

JOURNAL CLUB CRITIQUE

The role of noninvasive ventilation in acute cardiogenic pulmonary edema

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University of Pittsburgh Department of Critical Care Medicine: Evidence-Based Medicine Journal Club, edited by Eric B Milbrandt

Expanded Abstract

Citation

Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J: Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008, **359**:142-151 [1].

Background

Noninvasive ventilation (NIV) (continuous positive airway pressure [CPAP] or noninvasive intermittent positive-pressure ventilation [NIPPV]) appears to be of benefit in the immediate treatment of patients with acute cardiogenic pulmonary edema and may reduce mortality.

Methods

Objective: To determine whether noninvasive ventilation reduces mortality and whether there are important differences in outcome associated with the method of treatment (CPAP or NIPPV).

Design: Open, prospective, randomized controlled trial.

Setting: 26 emergency departments in hospital in the UK between July 2003 and April 2007.

Subjects: 1069 patients age >16 years with a clinical diagnosis of acute cardiogenic pulmonary edema, as determined by chest radiograph, respiratory rate >20 breaths/min, and arterial pH<7.35. Exclusion criteria included a requirement for a lifesaving or emergency intervention, inability to give consent, or previous recruitment in the trial.

Intervention: All patients received standard concomitant therapy. Patients were randomly assigned to standard oxygen therapy (up to 15 liters per minute via face mask), CPAP (5 to 15 cm of water), or NIPPV (inspiratory pressure, 8 to 20 cm of water; expiratory pressure, 4 to 10 cm of water).

Outcomes: The primary end point for the comparison between noninvasive ventilation and standard oxygen therapy was death within 7 days after the initiation of treatment, and the primary end point for the comparison between NIPPV and CPAP was death or intubation within 7 days.

Results

A total of 1069 patients (mean [±SD] age, 77.7±9.7 years; female sex, 56.9%) were assigned to standard oxygen therapy (367 patients), CPAP (346 patients), or NIPPV (356 patients). There was no significant difference in 7-day mortality between patients receiving standard oxygen therapy (9.8%) and those undergoing noninvasive ventilation (9.5%, $P=0.87$). There was no significant difference in the combined end point of death or intubation within 7 days between the two groups of patients undergoing noninvasive ventilation (11.7% for CPAP and 11.1% for NIPPV, $P=0.81$). As compared with standard oxygen therapy, noninvasive ventilation was associated with greater mean improvements at 1 hour after the beginning of treatment in patient-reported dyspnea (treatment difference, 0.7 on a visual-analogue scale ranging from 1 to 10; 95% confidence interval [CI], 0.2 to 1.3; $P=0.008$), heart rate (treatment difference, 4 beats per minute; 95% CI, 1 to 6; $P=0.004$), acidosis (treatment difference, pH 0.03; 95% CI, 0.02 to 0.04; $P<0.001$), and hypercapnia (treatment difference, 0.7 kPa [5.2 mm Hg]; 95% CI, 0.4 to 0.9; $P<0.001$). There were no treatment-related adverse events.

Conclusion

In patients with acute cardiogenic pulmonary edema, noninvasive ventilation induces a more rapid improvement in respiratory distress and metabolic disturbance than does standard oxygen therapy but has no effect on short-term mortality.

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Commentary

Acute cardiogenic pulmonary edema (ACPE) is common, costly, and lethal, with associated mortality rates of 10-20% [2,3]. When severe, it is traditionally managed with endotracheal intubation and mechanical ventilation. Interest in using noninvasive ventilation (NIV) in the treatment of ACPE has grown since the early work of Rasanen and colleagues from 1985 [4]. Whether delivered in the form of continuous positive airway pressure (CPAP) or noninvasive intermittent positive pressure ventilation (NIPPV), NIV improves physiologic parameters in patients with ACPE, including decreasing respiratory acidosis, respiratory rate, work of breathing, heart rate, and sensation of dyspnea [5,6]. It may also reduce rates of endotracheal intubation [5,7,8]. A variety of clinical trials have been conducted in this area, though most were small, single-centered studies lacking power to determine if NIV reduces mortality [4,9-18]. Recent systematic reviews and meta-analyses suggest that indeed it may [5-8]. However, the small size of included studies and variation in study populations, interventions, and endpoints leave some doubt to the generalizability of these findings.

To address these uncertainties, Gray and colleagues performed a large, multi-center, randomized controlled trial in 1069 patients with ACPE to determine whether NIV improves survival and if NIPPV is superior to CPAP [1]. Their trial, referred to as the 3CPO (Three interventions in Cardiogenic Pulmonary Oedema) study, was completed in 26 emergency departments in the UK. Patients were randomized to three groups: standard oxygen therapy, CPAP (5 – 15 cm of H₂O), or NIPPV (8/4 to 20/10 cm of H₂O). There were no differences in baseline characteristics, comorbid conditions, or the receipt of standard medical treatments, such as diuretics, nitrates and opiates. Though NIV did provide more rapid improvement in respiratory distress and metabolic disturbances, there were no differences in clinical outcomes, including mortality, rates of endotracheal intubation, length of stay, or myocardial infarction. There were no differences between CPAP and NIPPV in any of the primary or secondary outcomes. The authors conclude that in patients with ACPE, noninvasive ventilation produces more rapid resolution of metabolic abnormalities and respiratory distress but has no effect on short-term mortality.

This study has a number of strengths, most important of which is that it was the largest randomized trial to date in this area, enrolling more patients than the combined number of patients from all studies included in prior meta-analyses [5-8]. Some limitations deserve mention. This was a study of patients presenting to the emergency department and therefore may not apply to the use of NIV in the pre-hospital setting or to those patients who

develop ACPE later in their hospital stay. Patients were excluded if they required lifesaving or emergency intervention, a group that might have benefited most from NIV. The most concerning limitation, however, is the considerable cross-over between groups and the lack of objective criteria for intubation. Fifty-six patients who failed standard oxygen treatment were rescued with NIV. Assuming that all 56 would have required intubation, the control 7-day intubation rate would have increased from 2.8% to 18.0%, which would have made the intubation rate in the standard oxygen treatment group significantly greater than the NIV group (2.9%).

Recommendation

The results of this study should not limit the use of NIV in the setting of ACPE. NIV leads to more rapid improvement of symptoms of respiratory distress and metabolic disturbances as compared to standard oxygen therapy. We further argue that based on this study, one should not draw a conclusion that NIV is ineffective in preventing intubation. Though NIV has not been convincingly shown to reduce mortality, it remains a valuable adjunct in the treatment of ACPE.

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Competing interests

The authors declare that they have no competing interests.

Published: 12 March 2010

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doi:10.1186/cc8889

Cite this article as: Salman A, *et al.*: The role of noninvasive ventilation in acute cardiogenic pulmonary edema. *Critical Care* 2010, **14**:303.