NCCHTA

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The effect of Continuous Positive Airway Pressure and Non-invasive Positive Pressure Ventilation in Acute Cardiogenic Pulmonary Oedema

(The 3CPO trial)

Trial Literature

National HTA programme grant: 01/43/01

International Standardised RCT Number: ISRCTN 07448447

Contents:

1. Project Title

Prospective, randomised controlled trial of the use of continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NIPPV) in the management of patients presenting with acute cardiogenic pulmonary oedema. The 3CPO trial.

2. Research Objectives

- To assess the clinical effectiveness of non-invasive ventilation (CPAP or NIPPV) in addition to standard therapy against standard therapy alone in the early management of acute severe cardiogenic pulmonary oedema.
- To assess whether there is any difference in the effectiveness of CPAP and NIPPV in the early management of acute cardiogenic pulmonary oedema.
- To evaluate the safety of these interventions.
- To assess quality of life and patient satisfaction after treatment with NIV compared to standard therapy alone.
- To assess the incremental cost effectiveness of NIV versus standard therapy from a health and social care perspective, in terms of cost per quality adjusted life year gained.

3. Existing research

Non-invasive ventilation (NIV) augments respiration in spontaneously ventilating patients. CPAP and NIPPV, which are forms of NIV, have been used in the management of patients with a variety of clinical conditions, including acute cardiogenic pulmonary oedema (ACPO). It has been shown to improve oxygenation, reduce the work of breathing and improve cardiac output[1-4].

Clinical studies of NIV in patients with ACPO include case series and small randomised controlled trials. The majority compare CPAP against standard therapy and suggest CPAP improves short-term physiological parameters and reduces the need for intubation and invasive ventilation[5-11]. There is no definite evidence that CPAP reduces mortality. A systematic review by Pang[12] suggested an improvement in outcome with CPAP when compared to standard treatment. A more recent summary[13] of the pooled data suggested improved mortality in the CPAP treated patients.
There are limited and conflicting data on the role of NIPPV ventilation in the management of ACPO. NIPPV ventilation has been shown to improve physiological variables more rapidly than standard oxygen therapy[14] or CPAP[15]. Conflicting results were seen comparing pre-hospital standard drug treatment with NIPPV[16]. An increased rate of non-fatal myocardial infarction was also seen in patients treated with NIPPV in two studies[15-16].

Only two studies have compared all three treatments and both are small. One suggested a reduction in intubation rate for patients treated with NIPPV[17]. The other pilot study suggested no difference in physiological variables or intubation rate between the groups[18].
Most of the trials were performed on small sample sizes and the benefits of NIV remain unproven. A larger, multicentre study is therefore required to assess:
(i.) The effect of NIV on mortality compared with standard therapy
(ii.) To determine whether one form of NIV confers an advantage over the other
(iii.) To determine if the rate of myocardial infarction is affected by the use of NIV.

4. Results from pilot studies

The grant applicants have undertaken two pilot studies. The first study was based in Edinburgh and studied 58 consecutive patients with acute cardiogenic pulmonary oedema over a nine-month period. Patients were randomised to either control (n=31) or CPAP 7.5cm H_2O (n=27). Physiological parameters were significantly better in the CPAP group at one hour but these differences disappeared at six hours. None of the patients were intubated although two patients in the control arm developed criteria for treatment failure (defined *a priori*). Two patients in the CPAP group died compared to seven in the control group. There was no significant difference in myocardial infarction rate between the two groups.

The other pilot based in the Emergency Departments in Leeds[18] recruited 60 patients with ACPO. They were randomised to CPAP 10cm H_2O or NIPPV 15cm H_2O, 5cm H_2O. There was a trend towards improved rates of treatment success (defined *a priori*) in both the NIV groups compared to standard care. There was a significant difference in the mortality rate in the CPAP group (no deaths) when compared with control (six deaths) or NIPPV (five deaths). There was one intubation in each intervention group and no significant difference between myocardial infarction rates in each group.

5. Trial Design

This trial is an open prospective randomised study comparing two intervention arms (CPAP and NIPPV in addition to standard therapy) with standard therapy alone in patients presenting with acute cardiogenic pulmonary oedema.

5.1. Allocation to trial groups

Patients will be allocated on a 1:1:1 basis between the two intervention arms and standard therapy alone if patients meet the trial inclusion criteria without having any other indication for exclusion (inclusion and exclusion criteria on data collection sheets and trial posters).
The medical and nursing staff providing the normal clinical care for that patient within the Emergency Department (ED) will undertake patient recruitment, consent and randomisation. Once consent has been obtained randomisation to one of the three treatment groups will occur. Patients will be randomised by means of a telephone call to a central randomisation centre. Staff will be given a trial number and notified of treatment group allocation. The allocated regional research nurse will automatically receive e-mail confirmation when a patient has been recruited into the trial by one of the participating centres.

5.2. Inclusion and exclusion criteria

Inclusion criteria (all criteria below will have to be fulfilled):

- Patient greater than 16 years of age on the day of presentation.
- Signs and symptoms consistent with acute cardiogenic pulmonary oedema as the principal clinical complaint (acute dyspnoea and bilateral crackles on chest auscultation).
- Chest radiograph confirming the diagnosis of acute cardiogenic pulmonary oedema (typical features of interstitial oedema present).
- Arterial blood gases revealing a pH of <7.35 (H^+ >45 nmol/litre).
- Respiratory rate of >20 breaths per minute.

Exclusion criteria:

- Severely altered consciousness (scoring P or U on the AVPU scale) requiring immediate intubation.
- Any patient who requires an immediate lifesaving intervention-cardiopulmonary resuscitation, airway control, cardioversion or inotropic support.
- Patients requiring thrombolysis or angioplasty for ST elevation MI.
- A clear alternative primary diagnosis such as lobar pneumonia.
- An inability to provide informed consent at any time within the trial period e.g. dementia or mental handicap.
- Previous inclusion in 3CPO Study.

5.3. Planned interventions

All groups will receive any standard therapy the attending physician deems appropriate. A suggested treatment protocol is provided in the data collection documents. This suggests the use of intravenous loop diuretics, buccal or intravenous nitrates and high concentration supplemental oxygen therapy via facemask. All other drug therapy will be given at the discretion of the treating medical staff.

Standard therapy
Patients will continue to receive oxygen at a concentration to maintain oxygen saturation >92% and any other treatment deemed necessary by the treating clinical staff.

CPAP group
Patients randomised to CPAP will be fitted with a self-sealing full facemask connected to a BiPAP Synchrony ventilator (Respironics, UK) set to CPAP function, at a starting pressure of 5 cm H_2O. Oxygen will be entrained into the system at 15l/min initially and subsequently adjusted to maintain oxygen saturation >92%. CPAP pressure will be titrated in 2 cm H_2O steps at 2-3 minute intervals over the first 10-15 minutes to a maximum pressure of 15 cm H_2O according to clinical response and if tolerated by the patient.

NIPPV group
Patients randomised to NIPPV will be fitted with a self-sealing full facemask connected to a BiPAP Synchrony ventilator (Respironics, UK) set to NIPPV ventilation in spontaneous/timed mode with back up respiratory rate of 12 breaths/minute. The starting inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) will be preset to 8 and 4 cm H_2O respectively. Oxygen will be entrained into the system at 15l/min initially and subsequently adjusted to maintain oxygen saturation >92%. IPAP and EPAP will be titrated at 2-3 minute intervals over the first 15-18 minutes to maximum pressures of 20 and 10 cm H_2O respectively according to clinical response and tolerance by the patient. IPAP is increased by 2 cm H_2O and EPAP by 1 cm H_2O increments.

5.4. Duration of treatment
All patients will remain on the treatment to which they are randomised for a minimum period of two hours. Any continuing use of either of the two modalities of NIV will be at the discretion of the treating physician.

5.5. Clinical documentation
1. Physiological variables (pulse, non-invasive blood pressure, respiratory rate and oxygen saturation) will be recorded on admission and at 1 and 2 hours after commencing treatment.
2. Arterial blood gas tensions will be recorded on admission and 1 hour after commencing treatment.
3. Patients will be asked to score their severity of breathlessness at 1 and 2 hours after commencing treatment.
4. Copies of twelve lead electrocardiograms and results of biochemical markers of cardiac damage.
5. The following data will be collected:

- Patient demographics
- Preceding medical history
- Medication on admission
- Drug therapy required during admission
- Duration of treatment with oxygen, CPAP or NIPPV
- Maximum CPAP, IPAP and EPAP required
- Length of hospital stay including ICU, HDU and CCU stay
- Seven day and in-hospital mortality
- Complications related to treatment
  (patient discomfort, nasal skin necrosis, vomiting, gastric aspiration, pneumothorax)
- Treatment failure and intubation rate

Patient satisfaction with the treatment in the Emergency Department will be determined using a questionnaire consisting of the outcomes and attitudes towards care questions from the widely used Group Health Association of America (GHAA) Consumer Satisfaction Survey[19]. This will ideally be self-completed, although the Research Nurse or an individual from the hospital project team may assist completion if requested to do so when they visit the patient in the first week after recruitment.

5.6. Follow up

Patients will be reviewed within one week of admission by the regional research nurse or one of the local project team who will ensure written consent has been obtained, record patient satisfaction with treatment, side effects and document required data. Follow up by questionnaire at one, three and six months after hospital admission will be undertaken. Mortality to the end of the trial will be collated using routinely collected data including central death registers.

5.7. Equipment

The BiPAP Synchrony (Respironics, UK) will be used for patients randomised to CPAP or NIPPV. This is a compact, portable, user-friendly ventilator, which can be used to deliver either CPAP or NIPPV ventilation. Up to 15l/min of oxygen can be entrained into the facemask delivering a maximum oxygen concentration of 60% depending on an individual patient's tidal volume.

6. Ethical arrangements

CPAP and NIPPV are currently used in a number if countries to treat ACPO but it is not used as standard therapy in the United Kingdom. Experience in the use of NIV is increasing in the UK. Some evidence exists that non-invasive ventilation improves patients' symptoms and physiological parameters more rapidly than standard therapy and reduces the need for intubation. There is inconclusive evidence as to whether it has an effect on mortality.

6.1. Risks and anticipated benefits for trial participants and society

Trial patients

Trial participants may benefit from treatment with NIV by feeling less breathless and by an objective improvement in clinical variables during the first two hours of treatment. There may also be an improvement in intubation rate and mortality.

Uncommon complications from the use of NIV include intolerance of the mask, vomiting, skin abrasions from the mask and the potential risk of barotrauma. Two centres involved in this application have recently studied its effect on patients with ACPO and found a very low complication rate[11,18]. The possible increased risk of myocardial infarction found in some studies[15,16] using NIPPV in ACPO but not in others[14] will be kept under active review throughout the study by an independent data monitoring and ethics committee who will review the data at approximately six month intervals. If it becomes clear that one form of treatment is associated with a significantly higher rate of mortality or myocardial infarction this study group will be discontinued and patients randomised to the remaining groups for the remainder of the trial period.

Society

There are no obvious risks to society in conducting this study. Society will benefit from this research by determining if NIV improves outcome, including mortality. A significant influence on outcome at acceptable cost may justify its routine use in all UK departments treating patients with ACPO.

6.2. Informing potential trial participants of possible benefits and known risks of the intervention

Patients will be given an information sheet to read before consent is obtained. However, given that the trial patients will be acutely unwell, some may be given the risks and benefits of participation in the trial verbally. In these cases the fact that the information has been given verbally and has been understood by the patient will be witnessed and the information sheet left with the patient to read at a later time. Patient's relatives will also be given an information sheet at the time of patient consent or relative assent.

6.3. Method of gaining consent from potential trial participant or assent of appropriate relative

Patients will be recruited when they are extremely unwell. Written informed consent will be obtained prior to randomisation whenever possible. In the event of a patient being unable to give written consent, either witnessed verbal consent or relatives' assent will be obtained. Verbal patient consent will be witnessed in writing by a second individual involved in the patient's clinical care. Subsequent written consent will be obtained as soon as possible prior to the patient's data being used in the trial and normally within one week of recruitment.
In the event of a patient being unable to give informed written or verbal consent, and there is no accompanying relative who is willing to give assent, the patient will be excluded from the study and will be treated according to the Emergency Department's usual clinical practice.

6.4. Follow up of non-recruited patients

Non-recruited will be followed up to provide data to comply with CONSORT reporting of randomised controlled trials. The data protection act will be complied with at all times.

6.5. Time period for retention of trial documentation

Trial documentation will be stored for seven years after completion of the trial.

7. Statistical Issues

7.1. Sample size

The commission brief can be viewed as addressing two distinct questions:

(i.) Is non-invasive ventilation superior to standard facial oxygen therapy?

(ii.) Which form of non-invasive ventilation is the most efficacious: CPAP or NIPPV ventilation?

To maximise the ability to address these two distinct questions in the three groups, we will allocate 400 patients to each treatment group and undertake two independent and distinct analyses.

Is non-invasive ventilation superior to standard facial oxygen therapy?

The primary endpoint will be seven-day mortality. Seven previous studies of acute cardiogenic pulmonary oedema[5,7-11,18] (n=11-50 per treatment group) have assessed standard facial oxygen therapy in comparison to continuous positive airways pressure ventilation with only two further available studies[14,17] assessing NIPPV ventilation. The pooled data show a mortality rate of 21% (38/181) in patients receiving standard facial oxygen and 9% (16/173) in those receiving continuous positive airways ventilation. These small-scale studies are open to publication bias and there has been no single major multicentre trial to address definitively the question of whether non-invasive ventilation improves mortality in patients with ACPO.

In this trial we aim to be able detect a 6% absolute difference in mortality which is half the effect size previously reported[13.] In order to have an 80% chance of detecting a 6% difference (9% vs 15%) using a two-sided significance level of 0.05, we need approximately 400 patients randomised to standard facial oxygen therapy compared to 800 patients randomised to either CPAP or NIPPV.

Which form of non-invasive ventilation is the most efficacious?

It is likely that the treatment effect will be smaller than that observed compared to standard oxygen therapy. In order to draw out any plausible and clinically useful treatment effects, an additional primary endpoint will be a composite of seven-day mortality and intubation rate. There has been a suggestion from the literature that NIPPV is associated with an increased incidence of myocardial infarction[15,16] which resulted in the early termination of the trial by Mehta[15] . Myocardial infarction will be a secondary endpoint and will be monitored throughout to ensure trial safety.

The few studies which have assessed NIPPV[14-16,18] have had small treatment groups (n=20). Therefore, there is insufficient data to estimate the likely difference between these two treatment modalities. With n=400 patients in each of the CPAP and NIPPV arms, the trial will have an 80% power using a two-sided significance level of 0.05 to detect an absolute difference of approximately 7% in the composite end point (18% vs 11%), and approximately 6% in mortality (12% vs 6%).

7.2. Statistical analysis

The trial statistician, Professor Jon Nicholl, will perform the statistical analyses. All outcomes will be assessed by intention-to-treat analysis. The analysis will firstly compare patient and clinical characteristics of the three randomised groups to identify any statistically important imbalances in the randomisation; secondly, compare mortality in the three arms using a logistic regression model with the degrees of freedom for differences between the three treatments decomposed into the two orthogonal contrasts of (i) standard therapy versus non-invasive ventilatory support (CPAP and NIPPV), and (ii) CPAP versus NIPPV; and thirdly, if appropriate, compare mortality taking into account any statistically important imbalances. The analysis will then compare the composite endpoint death or intubation using the same statistical approach. Finally, data for other secondary endpoints, such as rate of myocardial infarction, patient satisfaction and QALYs, admission to a high dependency area, length of stay, and changes in physiology over the first two hours of treatment, will be examined using analysis of variance type models, with repeated measures and adjustment for baseline covariates as appropriate. Statistical significance will be taken at the 5% level.

7.3. Health Economic Analysis

Empirical data from the trial will be used to estimate comparative costs and QALYs up to six months after recruitment. Markov modelling will then be used to estimate subsequent long-term quality-adjusted survival and costs. The following comparisons will be presented with 95% CI's- seven day survival, QALYs gained by treatment, costs of index hospital admission, total cost implications of treatment, and incremental cost per QALY gained for each treatment compared to the next most effective alternative. Cost-effectiveness acceptability curves will be generated to demonstrate the probability of a more effective treatment being considered cost-effective at different cost per QALY thresholds. Sensitivity analysis will be undertaken to examine the influence of variation in key parameters upon overall estimates of cost-effectiveness.

7.4. Outcome measures

The primary endpoint for the comparison of NIV versus standard therapy, and CPAP versus NIPPV, is 7-day mortality. An additional primary endpoint for the comparison of CPAP versus NIPPV is the composite of 7-day mortality or intubation.

7.5. Secondary Endpoints

Based on data from our pilot studies[11,18] the rapidity and efficacy of response to treatment will be assessed using several secondary endpoints. These will be symptoms, tolerability, side effects and physiological variables. In addition, cost-effectiveness will be determined by assessing the use of health care resources, quality of life and long-term survival. Details of secondary endpoints are described in the table below.

Myocardial infarction can be defined using three variables:

1. Clinical history of chest pain and myocardial ischaemia. It is recognised that some patients will present in the absence of chest pain, such as those with diabetes mellitus or degenerative autonomic neuropathy.
2. Electrocardiographic changes consistent with myocardial ischaemia including (i) ST segment elevation, (ii) ST segment depression, (iii) T wave inversion, (iv) new onset bundle branch block, and (v) development of Q waves.
3. Elevated cardiac markers. Rise in cardiac troponin or creatine kinase MB isoemzyme above 99th centile of the reference range. In the absence of troponin or CK-MB estimations, a rise in creatine kinase twice the upper limit of normal will qualify.

It should be noted that some causes of acute shortness of breath also fulfil the above criteria, such as an acute pulmonary thromboembolism. For the purposes of this clinical trial, an acute coronary syndrome (myocardial infarction and unstable angina) will only be diagnosed in the absence of a clear alternative clinical diagnosis and:

1. Myocardial infarction will be defined as the presence of 3 in combination with 1 or 2.
2. Unstable angina will be defined by the presence of 1 in combination with 2 only.

It is recognised that serial electrocardiograms (on admission and the following day as a minimum) and cardiac markers (on admission and at 12 hours post symptom onset as a minimum) will be required.

It is recognised that a complete data set may not be available in exceptional circumstances. Therefore, two blinded Consultant Cardiologists will adjudicate on the diagnosis of myocardial infarction in the following categories:

1. Definite MI.
2. Probable MI
3. Possible MI
4. Definite no MI

Q wave myocardial infarction will be defined by Q wave present in V_1-V_3 or Q wave =0.03 s in leads I, II, aVL, aVF, V_4, V_5 or V_6.

Table of Secondary End-points

Physiology	Arterial blood analysis	Hydrogen ion concentration/pH
		Partial pressure of oxygen
		Partial pressure of carbon dioxide
	Pulse oximetry	Oxygen saturation
	Respiratory rate	Breaths per minute
	Blood pressure	Systolic, diastolic and mean
	Heart rate	Rate per minute
Symptoms	Dyspnoea	Visual Analogue Score
	Tolerability	
	Side-effects	Gastric Dilatation, Facial Abrasions
Serious Adverse Events		Myocardial Infarction
Treatment failure		Worsening acidosis, hyercapnia or hypoxaemia after 1 hour on arterial blood gas analysis Progressive respiratory distress
		Inability to tolerate allocated treatment
Patient satisfaction		

7.6. Health Economic Outcomes

Economic evaluation will assist policy makers to decide whether any benefit associated with treatment for ACPO, in terms of improved seven-day survival, is cost-effective, in terms of the cost per quality-adjusted years of life gained. A health and social care perspective will be taken for this analysis.

Any potential benefit of CPAP or NIPPV lies in reducing early mortality from ACPO. Once a patient has survived to the primary endpoint, it is not anticipated that subsequent quality of life or survival will be related to the initial treatment provided. However, the true value of the lives saved by initial treatment is determined by long-term survival and quality of life. Thus measurement of cost-effectiveness requires estimation of survival and quality of life for all patients surviving ACPO.

The costs of initial treatment will be principally determined by the staff time and consumables used in the initial hours of treatment, the length of hospital stay, and use of high dependency or intensive care facilities. However, patients who survive ACPO are likely to require long-term health and social care. If intervention improves survival from ACPO then this will incur additional costs for long-term care for these survivors.

This paradox, whereby the more effective a treatment is in saving lives the less cost-effective it is due to costs of care incurred by prolonged life, is well-

recognised and has been described in relation to the pharmacological treatment of heart failure[20].

Measurement and valuation of outcomes
The primary outcome measure is survival to seven days. Subsequent survival and quality of life will be measured using the EQ-5D by postal questionnaire (with telephone follow up for non responders after two mailings two weeks apart) at one, three and six months after initial hospital admission. Each patient's details will also be flagged at the NHS central registry. Outcomes will be valued as quality adjusted years of life (QALYs) gained by using the more effective treatment. Patients not achieving the primary endpoint (survival to 7 days) will be assigned zero QALYs.

Measurement and valuation of costs
Costs of hospital admission will be measured using a top-down costing strategy. Length of stay in each hospital location (ITU, HDU, general ward) will be measured for each patient in the trial and multiplied by national average costs[21] to provide the estimated cost per patient. These estimates will then be adjusted to take into account differences between the three interventions during the initial hours of treatment, estimated by micro-costing. Details of staffing requirements, drugs and consumables used, and length of Emergency Department stay will be recorded by staff in two study centres (York & Sheffield) for a sub-sample of the total study population (50 patients in each study group). Local unit costs for staff and consumables will be obtained from each hospital finance department.

Costs for long term care for survivors of ACPO will be measured using a patient questionnaire, sent with the EQ-5D to all surviving patients at one, three and six months. This questionnaire will ask patients for details of use of health and social services over the preceding month. National average costs will be used to value these costs[21].

8. Independent supervision of trial and project management structure

8.1. Trial Steering Committee
This committee will include a number of the grant applicants and as requested by the HTA programme three individuals not directly involved in the trial including a steering committee chair. A member of a relevant consumer group will sit on this committee as well as a representative from the HTA programme.

8.2. Trial management group

A trial management group will be formed which will consist of the grant applicants, the trial manager and the three regional research nurses. It is anticipated that this will meet every two months for the first eight months of the grant and then quarterly thereafter.

8.3. Local project groups

Each local site will form a project group including the recruitment site clinical lead (ED consultant), a member of senior nursing staff and middle grade medical staff for the Emergency Department and any other appropriate individuals. The regional research nurse will also sit on this group. One of the grant applicants will also act as a link person between local project group and the Trial Management group.

8.4. Data monitoring and ethics committee

A data monitoring and ethics committee will be formed. It is anticipated that this group would undertake data analysis for monitoring purposes at six and twelve months after the trial had begun.

Further information can be found on the trial web site at:
www.shef.ac.uk/trial3cpo

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