Critical Review Form
Meta-analysis

Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema. Systematic Review and Meta-analysis, *JAMA* 2005; 294; 24: 3124-3130

Objective: **"To investigate the effect of NIV on the main outcomes (intubation and mortality) comparing the two techniques to each other and to conventional oxygen therapy". (p 3125)**

Methods: **The authors conducted an electronic search for all RCT through 2005 in Cochrane, MEDLINE, and EMBASE without any language restrictions. Additionally the authors reviewed reference lists and contacted some authors for additional unpublished or un-cited materials. Included published studies were restricted to those comparing noninvasive ventilation (NIV) to conventional oxygen therapy or another NIV modality (CPAP vs. BIPAP) for acute pulmonary edema (not undifferentiated acute respiratory failure). Abstracts were excluded. A pre-standardized data abstraction form was used independently by two reviewers with abstraction accuracy confirmed by a third reviewer. Methodological quality was assessed using Jadad's criteria.**

Although the individual studies had a variety of primary outcome measures, this meta-analysis evaluated only treatment failure and in-hospital mortality "because all the included trials presented data about these items". (p. 3125). Treatment failure was defined as "need to intubate" whether intubation actually occurred or not. MI was considered a secondary outcome. Acute pulmonary edema was defined as "dyspnea of acute onset with physical and radiological signs of pulmonary edema in addition to hypoxia".

The study results were compiled and analyzed using REVMAN and a fixed-effects model into summary relative risks. Lost or withdrawn subjects were assumed to have the worst outcome (treatment failure) and the model was re-examined via sensitivity analysis. Publication bias was assessed with Egger's funnel plot.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes, whether the observed benefit of NIV in acute cardiogenic pulmonary edema (ACPE) could be quantified into significant patient-important outcomes (mortality, need to intubate) from a variety of small RCT's.)
2.	Was the search for relevant studies details and exhaustive?	Yes, multiple electronic search engines were used without any language restrictions. In addition, the authors attempted to identify gray literature.
3.	Were the primary studies of high methodological quality?	"In general methodological quality was acceptable." (p 3127) since the authors used Jadad's validated scale for rating RCT's, although they neglect to report the individual study's Jadad scores.

4.	Were the assessments of the included studies reproducible?	Yes. The authors used validated assessment tools previously demonstrated to be reproducible.
II.	***What are the results?***	
1.	What are the overall results of the study?	• 559 studies of 727 patients were identified by the search strategy with 15 ultimately included in the meta-analysis (see Fig 2, p 3127 for exclusion reasons). • The 15 included trials included patients from 11 countries. • 11 studies reported causes of CHF exacerbation: 31% ACS, 27% HTN, 14% worsening heart failure. • All trials used full-face masks. For CPAP, the most frequent pressure was 10cm H_20, for BIPAP 15cm H_20 IPAP, and 5cm H_20 EPAP. • All trials reported number of patients (if any) lost to follow-up. • No publication bias was noted. • <u>NIV significantly reduced mortality (NNT 11) and need to intubate (NNT 6)</u> (see Fig 2 and 3, pp 3127-3128) without any increased MI or adverse events noted. Intention-to-treat sensitivity analysis and inclusions of unpublished trials did not change these results. • <u>CPAP vs. BIPAP showed no significant differences with mortality</u> (event rate 6.4% vs. 7.2%) or need to intubate (event rate 11%% vs. 7.2%, p=0.39) although the trend for intubation favors BIPAP.

2.	How precise are the results?	Significant results display reasonably narrow CI's.
3.	Were the results similar from study to study?	No significant heterogeneity was noted by Cochrane's Q-test (X^2).

III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	In acute cardiogenic pulmonary edema subject with hypoxia, NIV represents the standard of care and probably reduces mortality and intubations for many patients. CPAP and BIPAP are essentially the same.
2.	Were all patient important outcomes considered?	Yes, although the skeptical reader might be uncertain how aggressively adverse events were sought.
3.	Are the benefits worth the costs and potential risks?	Yes. NIV is cheap, readily available technology already being used for a variety of conditions (obstructive sleep apnea, asthma, COPD) and may avert costly intubations saving uncomfortable RSI for refractory subjects.

Limitations

1) Heterogeneous definitions for ACPE.
2) Various ventilators used without any assessment of differences between individual devices' impact on outcomes.
3) Some study designs permitted rescue NIV perhaps reducing observed ARR (and ↑ NNT).
4) The results of this meta-analysis are based on multiple small trials, however if a single, large, adequately powered RCT existed the need for a meta-analysis would be diminished.
5) No definitions of when NIV therapy started. As with the 3-hr ischemic stroke thrombolytic window a critical period of intervention may exist with delayed presentations or therapy initiation intervals adversely effecting response to NIV.

Bottom Line

Compared with standard medical therapy in the management of acute cardiogenic pulmonary edema NIV (CPAP **and** BIPAP) reduce mortality (NNT 11) and need to intubate (NNT 6) without increasing MI or adverse event rates. BIPAP and CPAP appear equivalent and clinical equipoise may be insufficient to ethically justify RCT to examine differences between them. Future studies ought to examine the utility of NIV on pre-hospital ACPE and the relative advantage of BIPAP in hypercardic ACPE (suggesting respiratory muscle fatigue).