

Prehospital continuous positive airway pressure for acute respiratory failure: the ACUTE feasibility RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The ACUTE feasibility RCT

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Scientific summary

Background

Acute respiratory failure is a serious acute illness that occurs when diseases of the heart or lungs lead to failure of the respiratory system, over minutes or hours, in one or both of its gas exchange functions (oxygenation and carbon dioxide elimination). Common causes of acute respiratory failure include heart failure, pneumonia, chronic obstructive pulmonary disease, pulmonary embolism and asthma. The incidence of acute respiratory failure has been estimated at 80 cases per 100,000 per year. The overall risk of death is high, with estimates of 30-day mortality ranging between 14% and 20%. Acute respiratory failure has substantial health services costs, with patients often requiring prolonged hospital stays, ventilatory support and critical care admissions. Acute respiratory failure accounts for over 3 million NHS bed-days and hospital costs of £9.6M per year in England.

Current prehospital management of acute respiratory failure in the NHS uses a standard management approach of controlled oxygen therapy, supplemented by specific ancillary treatments directed at the underlying disease. Continuous positive airway pressure involves delivering oxygen-enriched air to the lungs at increased pressure through a tight-fitting face mask. Continuous positive airway pressure is widely used in hospitals to treat acute respiratory failure from a number of causes, and it has been suggested that it may be more effective if delivered earlier (i.e. en route to hospital). The difficulties of prehospital diagnosis mean that prehospital continuous positive airway pressure is likely to be applied generally to all cases of acute respiratory failure, rather than directed towards certain patients owing to a specific cause.

Existing research investigating prehospital continuous positive airway pressure is inconclusive. A previous Health Technology Assessment programme evidence synthesis [Pandor A, Thokala P, Goodacre S, Poku E, Stevens JW, Ren S, *et al.* Pre-hospital non-invasive ventilation for acute respiratory failure: a systematic review and cost-effectiveness evaluation. *Health Technol Assess* 2015;19(42)] suggested that prehospital continuous positive airway pressure could be effective in reducing mortality and intubation rates. However, included studies were deemed to be at a high risk of bias and the findings were not generalisable to the NHS. None of the included studies was undertaken in the UK and the methods used to deliver prehospital continuous positive airway pressure (physician or paramedics with online physician support) would not reflect normal NHS practice. An economic model developed for the same project suggested that prehospital continuous positive airway pressure was more effective than standard care, but was also more expensive, with an incremental cost-effectiveness ratio of £20,514 per quality-adjusted life-year. The model also indicated that further research costing up to £22.5M could represent value for money.

Although prehospital continuous positive airway pressure is a promising therapy, further research is needed to examine whether or not the reported clinical effectiveness and cost-effectiveness are confirmed in the UK setting, with unsupported paramedic delivery and limited additional training. Prior to a large pragmatic trial and economic evaluation, it is first necessary to estimate the incidence of eligible patients to determine whether or not a trial would be feasible and cost-effective. It is also important to determine whether or not prehospital continuous positive airway pressure can be delivered successfully in the context of the NHS ambulance services. For these reasons, a stand-alone feasibility study is necessary to estimate the incidence of eligible patients, to test the feasibility and acceptability of potential definitive trial methods, and to address important uncertainties, such as patient selection, delivery of the intervention and event rates.

Objectives

Primary objectives were to estimate the following feasibility outcomes:

- The rate of eligible patients per 100,000 persons per year.
- The proportion of participants recruited and allocated to treatment appropriately.
- Adherence to allocated treatment.
- Retention and data completeness up to 30 days.

Secondary objectives were to estimate the following summary clinical outcome measures:

- The proportion of participants surviving to 30 days.
- The proportion of participants undergoing endotracheal intubation by 30 days.
- The proportion of participants admitted to critical care at any point up to 30 days.
- The mean and median lengths of hospital stay.
- Change in visual analogue scale dyspnoea score from presentation to immediately before emergency department arrival.
- The mean EuroQol-5 Dimensions, five-level version, score at 30 days.
- Key elements of health-care resource use up to 30 days.

Methods

Pilot trial

An open-label, individual patient randomised, parallel-arm, controlled, external pilot trial was conducted to determine the feasibility of a definitive trial evaluating the clinical effectiveness and cost-effectiveness of prehospital continuous positive airway pressure compared with standard oxygen therapy in acute respiratory failure. A sample size of 120 participants was planned, allowing mortality to be estimated with a standard error of 2.7% for use in the sample size calculation of an eventual large-scale trial and estimation of feasibility outcomes with a precision of < 5%.

Recruitment took place across four West Midlands Ambulance Service hubs between August 2017 and July 2018. Adults with respiratory distress and peripheral oxygen saturation below the British Thoracic Society's target levels, despite supplemental oxygen, were eligible. Patients with pre-existing lack of capacity, or with limited potential to benefit from, or contraindications to, continuous positive airway pressure were excluded.

Participants in the intervention arm were treated with prehospital continuous positive airway pressure (O-Two unit, O-Two Medical Technologies Inc., Brampton, ON, Canada). Participants in the control arm received standard oxygen therapy. Ancillary condition-specific treatments were administered in both arms according to standard practice guidelines. Interventions were provided in identical sealed boxes to ensure allocation concealment. Participants were individually randomised in a 1 : 1 ratio using simple randomisation, constrained by the maximum number of boxes supplied for trial use ($n = 160$).

Feasibility outcomes comprised incidence of eligible patients (target 120); the proportion recruited and allocated to treatment appropriately (target ≥ 90); adherence to allocated treatment (target $\geq 75\%$); and retention and data completeness (target $\geq 90\%$). Effectiveness outcomes were survival at 30 days (definitive trial primary end point); endotracheal intubation; admission to critical care; length of hospital stay; EuroQol-5 Dimensions, five-level version, score; and health-care resource use at 30 days.

Economic evaluation

Cost-effectiveness and value-of-information analyses were also performed, updating the previously described economic model and evidence synthesis with data from the Ambulance continuous positive

airway pressure (CPAP): Use, Treatment Effect and economics (ACUTE) pilot trial. Prehospital continuous positive airway pressure and standard care were compared in a probabilistic sensitivity analysis following the National Institute for Health and Care Excellence base-case recommendations. The cost-effectiveness of the different interventions was estimated using the incremental cost-effectiveness ratio approach. The population expected value of perfect information and expected value of partial perfect information were calculated to indicate the cost-effectiveness of further research.

Ancillary substudies

West Midlands Ambulance Service patient records between 1 August 2017 and 31 July 2018 were electronically screened and examined by research paramedics to identify patients presenting with acute respiratory failure who were potentially eligible for the ACUTE trial. The incidence rate was then calculated using a population denominator determined from Office for National Statistics data. Agreement between the prehospital clinical impression and final hospital diagnosis was compared for patients enrolled in the pilot trial. The experiences of ambulance service clinicians participating in the ACUTE trial were examined in a mixed-methods study consisting of a survey and focus groups. The robustness of allocation concealment was investigated in a convenience sample of no-trial ambulance service clinicians from Yorkshire Ambulance Service and West Midlands Ambulance Service. Clinician participants were asked to indicate whether or not they could differentiate between a randomly selected pair of control and intervention arm boxes.

Results

Pilot trial

Over 12 months, 77 participants were enrolled (continuous positive airway pressure arm, $n = 42$; standard oxygen control arm, $n = 35$; target, $n = 120$). Continuous positive airway pressure was fully delivered as planned in 74% of intervention arm participants (target 75%). There were no major protocol violations or non-compliances (target 0%). Full data were available for key outcomes, including all feasibility end points and vital status at 30 days (targets of $\geq 90\%$). There was missing information on other clinical outcomes, with data completeness ranging from 79% to 100%.

Mortality was higher than expected [overall 27.3%: continuous positive airway pressure arm, $n/N = 12/42$ (28.6%); standard care arm, $n/N = 9/35$ (25.7%)]. Of the 21 deceased participants, 14 (68%) either did not have a respiratory condition or had explicit or implicit ceiling-of-treatment decisions, which excluded hospital non-invasive ventilation or critical care. The risk of intubation was low (overall 4.8%: continuous positive airway pressure arm, 6.1%; standard care arm, 3.4%) and only a small proportion of participants were admitted to critical care (overall 9.2%: continuous positive airway pressure arm, 11.4%; standard care arm, 6.7%).

Hospital length of stay was similar for both trial arms (continuous positive airway pressure arm, median 10 days; standard oxygen therapy arm, median 7 days). Breathlessness was similar across trial arms and improved over the prehospital interval from an initial clinician-assessed visual analogue scale median score of 9 out of 10 ($n = 76$, interquartile range 8–10) to 6 out of 10 ($n = 76$, interquartile range 5–8) on arrival at hospital. The median follow-up EuroQol-5 Dimensions, five-level version, score at 30 days was 0.82 ($n = 22$, interquartile range 0.58–0.95) in the continuous positive airway pressure arm and 0.73 ($n = 18$, interquartile range 0.43–0.89) in the standard care arm.

Adverse events related to continuous positive airway pressure comprised mild claustrophobia or distress associated with continuous positive airway pressure mask use. Two participants were diagnosed with a pneumothorax in the emergency department (expected related serious adverse events, neither receiving continuous positive airway pressure). There were no other expected or unexpected related serious adverse events.

Economic evaluation

The base-case analysis, using continuous positive airway pressure effectiveness estimates from the ACUTE pilot trial, indicated that a standard oxygen therapy strategy was likely to be cost-effective at a threshold of £20,000 per quality-adjusted life-year (mean incremental cost-effectiveness ratio £5685/quality-adjusted life-year, 67% probability). Values-of-information analyses demonstrated that there was considerable uncertainty about whether or not to adopt prehospital continuous positive airway pressure. Base-case population expected value of perfect information suggested that it would be worth spending up to £16.5M on further research. Expected value of partial perfect information analysis indicated that the effectiveness of prehospital continuous positive airway pressure on mortality was the only important variable for future investigation (expected value of partial perfect information was £16.5M, expected value of partial perfect information was zero for all other model parameters).

Ancillary substudies

Between 1 August 2017 and 31 July 2018, a total of 1017 patients were identified from the West Midlands Ambulance Service with acute respiratory failure and eligibility for the ACUTE pilot trial, giving an overall incidence rate of 17.4 per 100,000 persons per year (95% confidence interval 16.3 to 18.5 per 100,000 persons per year).

The most common final hospital diagnoses for acute respiratory failure were chronic obstructive pulmonary disease (21/65, 32.3%) and lower respiratory tract infection (28/65, 43.1%). In seven cases (10.8%), a final diagnosis was present in which continuous positive airway pressure would not be expected to be effective, or could be harmful; these included myocardial infarction, ruptured abdominal aortic aneurysm, liver failure, sepsis and pneumothorax. There was moderate agreement between the primary prehospital and hospital diagnoses (raw agreement 58.5%, Gwet's AC1 coefficient 0.56, 95% confidence interval 0.43 to 0.69).

Ambulance service clinicians felt confident in the diagnosis of acute respiratory failure, determining trial eligibility and delivering continuous positive airway pressure. Important factors identified as facilitators of participation in the pilot trial were ease of use of trial boxes and trial documentation, and simplicity of consent processes. Conversely, lack of awareness of the ACUTE trial in receiving hospitals, limited time to complete web-based trial training and a desire to provide continuous positive airway pressure treatment were highlighted as important challenges.

During week 10 of recruitment, some intervention arm equipment boxes began to 'rattle'. After repackaging and redistribution, no further concerns were noted during weekly randomisation schedule audits. Of the 278 ambulance service clinicians participating in the allocation concealment substudy, 58.6% were unable to distinguish a difference between control and intervention arm boxes. Of the participants indicating a difference, 70.4% (95% confidence interval 61.1% to 78.4%) correctly chose continuous positive airway pressure.

Conclusions

The pilot trial recruitment rate was below the target rate and feasibility was not demonstrated. The economic evaluation results suggested that a large definitive trial could represent value for money. However, the limited compliance with continuous positive airway pressure and the trial population, including patients who could not benefit from continuous positive airway pressure, indicate that a clinically significant effect size is not plausible. A definitive clinical effectiveness trial of continuous positive airway pressure in the NHS is therefore not recommended. These findings also argue against routine implementation of continuous positive airway pressure in NHS ambulance services, but would not preclude a continuous positive airway pressure service provided by clinicians, with extended training (e.g. prehospital physicians), which might allow selective targeting of treatment to an appropriate subgroup of patients.

Trial registration

This trial is registered as ISRCTN12048261.

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This report

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