Pre-hospital non-invasive ventilation for acute respiratory failure: a systematic review and cost-effectiveness evaluation

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Scientific summary

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Background

Acute respiratory failure is a common but life-threatening medical emergency. It is caused by a number of common cardiac or respiratory conditions, including heart failure, pneumonia and exacerbation of chronic obstructive pulmonary disease (COPD).

Non-invasive ventilation (NIV) involves providing respiratory support through a tight-fitting mask, which is usually applied around the patient's mouth and nose. It may take the form of continuous positive airway pressure (CPAP) or bilevel inspiratory positive airway pressure (BiPAP). It is usually used in hospital, but it may be more effective if treatment is commenced prior to arrival at hospital.

Pre-hospital NIV has been evaluated in a number of trials, with the results suggesting that it reduces mortality and intubation rates, but these trials were small and the findings were not consistent. Implementing pre-hospital NIV would require additional training for many paramedics and additional equipment for many ambulances. The substantial costs associated with this intervention means that robust evidence of clinical effectiveness and cost-effectiveness is required prior to implementation.

Objectives

We aimed to determine the clinical effectiveness and cost-effectiveness of pre-hospital NIV for acute respiratory failure and to identify priorities for future research. Our specific objectives were:

1. to undertake a systematic review, network meta-analysis (NMA) and individual patient-level data (IPD) meta-analysis to determine the effectiveness of pre-hospital NIV
2. to develop an economic model to (a) estimate the incremental cost per quality-adjusted life-year (QALY) gained by providing pre-hospital NIV instead of standard care; (b) estimate the additional costs incurred by establishing and providing pre-hospital NIV, and the lives saved and QALYs gained across the population served by a typical ambulance service; and (c) estimate the expected value of information associated with reducing uncertainty around key parameters.

Methods

We carried out a systematic review in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We searched the following electronic databases and research registers: MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Database of Abstracts of Review of Effects, Bioscience Information Service Previews, Science Citation Index Expanded, Conference Proceedings Citation Index – Science, UK Clinical Research Network Portfolio Database, National Research Register Archive, Current Controlled Trials and ClinicalTrials.gov. Resources were initially searched from inception to October 2012 and then updated to August 2013. We also checked the reference lists and undertook a citation search of relevant articles, contacted key experts in the field and undertook systematic internet keyword searches using the Google search engine

(Google Inc., Mountain View, CA, USA). We included randomised or quasi-randomised controlled trials that compared pre-hospital NIV with a relevant comparator treatment in patients with acute respiratory failure. We assessed the methodological quality of each included study according to established criteria for randomised controlled trials (RCTs).

We conducted a NMA based on aggregate data of the number of events (i.e. mortality and intubation) using Markov chain Monte Carlo simulation to jointly estimate the intervention effects relative to standard care. We carried out a NMA using IPD and aggregate data where IPD were not available to assess if covariates (i.e. age, sex, provider, primary diagnosis and severity of acute respiratory failure) were treatment effect modifiers.

We developed a de novo economic model, using the statistical software R Version 3.0.2 (the R Foundation for Statistical Computing, Vienna, Austria), to explore the costs and health outcomes when pre-hospital NIV (specifically CPAP provided by paramedics) and standard care (in-hospital NIV) were applied to a hypothetical cohort of patients with acute respiratory failure. The economic perspective of the model was the NHS in England and Wales. The model assigned to each patient a probability of intubation or death depending on their characteristics and whether they had pre-hospital NIV or standard care. The patients who survived accrued lifetime QALYs and health-care costs according to their age and sex. Costs were also accrued through costs of intervention and hospital treatment costs, which depended on patient outcomes.

The effect of pre-hospital NIV on intubation and mortality was estimated from the aggregate data meta-analysis. Utilities were estimated from a large trial of in-hospital NIV for acute cardiogenic pulmonary oedema (ACPO). The costs of pre-hospital NIV were estimated by calculating the total costs required for an ambulance service to set up and run pre-hospital NIV over 5 years, divided by the number of patients appropriately treated during this time.

We assumed that the effectiveness of pre-hospital NIV would depend on the risk of mortality from acute respiratory failure and this would increase with the distance travelled to hospital. We therefore modelled cost-effectiveness in general, urban and rural scenarios to reflect variation in the distance travelled to hospital.

Cost-effectiveness was estimated in terms of the incremental cost-effectiveness ratio (ICER) of pre-hospital NIV compared with standard care, and net monetary benefit of pre-hospital care and standard care. Uncertainty was explored using probabilistic sensitivity analysis and the expected value of perfect information (EVPI). We also conducted partial EVPI analysis, which evaluates the uncertainty associated with a subset of one of more parameters, and expected value of sample information (EVSI) analysis, which seeks to provide an optimal number of patients to study within a future trial.

Results

The literature searches identified 2284 citations. We identified and selected eight RCTs and two quasi-randomised trials for inclusion (participant numbers ranging from 23 to 207). The authors of seven of these 10 trials provided data from 650 patients for IPD meta-analysis.

The studies were undertaken in Australia, France, Germany, Canada and the USA and the results were published between 2000 and 2012. Six trials were limited to patients with ACPO and two to patients with exacerbation of COPD. Six trials evaluated CPAP and four trials evaluated BiPAP. One trial compared early CPAP with delayed CPAP; use of in-hospital NIV in the control arm was allowed in three of the other trials, prohibited in one and not recorded in five. The potential sources of bias most frequently identified in studies concerned lack of blinding of outcome assessment and lack of adequate power to detect differences in the primary outcome.

Network meta-analysis of the mortality aggregate data from all 10 trials suggested that CPAP is the most effective treatment (probability = 0.989), with an odds ratio (OR) for mortality of 0.41 [95% credible interval (CrI) 0.20 to 0.77] compared with standard care. There was considerable uncertainty associated with the effect of BiPAP relative to standard care (OR 1.94, 95% CrI 0.65 to 6.14). Sensitivity analysis, excluding two quasi-randomised trials and one trial comparing early pre-hospital CPAP with late pre-hospital CPAP, produced similar results, with CPAP being more effective than standard care (OR 0.45, 95% CrI 0.21 to 0.93), whereas the effect of BiPAP relative to standard care remained uncertain (OR 1.95, 95% CrI 0.43 to 9.46).

Network meta-analysis of the intubation aggregate data from 8 of the 10 trials (five CPAP trials and three BiPAP trials) suggested that CPAP was the most effective treatment (probability = 0.639), with an OR for intubation of 0.32 (95% CrI 0.17 to 0.62) compared with standard care. There was uncertainty associated with the effect of BiPAP relative to standard care (OR 0.40, 95% CrI 0.14 to 1.16). Sensitivity analysis, excluding one quasi-randomised trial and one trial comparing early pre-hospital CPAP with late pre-hospital CPAP, produced similar results, with CPAP being more effective than standard care (OR 0.34, 95% CrI 0.15 to 0.77), whereas the effect of BiPAP relative to standard care remained uncertain (OR 0.53, 95% CrI 0.11 to 2.28).

Combining the IPD and aggregate data in the NMA suggested that sex was a statistically significant treatment effect modifier of mortality at a conventional 5% significance level. There was evidence that gender modifies the effect of CPAP relative to usual care [males : females OR 0.18, 95% CrI (0.04 to 0.74)] but no evidence that gender modifies the effect of BIPAP relative to usual care. The NMA of the combined IPD and aggregate data on intubation suggested that none of the covariates was a treatment effect modifier at a conventional 5% significance level.

The economic analysis showed that pre-hospital CPAP was more effective than standard care but was also more expensive, with an ICER of £20,514 per QALY and a 49.5% probability of being cost-effective at the £20,000 per QALY threshold. Scenario analysis showed that, compared with the general population scenario, pre-hospital CPAP was more likely to be cost-effective in a rural population scenario (ICER £18,744 per QALY, 58.8% probability of being cost-effective at the £20,000-per-QALY threshold) and less likely to be cost-effective in an urban population scenario (ICER £21,284 per QALY, 41.5% probability).

Scenario analysis also showed that the incidence of patients likely to benefit from pre-hospital CPAP was an important determinant of cost-effectiveness. A low estimate of incidence resulted in a high ICER (£22,368 per QALY) and a low probability of being cost-effective (35.4% at the £20,000 per QALY threshold), while a high estimate of incidence resulted in a lower ICER (£11,248 per QALY) and a high probability of being cost-effective (93.8% at the £20,000-per-QALY threshold). If a typical ambulance service treated 175 appropriate patients per year, it could save 10.81 lives while incurring £235,683 additional costs, whereas, if a typical ambulance service treated 2000 appropriate patients per year, it could save 123.52 lives while incurring £582,300 additional costs.

Expected value of information analysis was also dependent on the estimated incidence of appropriate patients. The population EVPI is £1.9M at a low incidence and £22.5M at a higher incidence. Expected value of partial perfect information (EVPPI) analysis suggested that the 'effect of pre-hospital CPAP on mortality', 'total costs of pre-hospital CPAP' and 'baseline mortality' are the key parameters, with EVPPI values of £156.12, £37.54 and £14.85 per patient, respectively. Population EVPPI for the three parameters together at the threshold is estimated as £1.83M at a low incidence and £21.3M at a higher incidence of appropriate patients. Similarly, the population EVSI for a RCT with 100 patients in each arm to estimate baseline mortality and the effect of pre-hospital CPAP on mortality is estimated as £1.08M at low incidence and £12.67M at a higher incidence. The cost of a trial would probably lie between these values, so the value of further research depends on the incidence of appropriate patients.

Discussion

Pre-hospital CPAP appears to reduce mortality and intubation rate in acute respiratory failure. The effectiveness of pre-hospital BiPAP is uncertain, with estimates of the effect on mortality and intubation including the possibility of either worthwhile benefit or considerable harm. These findings were robust to sensitivity analysis in which three trials were excluded on the basis of potential risk of bias or having an inappropriate control group.

The NMA using both IPD and aggregate data suggested that male sex was a significant treatment effect modifier of mortality, with CPAP being more effective in males. The pathological basis of this finding is not clear, so it should be interpreted with caution. We found no such association in the analysis of intubation data.

The implementation of pre-hospital CPAP is likely to incur substantial costs and, even if the estimates of effectiveness from our meta-analysis are confirmed, it is uncertain if implementation would represent a worthwhile use of NHS resources. There was particular uncertainty in our estimate of the incidence of patients likely to benefit from pre-hospital CPAP, and variation in this parameter had a marked effect on the cost-effectiveness of pre-hospital CPAP and the expected value of further research. It would be cost-effective to conduct a trial with 100 patients in each arm if the overall cost of the trial is less than £1.08M and the incidence of appropriate patients is at the lowest end of our range of estimates, or if the overall cost is less than £12.67M and the incidence is at the highest end of our range of estimates.

Our systematic review includes more studies than previous reviews despite being the first to limit analysis to randomised data. It is therefore more comprehensive and carries a lower risk of bias. It is possible, however, that we may have missed unregistered trials, while the inclusion of quasi-randomised trials may have introduced some bias. The primary studies were relatively small so meta-analysis may lack statistical power to detect potentially important differences in mortality and intubation rates, particularly for the comparison between pre-hospital BiPAP and standard care. Intervention was not always compared with best alternative care. Patients eligible for pre-hospital NIV would be expected to receive in-hospital NIV if pre-hospital treatment was not available, but this was clearly mandated in only one trial.

Additionally, the findings may not be generalisable to the NHS. The trials were small and may have recruited highly selected patient groups. None of the trials was undertaken in the UK and the methods used to deliver pre-hospital NIV (physician or paramedics with online physician support) would not be usual NHS practice.

The validity of the economic analysis depended on the validity of the effectiveness analysis. If the effect of pre-hospital CPAP on mortality has been overestimated, then the cost-effectiveness of pre-hospital CPAP has also been overestimated.

Conclusions

Pre-hospital CPAP can reduce mortality and intubation rates for patients with acute respiratory failure, but the available evidence has some limitations and may not be generalisable to the NHS. Furthermore, the costs of establishing and running pre-hospital CPAP are substantial, and cost-effectiveness is uncertain. Further evidence of feasibility, clinical effectiveness and cost-effectiveness in the NHS setting is therefore required before implementation of pre-hospital CPAP can be recommended. The available evidence does not support the use of pre-hospital BiPAP, and providing pre-hospital NIV by this method is unlikely to be appropriate in the NHS.

A feasibility study of pre-hospital CPAP in one ambulance service could address important uncertainties without incurring prohibitive risks or costs. It could determine the incidence of patients transported by emergency ambulance who are eligible for pre-hospital CPAP (an important determinant of cost-effectiveness and the feasibility of any trial) and if pre-hospital CPAP can be appropriately used in the NHS, and explore if barriers to pre-hospital recruitment and randomisation can be overcome. If feasibility is demonstrated, a large pragmatic trial could compare pre-hospital CPAP with best alternative practice.

Study registration

The study is registered as PROSPERO CRD42012002933.

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