Critical Review Form
Therapy

Doshi P, Whittle JS, Bublewicz M, et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Ann Emerg Med. 2018 Jul;72(1):73-83.e5.

Objectives: **"to assess the ability of high-velocity nasal insufflation to support patients with undifferentiated respiratory failure in the ED who required ventilatory support. The hypothesis of this trial was that high-velocity nasal insufflation is noninferior to noninvasive positive-pressure ventilation in treatment of undifferentiated respiratory failure with respect to therapy failure, as indicated by the requirement for intubation or crossover to the alternate therapy." (p. 74)**

Methods: **This prospective, multicenter, parallel-group, noninferiority randomized controlled trial comparing high-velocity nasal insufflation to noninvasive positive-pressure ventilation (NIPPV) was conducted at five centers in the southeastern US (two academic and three community centers) between October 2014 and September 2016. Enrollment criteria included being over 18 years and requiring noninvasive ventilatory support as determined by the treating clinician. A consecutive sample of patients was enrolled. Exclusion criteria included suspected drug overdose, cardiovascular instability, severe respiratory depression, GCS score < 9, recent cerebrovascular events, severe comorbidities, end-stage cancer, life expectancy less than 6 months, significant respiratory depression on presentation, cardiac or respiratory arrest on presentation, need for emergency intubation, known or suspected STEMI, or increased risk of aspiration, agitation, or uncooperativeness.**

Participants were randomized in a 1:1 ratio to high-velocity nasal insufflation or NIPPV with an oronasal mask. Primary outcomes were treatment failure rate (defined as the need for intubation) and arm failure rate (defined as crossover to alternate therapy) within 72 hours of enrollment. Secondary outcomes included changes in PCO2, pH, vital signs, and perceived exertion scores. Vital signs were recorded at baseline, 30, 60, and 90 minutes, and at 4 hours post-therapy initiation. Blood samples were drawn at 0, 1, and 4 hours.

A total of 228 patients were randomized and 204 were enrolled in the trial (104 to high-velocity nasal insufflation; 100 to NIPPV). Exclusions were due to meeting exclusion criteria, consent withdrawal, clinician discomfort, or reevaluation revealing no need for NIPPV. Median time from presentation to therapy initiation was 35 minutes, with a setup time of 10 minutes.

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion to high-velocity nasal insufflation or NIPPV.
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	Yes. "A computer-generated block-randomization schedule was used to produce the randomization sequence. Sealed, sequentially numbered envelopes were prepared to provide a 1:1 randomization ratio for each center in the study and were opened when the decision was made to randomize a patient." (p. 75) This should be sufficient to maintain allocation concealment.
Were patients analyzed in the groups to which they were randomized?	Yes. "All analyses were based on an intention-to-treat model defined according to the protocol." (p. 76) Crossover to the alternate therapy was allowed at clinician discretion, but patients were analyzed according to the group to which they were randomly assigned.
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, BMI, APACHE II score, gender, race, presenting condition (e.g. asthma, CHF, COPD, etc.), time to initiation of therapy, and initial viral signs.
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Yes. Given the nature of the intervention, it would not have been possible to blind patients or clinicians. It is possible that performance bias could have influenced outcomes.
Were clinicians aware of group allocation?	Yes. See above.
Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors, hence there is some risk of observer bias.
Was follow-up complete?	Yes. There were no patients lost to follow-up.
What are the results?	
How large was the treatment effect?	**Intubation Rates** • No significant difference was seen. Intubation occurred in 7% of patients in the HVNI group and 13% in the NIPPV group for a risk difference of -6% (95% CI -14% to 2%). The CI did not pass the noninferiority margin of 15% and hence HVNI was found to be noninferior to NIPPV. **Arm Failures** • No significant difference was seen. Failure occurred in 26% of patients in the HVNI group and 17% in the NIPPV group for a risk difference of 9% (95% CI -2% to 20%). **Therapy Crossover and Subsequent Intubation** • For HVNI non-responders, 85% switched to NIPPV and 13% were intubated. • For NIPPV non-responders, 35% switched to HVNI and 50% were intubated. **Heterogeneity Analysis** • There were no significant differences between academic and community centers. **Vital Signs and Blood Gas Analyses** • Both HVNI and NIPPV showed similar trends and improvements. Seventeen percent of blood samples were venous, with 18%

	from the HVNI group and 16% from the NIPPV group, showing similar PCO2 changes. **Patient and Physician Perception** • Dyspnea scores and physician perceptions of respiratory response, comfort, and ease were similar, with physicians favoring HVNI. **Length of Stay** • No differences were observed in the length of stay in the ED, ICU, and hospital.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above.

How can I apply the results to patient care?	
Were the study patients similar to my patient?	Yes. This study was conducted at five centers in the southeastern US at a mix of academic and community centers, where I would expect patients to be similar to those seen in our institution.
Were all clinically important outcomes considered?	Yes. The authors considered need for intubation, need for crossover to the other intervention, ED/ICU/hospital length of stay, and change in blood gas measurements as well as comfort and levels of dyspnea.
Are the likely treatment benefits worth the potential harm and costs?	Yes. HVNI was found to be noninferior to NIPPV for the primary outcome of intubation. While there was no definitive proof of benefit from HVNI, 72% of patients in this group rated comfort at excellent compared to only 34% in the NIPPV group with trends towards better simplicity of use and decreased monitoring required.

Limitations:

1. **Given the nature of the intervention, it would not have been possible to blind patients or clinicians. It is possible that performance bias could have influenced outcomes.**
2. **The noninferiority margin allowed for a rather large difference in intubation rates between group (15%).**
3. **This study included a rather heterogenous group of all patients requiring noninvasive ventilatory support and was not powered for subanalyses across specific respiratory failure causes.**

Bottom Line:

This multicenter, unblinded, randomized controlled trial found that compared with NIPPV, HVNI was not inferior with regards to failure and need for intubation (risk difference -6% (95% CI -14% to 2%). There were, however, trends towards improved comfort, better simplicity of use, and decreased monitoring required with HVNI. No differences were seen with respect to ED, ICU, and hospital length of stay or changes in blood gas measurements.