Critical Review Form

Meta-Analysis

Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with ACPE: A Meta-Analysis, *Lancet* 2006; 367,1155-1163

Objective: **"To access and compare the benefits of CPAP and bi-level ventilation beyond a reduction in mechanical ventilation needs to other clinically relevant endpoints in patients with acute cardiogenic pulmonary oedema, such as mortality and length of hospital stay". (p.1155)**

Methods: **The authors conducted electronic search (1966-2005) of MEDLINE, EMBASE, CINAHL, Cochrane, DARE, and ACP JC of RCT on ACPE reporting mortality or need to intubate. Additionally, scientific forum abstracts of eight journals were hand-searched and review article bibliographies were scanned. Original study authors were contacted to clarity data details if necessary. Using Cook's 11-point quality assessment score (Keenan, et al. Annals IM 2003; 138:861-870), individual study quality was assigned. One reviewer pruned the 1354 abstracts down to 110 studies for detailed analysis and then 3 reviewers weeded these down to 20 included studies. Data abstraction was done independently by two investigators.**

The primary outcomes were hospital mortality and need for mechanical ventilation. Secondary outcomes included treatment failure, length of hospital stay, duration of NIPPV and MI incidence. Since studies had variably defined failure thresholds, the meta-analysis authors analyzed authors – defined failure rates and composite (failure rate and mechanical ventilation rate combined) failure rates separately.

The authors used a random-effects model and utilized the quality scores as weights. Treatment effect heterogeneity was assessed with the Q-statistic and pooled treatment effect variation reported with the I^2 measure. Meta-regression was used to determine if any confounders such as age, gender, quality score, $PaCO_2$, pH, or $Pa0_2$ at admission – independently affected the primary or secondary outcomes. Additionally cumulative meta-analysis was done to study possible time trends in treatment effects. Publication bias was assessed by Begg's rank correlation test, Egger's regression test, and Duval's parametric trim and fill method. Bayesian meta-analysis regression was used to ascertain whether underlying population risk impacted therapeutic response. Sensitivity analysis was conducted by excluding non-published abstracts and re-analyzing treatment effects.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes, whether NIPPV for ACPE reduces mortality, mechanical ventilation and hospital length of stay.
2.	Was the search for relevant studies details and exhaustive?	Yes, extensive electronic, and hand-search through relevant search engines.
3.	Were the primary studies of high methodological quality?	Yes, using the modified quality assessment score the mean score was 6 (range 4 – 10) on a scale of 0 – 11. Oxman, Cook, and Guyatt proposed several criteria to assist the critical reader in assessing the quality of a SR: • reporting on adequate search methods • individual study inclusion criteria • assessment of selection bias • appropriateness of the validity criteria used • appropriateness of pooling study results • extent to which the SR conclusions were supported by the data • global assessment of scientific quality. Similarly, authors of SR's must assess the quality of evidence they include because "garbage in is garbage out". So critical readers should assess whether individual SR's included: • a clear relevant question • authors without conflicts of interest who reported study design and conduct explicitly • study of all possible interventions for all possible variations of the conditions of interest in all possible patient types in all settings using all relevant outcome measures • describe in clear, unambiguous language the efforts to minimize bias and statistical analysis
4.	Were the assessments of the included studies reproducible?	Two investigators assigned the quality scores. No Kappa analysis or discrepancies were reported to assess reproducibility.

II.	*What are the results?*	
1.	What are the overall results of the study?	• 43 160 articles were identified studying respiratory failure with 110 articles screened in detail and 20 articles (including three unpublished abstracts) fully reviewed by three investigators. (p 1158) CPAP vs. standard therapy • Reduced **mortality** significantly with RR 0.59 (0.38 – 0.90), **NNT 10**. • Reduce need for **mechanical ventilation** significantly with RR 0.44 (0.29-0.66), **NNT 6**. • Significantly reduced composite failure rate and author-defined failure rates (NNT 5). • No increase in MI rates noted RR 0.83 (0.43-1.61). BIPAP vs. Standard therapy • Insignificantly reduced mortality (RR 0.63 (0.37-1.10), but significantly reduced need for mechanical ventilation RR 0.50 (0.27-0.90), NNT 7. • Significantly reduced composite failure rates (NNT 7), but no significant effect on author-defined failure rates or MI incidence. CPAP vs. BIPAP • Trend towards increased MI in BIPAP group (RR 1.19 – 0.68-2.10, p=0.11). • **No difference** in mortality need for mechanical ventilation, composite or author-defined failure rates. <Table2, p.1158 and Fig 1-2, pp1159-1160> • No reduction in hospital length of stay. • No threshold value of pH and $PaCO_2$ to define efficacy thresholds were identified on meta-regression univariate analysis. • No evidence of publication bias. • No significant heterogeneity identified by Q-test or I^2 measure. • Removal of unpublished abstracts on sensitivity analysis did not significantly change any of the results. • Using time of enrollment as an independent variable, there was no effect on outcomes noted from year of enrollment.

2.	How precise are the results?	Narrow CI on significant results (see above)
3.	Were the results similar from study to study?	No significant heterogeneity was noted between studies for author defined failure rates of CPAP vs. standard therapy (I^2 = 40%) p.1159
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?	NIPPV benefits patients with ACPE by reducing need to intubate and mortality rates, although no threshold (of hypoxia, hypercarbia, age, etc.) has been identified upon which to focus therapy or higher risk groups.
2.	Were all patient important outcomes considered?	Yes, although patient satisfaction scores might be a future consideration.
3.	Are the benefits worth the costs and potential risks?	No cost-effectiveness analyzed or hypothesized, but if readily available easily mastered NIPPV can reduce mortality and need to intubate with impressively low NNT than NIPPV should become the standard of care.

Limitations

1. Conclusions are based upon a small number of outcome events – 100 deaths in the CPAP group, 45 deaths in the BIPAP group. Flather suggests a minimum of 200 to generate "more reliable… and clinically useful" meta-analyses (*Control Clin Trials* 1997; 18: 568-79).
2. Individual trials recruited only a fraction of eligible subjects presenting with ACPE (ranging from 11-31%) limiting the generalization of these results.
3. The observed increased MI trend in BIPAP was disproportionately affected by one trial (Mehta).

Bottom Line

Compared with standard therapy, NIPPV (CPAP and BIPAP) significantly reduce mortality (NNT = 10) and need to intubate (NNT = 6 for CPAP, NNT = 7 for BIPAP), although neither effects hospital length of stay. No age, gender, arterial oxygenation or hypoventilation thresholds were identified to focus therapies or high risk groups were likely to benefit. BIPAP may increase MI incidence, although the mechanism for this observation is unclear.