Critical Review Form

Therapy

Non-invasive Ventilation in Cardiogenic Pulmonary Edema: A Multicenter Randomized Trial, *Am J Respir Crit Care Med* 2003; 168:1432-1437

Objective: "To assess the feasibility of NPSV (BIPAP) outside the ICU and to detect any differences in mortality, intubation rate, and some physiological variables such as dyspnea and respiratory rate." (p 1432)

Methods: Multi-center (five Italian centers), randomized, prospective, ED-based study comparing BIPAP to conventional oxygen therapy in the acute management of acute cardiogenic pulmonary edema. Inclusion criteria included severe respiratory failure ($Pa0_2/FI0_2$ <250), supplemental oxygen <102/min for at least 15 min, respiratory rate >30 with sudden onset dyspnea and "typical physical signs of pulmonary edema". Note that CXR evidence of pulmonary edema were *not* required and that physical findings lack discriminatory power for CHF (Does this Dyspnic Patient in the Emergency Department Have Congestive Heart Failure? *JAMA* 2005; 294: 1944-1956). Exclusion criteria included immediate need for intubation sensorial impairment, shock, ventricular arrhythmia, oxygen saturation < 80%, AMI requiring reperfusion, chronic renal failure, and thrombolysis. EPAP was started at 5cm H_20 and IPAP at 10cm H_20.

The primary outcome was need for intubation. Secondary outcomes included cardiac enzymes as marker of MI, ABG, respiratory rate, heart rate, systolic BP, diastolic BP, and dyspnea. The study had 90% power to detect intubation difference of 35% based on a two-tailed p-value of 0.05. Subjects were stratified equally a priori for PaCO2>45 mm Hg or <45 mg Hg prior to randomization and a logistic regression model was built to verify the hypothesis that hypercapnia was a determinant of intubation.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, "patients were randomly assigned to receive standard medical treatment, plus oxygen or standard treatment plus NPSV through a full face mask."(p 1433) The details of randomization were not reported.

2.	Was randomization concealed (blinded)?	Blinding of treating clinicians and patients would be difficult without sham BIPAP/CPAP (would that be ethical?) and the authors do not report on any blinding methods. The outcomes assessors, however, could and should have been blinded to allocation.
3.	Were patients analyzed in the groups to which they were randomized?	Yes, "analyses were performed on an intention to treat basis" (p 1433)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "The two groups had similar characteristics on admission". (p 1433). Note that to verify this fact readers need to access Table 2 online at www.atsjournals.org. Increasingly publishers are trying to reduce costs by putting tables and graphs online rather than in print. This is inconvenient for readers who likely do not often access this information independently.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. The authors do not explicitly state blinding and doing so would be difficult, perhaps unethical. Patient knowledge of allocation status leaves open the possibility of *co-intervention bias*.
2.	Were clinicians aware of group allocation?	Yes, possible *ascertainment bias* and/or *work-up bias*.
3.	Were outcome assessors aware of group allocation?	Yes. The authors do not explicitly state blinding outcome assessed so *ascertainment bias* possible.
4.	Was follow-up complete?	No lost to follow-up was reported in the print manuscript. The authors do not report the follow-up interval.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 65 subjects were randomly assigned to each treatment arm with similar pre-existing cardiac disease, NYHA CHF class, etiology of cardiogenic pulmonary edema, medical management and echocardiographic findings. • BIPAP settings averaged 14.5 ± 21 cm H_2O IPAP and 6 ± 3 H_20 EPAP. The mean duration of BIPAP was 11.4 ± 3.6 hours (p 1433). • For all subjects, there was no significant differences between the two treatment groups in-hospital mortality or need for intubation. However, when dividing the groups into hypercapnia and non-hypercapnia groups, the percentage of patients needing intubation was significantly lower in those with a $PaCO_2$ > 45mm Hg (NNT = 4). • Logistic regression analysis based on need for intubation (DV) and $PaCO_2$ (IV) did not show any statistically significant correlation. • Notably, the PaCO2 <45mm Hg group showed a trend toward *more intubation* in the BIPAP group (34% compared with 10% intubation rate for acidotic cardiogenic pulmonary edema (Eur J EM 2002; 9: 320-324) suggesting that few of these failures could be attributed to BIPAP problems (most were cardiac related hemodynamic instability). • Marked trend in hypercapnic group towards improved mortality BIPAP (16% vs. 3% p=0.100)

2.	How precise was the estimate of the treatment effect?	Confidence intervals were not provided so precision cannot be addressed.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Although online demographic tables are inconvenient for readers, dyspneic hypoxic CHF patients presenting to ED's for symptomatic management are likely similar to BJH patients and presentations.
2.	Were all clinically important outcomes considered?	Yes, patients likely care most about mortality, need for intubation, symptomatic relief, and adverse side effects of BIPAP. All were addressed in this study.
3.	Are the likely treatment benefits worth the potential harm and costs?	No cost-effectiveness analysis was performed or discussed, but likely yes.

Limitations

1) **Difficult to elucidate subject demographics or protocol of "need to intubate" without accessing online e-tables.**

2) **Outcome assessors were not blinded to subject allocation.**

3) **No Confidence Intervals were reported.**

4) **Inadequately powered for mortality and secondary outcomes. In addition, the unexpectedly high and unprecedented increase in BIPAP subjects intubated in the normocapnic subgroup may have impaired the researcher's ability to detect a true difference between the medical care and BIPAP treatment arms.**

5) **No requirement for CXR evidence of pulmonary edema.**

6) **No discussion of randomization methods in print version.**

7) **Most physicians identify hypoxia with pulse ox, not ABG so limited external validity unless you order ABG on all CHF patients.**

Bottom Line

Multi-center ED based Italian randomized trial which demonstrates no significant mortality benefit for BIPAP over routine medical care in hypoxic CHF exacerbation management. Among the a priori subset of PaCO2 >45 mm Hg, though, a significant reduction in need to intubate (NNT = 4) and a marked trend in improved mortality favoring BIPAP is noted. BIPAP does produce faster gas exchange, dyspnea score, and respiratory rate improvements. Future adequately powered clinical trials or meta-analysis ought to assess the impact of BIPAP on mortality, intubations, and symptom scores among cohorts with more standard intubation rates.