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High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure: the FLORALI study [version 1; referees: not peer reviewed]

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Abstract

An evaluation of a recent study by Frat JP, Thille AW, Mercat A et al: High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. New England Journal of Medicine 2015;372(23):2185-96. PubMed PMID: 25981908. Clinicaltrials.gov number NCT01320384.

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Critique of:

Citation

Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M, Constantin JM, Tonneliar JM, Pierrot M, Mathonnet A, Beduneau G, Deletage-Metreau C, Richard JC, Brochard L, Robert R, for the FLORALI Study Group and the REVA Network. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. New England Journal of Medicine 2015;372(23):2185–96[1]. PubMed PMID: 25981908. Clinicaltrials.gov number NCT01320384

Background

Whether noninvasive ventilation should be administered in patients with acute hypoxemic respiratory failure is debated. Therapy with high-flow oxygen through a nasal cannula may offer an alternative in patients with hypoxemia.

Methods

Objective

To determine whether high-flow nasal cannula oxygen therapy reduces the need for intubation in patients with acute hypoxemic respiratory failure without hypercapnia.

Design

Prospective, randomized, multicenter, open-label 3-arm trial.

Setting

Twenty-three intensive care units in France and Belgium.

Subjects

A total of 310 patients without hypercapnia who had acute hypoxemic respiratory failure and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (P/F ratio) of 300 mm Hg or less on face mask oxygen. Patients with hypercarbia, chronic respiratory failure, obstructive lung disease or congestive heart failure exacerbation or acute indication for intubation were excluded.

Intervention

High-flow oxygen therapy using the OptiFlow device, standard oxygen therapy delivered through a face mask, or noninvasive positive-pressure ventilation.

Outcomes

The primary outcome was the proportion of patients intubated at day 28; secondary outcomes included all-cause mortality in the intensive care unit and at 90 days and the number of ventilator-free days at day 28.

Results

The intubation rate (primary outcome) was 38% (40 of 106 patients) in the high-flow–oxygen group, 47% (44 of 94) in the standard group, and 50% (55 of 110) in the noninvasive-ventilation group (P = 0.18 for all comparisons). The number of ventilator-free days at day 28 was significantly higher in the high-flow–oxygen group (24 +/- 8 days, vs. 22 +/- 10 in the standard-oxygen group and 19 +/- 12 in the noninvasive-ventilation group; P = 0.02 for all comparisons).The hazard ratio for death at 90 days was 2.01 (95% confidence interval [CI], 1.01 to 3.99) with standard oxygen versus high-flow oxygen (P = 0.046) and 2.50 (95% CI, 1.31 to 4.78) with noninvasive ventilation versus high-flow oxygen (P = 0.006).

Conclusions

In patients with nonhypercapnic acute hypoxemic respiratory failure, treatment with high-flow oxygen, standard oxygen, or noninvasive ventilation did not result in significantly different intubation rates. There was a significant difference in favor of high-flow oxygen in 90-day mortality.

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Commentary

Acute respiratory failure (ARF) accounts for one-third of intensive care unit (ICU) admission, resulting in a twofold increase in ICU mortality and prolonged ICU length of stay[2,3]. ARF requiring endotracheal intubation and mechanical ventilation brings increased risk of mortality and morbidity, yet the optimal time to initiate ventilator support remains unclear. Noninvasive positive-pressure ventilation (NIPPV) reduces the risk of intubation and mortality in patients with hypercarbic ARF from exacerbation of obstructive lung disease[4] and in patients with cardiogenic pulmonary edema[4,5]. NIPPV has not shown consistent benefits in patients with hypoxemic ARF from pneumonia or acute respiratory distress syndrome (ARDS), with some suggestion of worsened outcomes with "de novo" pneumonia[6,7]. NIPPV may prevent secretion clearance and is not advisable on patients unable to remove the mask due to aspiration risk[6,7]. In such patients, alternative means of non-invasive respiratory support may be desirable.

High-flow nasal cannula (HFNC) oxygen devices deliver up to 40–60L/min at a precise fraction of inspired oxygen (F_iO_2). High flow rates match the patient's peak inspiratory flow to prevent room air entrainment and improve comfort, while heat and humidification may prevent airway desiccation to improve mucociliary clearance[8]. By flushing carbon dioxide from the airways, HFNC reduces anatomic dead space to increase ventilatory efficiency and reduce work of breathing, in addition to producing minimal levels of positive end-expiratory pressure[8].

The FLORALI study randomized 310 patients with hypoxemic ARF to nonrebreather face mask, HFNC using the OptiFlow device (Fisher and Paykel Healthcare) or NIPPV with inspiratory pressure titrated to achieve tidal volume 7–10cc/kg[1]. The majority of patients had pneumonia and met criteria for ARDS, with bilateral infiltrates and a ratio of P_aO_2 to F_iO_2 (P/F ratio) <=200 on face mask oxygen. The study excluded patients likely to benefit from NIPPV, including those with hypercarbia, exacerbations of obstructive lung disease or cardiogenic pulmonary edema, along with patients likely to be harmed by NIPPV, including those with hemodynamic instability or depressed mental status. There was no significant reduction in the rate of intubation between groups in the main study population (p = 0.18). A *post hoc* subgroup analysis in patients with a PF

ratio <=200 showed a significantly higher risk of intubation with face-mask oxygen (HR 2.07) or NIPPV (HR 2.57) compared to HFNC (p = 0.009). HFNC was associated with lower mortality in the ICU (p = 0.047) and at 90 days (p = 0.02) in both unadjusted and adjusted analyses, with HR's ranging from 1.85 to 2.60. Patients in the HFNC group had more ventilator-free days and lower dyspnea scores.

Strengths of this study include multi-center, randomized, intention-to-treat design with enrollment from 23 large ICU's[9]. Patients expected to benefit from NIPPV were systematically excluded. Since rate of intubation was the primary endpoint, a protocol was used to standardize indications for intubation. Study groups were well-matched at baseline and follow-up was complete. The study has a number of limitations that must be considered when applying the results. This was a highly-selected population enriched in patients with ARDS due to pneumonia without obstructive lung disease or heart failure; only 21% of screened patients with hypoxemic ARF were eligible and 12.5% were included. Patients had limited extrapulmonary organ failure, which is a risk factor for HFNC failure in ARDS[10]. The study had limited statistical power for the primary endpoint, with an observed intubation rate of 45% compared to an anticipated intubation rate of 60%. Because the study failed to meet its prespecified primary endpoint, the significant results of the *post hoc* subgroup analysis and the secondary mortality endpoints are hypothesis-generating rather than conclusive. One-fourth of patients in the face mask arm and one-eighth of patients in the HFNC arm crossed over to receive NIPPV; approximately two-thirds of these patients required intubation. It remains unclear why fewer people died in the HFNC arm, although the 7–10cc/kg tidal volume in the NIPPV arm exceeds the recommended 6cc/kg that has been associated with lower mortality in patients with ARDS[11,12]. Protocolized intubation criteria may have delayed intubation, as reflected by the occurrence of two deaths during intubation. While the study's protocolized intubation criteria seem reasonable as part of a research study, the decision to intubate requires considerable judgment and is difficult to fit to a protocol.

The FLORALI study emphasizes that the approach noninvasive respiratory support in ARF should be tailored to both the underlying physiology (hypoxemic versus hypercarbic ARF) and the causative disease process. HFNC may become the preferred noninvasive modality for patients with hypoxemic ARF due to pneumonia or ARDS, while NIPPV will remain preferred for patients with obstructive lung disease or cardiogenic pulmonary edema. Other recent studies of HFNC have shown mixed results depending on the population studied. HFNC failed to show a benefit over NIPPV for pre-oxygenation prior to intubation, although HFNC during intubation did reduce the risk of desaturation during intubation when compared to face mask[13,14]. HFNC was inferior to NIPPV for respiratory support during bronchoscopy[15]. HFNC performed equally compared to NIPPV for patients developing ARF after cardiothoracic surgery[16]. Further studies are needed to guide our use of HFNC for patients with ARF, and several ongoing studies of HFNC are listed on clinicaltrials.gov.

Recommendation

HFNC is safe and can be considered for first line support of patients with severe hypoxemic ARF not requiring immediate intubation, including pneumonia and early ARDS in the absence of hypercarbia, obstructive lung disease or heart failure exacerbation. Careful monitoring in an ICU during HFNC is essential to ensure timely escalation of therapy in the event of HFNC failure. With either HFNC or NIPPV, intubation should be performed before the patient exhausts their physiologic reserves and decompensates.

Competing interests

The authors declare that they have no competing interests.

Grant information

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