includes early extubation on to NIV is clinically effective and cost-effective compared with weaning without NIV (the Breathe trial). The trial was sponsored by Heart of England NHS Foundation Trust. The trial was reviewed and approved by the Oxford C Research Ethics Committee (REC). The trial was managed on a day-to-day basis by a Trial Management Group. Independent oversight was provided through a Trial Steering Committee, and a Data Monitoring and Ethics Committee.

Setting and participants

Patients in critical care units were eligible to participate in the trial if they were aged > 16 years, had received IMV for > 48 hours, were classified as ready to wean by the critical care clinical team and had

failed a SBT. Key exclusion criteria included pregnancy, contraindication to NIV, inability to protect airway because of neurological deficit, and decision not to reintubate or planned withdrawal of treatment.

Interventions

The method [T-piece, continuous positive airway pressure (CPAP) or low-pressure support (P_{supp})] and duration (30–120 minutes) of the SBT were at the discretion of the clinical team. To be deemed to have failed the SBT, the patient were required to meet one of the predefined failure criteria, such as tachypnoea ($\geq$ 50% of baseline value or > 35 breaths per minute), hypercapnia (> 6.5 kPa or increase by > 1 kPa), acidaemia (a pH of < 7.32 or a fall in pH by > 0.07) or increased respiratory effort (e.g. accessory muscle use, facial distress, dyspnoea).

Following confirmation of eligibility and patient consent or consultee agreement, patients were randomised in a 1 : 1 ratio to invasive or non-invasive weaning strategies using an electronic randomisation system. Randomisation was minimised by centre, presence of COPD and reason for critical care admission (postoperative/non-operative).

Participants in the invasive weaning group were returned to P_{supp} ventilation after the failed SBT. P_{supp} was reduced every 2 hours during daytime based on patient condition, in accordance with a weaning protocol. Participants underwent daily SBTs to assess readiness for extubation. The weaning process was followed until a tracheostomy was performed or the participant was extubated.

Participants in the non-invasive weaning group were extubated to NIV after the failed SBT. Initial NIV settings were based on ventilatory settings prior to extubation. P_{supp} was reduced every 2 hours during daytime, based on the participant's condition, in accordance with a weaning protocol. If the participant was considered suitable by the clinical team, a trial of face-mask oxygen was attempted. The weaning process was discontinued when the participant tolerated 12 hours of unsupported spontaneous ventilation.

In both groups, the clinical team titrated fraction of inspired oxygen and/or positive end-expiratory pressure (PEEP)/expiratory positive airway pressure (depending on treatment group) to maintain saturation of oxygen in peripheral blood (SpO_2) of > 90%. The decision to reintubate or perform a tracheostomy was at the discretion of the clinical team, although teams were encouraged not to perform a tracheostomy until at least 7 days after randomisation.

Main outcome measures

The primary effectiveness outcome was time (in hours) from randomisation to successful liberation from ventilation. Liberation from ventilation was defined as the time point at which the patient was free of ventilatory (invasive or non-invasive) support for > 48 hours. Secondary outcomes included mortality (30/90/180 days), duration of IMV, total number of ventilator days (IMV and NIV), time to meeting intensive care unit (ICU) discharge criteria, proportion of patients receiving antimicrobials for presumed respiratory infection and total number of days receiving antimicrobials, reintubation rates and the proportion of patients receiving a tracheostomy. Safety outcomes were adverse events (AEs) and serious adverse events (SAEs). Health-related quality of life (HRQoL) was assessed by the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), and Short Form questionnaire-12 items (SF-12) at baseline (estimated retrospectively), and at 90 and 180 days.

The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained from the perspective of the NHS and Personal Social Services.

The original sample size was 920 participants to reliably detect a hazard ratio (HR) of 0.8 between the intervention and control groups for the primary outcome at 80% power, allowing for attrition as a result of ICU death and missing outcome data. This equated to a 36-hour difference in the time to liberation from ventilation, based on an average of 6.4 days in the control group. Interim data analysis identified a skewed data distribution, such that 2.9 days was considered a better estimate for the sample size calculation. Based on these data, it was calculated that a sample size of 280 participants would provide 90% power to

detect a clinically meaningful median difference of 24 hours between the intervention and control groups for the primary outcome at a 5% significance level. This was inflated to 364 participants to account for attrition.

The primary statistical analysis was based on intention-to-treat principles. For analysis of the primary outcome and other time-to-event outcomes, survival analysis methods were used to estimate the HR and the associated 95% confidence interval (CI). For mortality outcomes, logistic regression models were used to estimate the odds ratio (OR) and 95% CIs for differences between groups. Linear regression models were used to estimate the mean treatment difference and 95% CIs for continuous outcomes. For count data, depending on the distribution of the data, negative binomial models were used to estimate the incidence rate ratio and the associated 95% CI or non-parametric tests. All of the analyses were adjusted for age, sex, centre, post-SBT partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and stratification variables (COPD and operative status).

In addition, sensitivity analyses were conducted, namely a per-protocol analysis to explore any apparent baseline differences between the groups. Predefined subgroup analyses comprised presence/absence of COPD and postoperative/non-operative status.

The complementary health economic evaluation examined the cost-effectiveness of interventions. It incorporated the costs of the intervention and the broader health and social care costs over the trial period. Health and social care resource and HRQoL (measured using the EQ-5D-3L and SF-12) data were collected through questionnaires at 3 and 6 months. Multiple imputation was used to impute missing data. For the cost-effectiveness analysis, the incremental cost-effectiveness ratio was estimated as the difference between trial groups in mean total cost divided by the difference in mean total QALYs.

Results

The Breathe trial was conducted between March 2013 and October 2016 across 51 hospitals. In total, 17,126 patients were screened, of whom 1752 underwent a SBT. A total of 432 patients failed the SBT and were therefore eligible for the trial, of whom 68 declined participation and 364 (invasive weaning, $n = 182$; non-invasive weaning, $n = 182$) were randomised.

Groups were well matched at baseline, in relation to demographics, diagnosis, ventilation/haemodynamic characteristics and the SBT process. The mean age of participants was 63.1 years [standard deviation (SD) 14.8 years] and half were male ($n = 184$, 50.5%). The mean duration of ventilation prior to randomisation was 5.8 days (SD 3.5 days). The two most common diagnoses were pneumonia/respiratory infection ($n = 130$, 35.7%) and post-surgery respiratory failure ($n = 78$, 21.4%). The mean baseline PEEP was 6.2 cmH_2O (SD 1.8 cmH_2O) and $PaCO_2$ was 5.7 kPa (SD 1.3 kPa). The most common SBT strategy was CPAP with a mean duration of 47.4 minutes (SD 36.5 minutes). Tachypnoea and increased respiratory effort were the most frequently cited reasons for SBT failure.

Treatment compliance was high in both groups (invasive weaning $n = 158$, 86.8%; non-invasive weaning $n = 175$, 96.2%). Follow-up data at 3 and 6 months were available for 186 (51%) participants in the invasive weaning group and 177 (49%) participants in the non-invasive weaning group.

For the primary outcome, the median time to liberation from ventilation was similar between groups {invasive weaning 108 hours [interquartile range (IQR) 57–351 hours vs. non-invasive weaning 104.3 hours (IQR 34.5– 297 hours); HR 1.10, 95% CI 0.89 to 1.39]. There was also no difference in mortality between groups at any time point [e.g. 30-day mortality in the invasive weaning group was 86.3% ($n = 157$) vs. 86.8% ($n = 158$) for the non-invasive weaning group; adjusted OR 0.90, 95% CI 0.51 to 1.73].

There was no difference in median total (non-invasive and invasive) ventilator days between groups [invasive weaning 4 days (IQR 2–12 days) vs. non-invasive weaning 3 days (IQR 1–9 days); adjusted mean

difference –2 days, 95% CI –4.61 to 0.69]. However, participants in the non-invasive weaning group had fewer IMV days [invasive weaning 4 days (IQR 2–11 days) vs. non-invasive weaning 1 day (IQR 0–7 days); adjusted mean difference –3.1 days, 95% CI –5.75 to –0.51]. In addition, fewer participants in the non-invasive weaning group required antibiotics for a respiratory infection than participants in the invasive weaning group (OR 0.60, 95% CI 0.41 to 1.00).

A higher proportion of participants in the non-invasive weaning group required reintubation than those in the invasive weaning group (OR 2.00, 95% CI 1.27 to 3.24). The frequencies and types of AEs and SAEs were similar between groups. Findings from subgroup and sensitivity analyses were similar to those from the main analysis.

In the cost-effectiveness analysis, a complete QALY profile was available for 182 (50%) participants. Between randomisation and hospital discharge, mean cost was similar between groups [invasive weaning £32,052 vs. non-invasive weaning £29,697; mean difference –£2355, 95% CI –£7292 to £2750]. HRQoL outcomes were similar between groups. The within-trial economic evaluation showed that NIV was associated with a lower net cost and a higher net effect and was dominant in health economic terms; the probability that NIV was cost-effective was estimated at 0.58 at a cost-effectiveness threshold of £20,000 per QALY.

Conclusions

Protocolised weaning that included early extubation to NIV did not reduce overall time to liberation from ventilation. However, patients who underwent non-invasive weaning were less likely to require respiratory antibiotics and had fewer days requiring IMV. The economic evaluation revealed that the non-invasive weaning has some potential to be cost-effective.

In patients who fail a SBT, which factors predict an adverse outcome (reintubation, tracheostomy, death) if extubated and weaned using NIV?

Trial registration

This trial is registered as ISRCTN15635197.

Funding

Funding for this study was provided by the HTA programme of the NIHR.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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

Editorial contact: journals.library@nihr.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: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/134/06. The contractual start date was in January 2013. The draft report began editorial review in September 2017 and was accepted for publication in June 2018. 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).