EDITORIAL

Saving Lives with High-Flow Nasal Oxygen

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First reported in 1890,[1] therapy with oxygen constitutes one of the fundamental advances in clinical medicine. It is an essential treatment for acute and chronic respiratory failure, a supportive therapy for general anesthesia and most surgical procedures, and an adjunctive treatment for patients with shock from sepsis, trauma, or cardiac failure.

For spontaneously breathing patients with acute respiratory failure, various methods for providing supplemental oxygen have been studied. Noninvasive positive-pressure ventilation with a tight-fitting face mask reduces morbidity and mortality among selected patients with acute respiratory failure caused by an exacerbation of chronic obstructive pulmonary disease.[2,3] Noninvasive ventilation also has proven value in some patients with hypoxemia from cardiogenic pulmonary edema.[4]

However, among commonly used approaches, the best option for patients with acute hypoxemic respiratory failure remains uncertain. In the past decade, high-flow oxygen delivered through a nasal cannula has emerged as an alternative to noninvasive ventilation or oxygen delivered through a face mask.[5] This form of delivery provides a high concentration of heated and humidified oxygen through a nasal cannula, with flow rates from 40 to 60 liters per minute that generate low levels of positive end-expiratory pressure. It is thought to be more comfortable for the patient than the other strategies and may reduce the work of breathing; importantly, it increases the excretion of carbon dioxide.[5,6] Some studies have shown a potential role for high-flow oxygen in supporting patients with hypoxemia after extubation[7] and in treating newborn infants with respiratory distress.[5] However, randomized trials to compare the efficacy of high-flow oxygen with other oxygen-delivery systems in patients with acute hypoxemic respiratory failure have been lacking.

Frat et al.[8] now report in the *Journal* the results of a randomized, multicenter trial involving 310 patients that was designed to assess clinical outcomes with high-flow oxygen, noninvasive ventilation, and standard oxygen therapy for acute, nonhypercapnic, hypoxemic respiratory failure (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [Pao_2:FIO_2], ≤300 mm Hg); the acute respiratory failure was caused predominantly by pneumonia. The primary outcome, the rate of endotracheal intubation, was lower among patients treated with high-flow oxygen than among those who received standard oxygen therapy or noninvasive ventilation, but the rates did not differ significantly (38% vs. 47% and 50%, respectively) ($P=0.18$). However, in a post hoc adjusted analysis that included the 238 patients with severe initial hypoxemia (Pao_2:FIO_2, ≤200 mm Hg), the intubation rate was significantly lower among patients who received high-flow oxygen than among patients in the other two groups ($P=0.009$).

In the entire cohort of 310 patients, the high-flow delivery mode significantly increased the number of ventilator-free days and also reduced 90-day mortality, as compared with standard oxygen therapy alone ($P=0.046$) or noninvasive ventilation ($P=0.006$). As compared with the other strategies, high-flow oxygen was associated with less respiratory discomfort and a reduction in the severity of dyspnea, as measured by validated assessments of patient comfort. It appears that the system for delivering high-flow oxygen through a nasal cannula decreased the pulmonary dead

space, as indicated by a lower respiratory rate than was observed with the other strategies at the same partial pressure of arterial carbon dioxide ($Paco_2$) (Table S5 in the Supplementary Appendix, available with the full text of the article at NEJM.org). This finding is important because elevated pulmonary dead space contributes to increased mortality among patients with acute respiratory failure from arterial hypoxemia and the acute respiratory distress syndrome.[9]

The trial had several strengths. The baseline characteristics in the three groups were well matched, the use of intubation was guided by sound prespecified criteria, and patients underwent randomization within 3 hours after qualifying for the trial. The trial excluded patients with a history of chronic respiratory failure including a $Paco_2$ of more than 45 mm Hg, and stratification was performed according to study center and a history of cardiac disease.

There were some limitations. By necessity, the trial could not be blinded, and some patients were allowed to cross over to noninvasive ventilation if they did not have a good response to standard oxygen therapy or high-flow oxygen therapy, although the number of crossovers was small. The total number of patients enrolled for a three-group trial was modest (310 patients), and the trial was really a negative trial, because the primary outcome of intubation rate did not reach significance and the significantly reduced rate of intubation among the 238 patients with severe hypoxemia was not a prespecified outcome.

Nevertheless, and remarkably, therapy with high-flow oxygen significantly reduced 90-day mortality. Why? Since the mean tidal volume in the noninvasive-ventilation group was greater than 9 ml per kilogram of predicted body weight, the degree of lung injury might have been increased in this group, contributing to a higher mortality than that observed in the high-flow oxygen group.[10] Alternatively, because the rate of death from shock was significantly lower among patients treated with high-flow oxygen than among those treated with one of the other strategies, there may have been better containment of the microbial and inflammatory components of pneumonia to the lung because of the reduced need for endotracheal intubation and positive-pressure ventilation, especially in patients with severe hypoxemia.

I believe that high-flow oxygen therapy through a nasal cannula should be considered to be an effective and safe therapy for the treatment of spontaneously breathing patients with acute hypoxemic respiratory failure. Although additional trials are needed, high-flow oxygen should be used for the treatment of patients without hypercapnia and with acute severe hypoxemic respiratory failure in the emergency department, the intensive care unit, and hospital settings in which appropriate monitoring is available.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article was published on May 17, 2015, at NEJM.org.

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DOI: 10.1056/NEJMe1504852