NEJM GROUP

TOPIC COLLECTION: OPTIMAL OXYGEN THERAPY FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Letter from the Editor

Prescription of supplemental oxygen to critically ill adults in an intensive care unit (ICU) is a ubiquitous intervention practiced for decades. Surprisingly, research on the correct supplemental oxygen dose for critically ill patients has only been available within the last decade. The articles included in this collection focus on the care of critically ill adults with acute respiratory distress syndrome (ARDS), with an eye to oxygen dose, the use of neuromuscular blockade, extracorporeal membrane oxygenation (ECMO), and esophageal balloon-guided positive end expiratory pressure (PEEP) titration.

Providing supplemental oxygen is necessary both to fulfill the diagnostic criteria of ARDS and to support ARDS patients. Several recent trials (CLOSE, Oxygen-ICU, ICU-ROX) have investigated the optimal oxygen dose for these patients. Now, the Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome ($LOCO_2$) trial presented here compared lower versus higher partial pressure of arterial oxygen (PaO_2) targets in the treatment of ARDS patients.

Within 12 hours of mechanical ventilation initiation, patients were randomized to a goal PaO_2 of 55–70 mm Hg (conservative group) or 90–105 mm Hg (liberal group). The trial was stopped early for safety and futility concerns after 205 patients were enrolled. The primary outcome of 28-day mortality occurred in 34.3% of the conservative group and 26.5% of the liberal group — not a statistically significant difference. However, a secondary analysis of 90-day mortality showed an increased hazard of death in the conservative group. This signal of possible harm is concerning, and taken with the CLOSE, Oxygen-ICU, and ICU-ROX data, suggests we have not yet identified the optimal supplemental oxygen dose for ARDS patients.

Many critical care trials have been stopped early before producing accurate measures; point estimates of an effect can vary wildly early in a trial. Not until large numbers are enrolled can we finally see the true outcomes; this is vital because oxygen is prescribed to millions of ICU patients each year. Some large trials are currently enrolling, such as the Preliminary Investigation of Optimal Oxygen Targets (PILOT) trial and the Mega Randomized Registry trial comparing conservative versus liberal oxygenation targets.

Also in this collection are summaries of research addressing other aspects of ARDS care. A promising signal previously seen in the use of esophageal balloons to guide PEEP titration was now found not to significantly improve outcomes. Similarly, the largest trial of neuromuscular blockade for ARDS showed no improvement in patient outcomes. Finally, the use of ECMO for ARDS treatment did not result in a significant survival benefit, although this technique seems to be safe and promising for future study.

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ORIGINAL ARTICLE

Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND

In patients with acute respiratory distress syndrome (ARDS), the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network recommends a target partial pressure of arterial oxygen (Pao_2) between 55 and 80 mm Hg. Prospective validation of this range in patients with ARDS is lacking. We hypothesized that targeting the lower limit of this range would improve outcomes in patients with ARDS.

METHODS

In this multicenter, randomized trial, we assigned patients with ARDS to receive either conservative oxygen therapy (target Pao_2, 55 to 70 mm Hg; oxygen saturation as measured by pulse oximetry [Spo_2], 88 to 92%) or liberal oxygen therapy (target Pao_2, 90 to 105 mm Hg; Spo_2, ≥96%) for 7 days. The same mechanical-ventilation strategies were used in both groups. The primary outcome was death from any cause at 28 days.

RESULTS

After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four patients who did not meet the eligibility criteria were excluded. At day 28, a total of 34 of 99 patients (34.3%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 95% confidence interval [CI], −4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group had died (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2). Five mesenteric ischemic events occurred in the conservative-oxygen group.

CONCLUSIONS

Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a Pao_2 between 55 and 70 mm Hg did not increase survival at 28 days. (Funded by the French Ministry of Health; LOCO$_2$ ClinicalTrials.gov number, NCT02713451.)

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*A complete list of investigators in the LOCO$_2$ trial is provided in the Supplementary Appendix, available at NEJM.org.

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No Benefit to Early Neuromuscular Blockade in Moderate-to-Severe ARDS

However, this strategy might be considered for selected patients with acute respiratory distress syndrome and ventilator dyssynchrony.

Ten years ago, a large randomized trial demonstrated lower mortality when patients with severe acute respiratory distress syndrome (ARDS) were treated with neuromuscular blockade (NMB; *NEJM JW Hosp Med* Oct 2010 and *N Engl J Med* 2010; 363:1107). Concerns about the deep sedation required for NMB, as well as the neuromuscular weakness associated with its use, led investigators to reexamine this benefit.

More than 1000 patients with moderate-to-severe ARDS (partial pressure of oxygen: fraction of inspired oxygen [PaO_2:FIO_2], <150) were randomized to 48 hours of either cisatracurium with deep sedation or light sedation without NMB. More than half of patients had pneumonia; prone positioning was used rarely. The trial included a high positive end-expiratory pressure (PEEP) strategy.

The trial was stopped early for futility. Mortality was quite high (43%) but was not different between groups. Lengths of stay (hospital and intensive care unit) and days free from mechanical ventilation were similar between groups; neuromuscular weakness and patient-reported quality of life at 3, 6, and 12 months also did not differ between groups.

COMMENT

The high mortality seen in this study is perplexing. Some people have proposed that higher PEEP was not helpful (as the authors suggest) but potentially harmful. Despite this, the results mean that patients with moderate-to-severe ARDS should not be treated uniformly with early NMB. However, I agree with the editorialists' position that NMB still should be considered on an individual basis, particularly for patients with ventilator dyssynchrony. In other patients, early, "moderate-to-severe" ARDS might resolve relatively quickly, mitigating the need for NMB and the downsides of deep sedation. ***— Patricia Kritek, MD***

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. **N Engl J Med** *2019 May 19; [e-pub]. (https://doi.org/10.1056/NEJMoa1901686)*

Slutsky AS and Villar J. Early paralytic agents for ARDS? Yes, no, and sometimes. **N Engl J Med** *2019 May 19; [e-pub]. (https://doi.org/10.1056/NEJMe1905627)*

Is Esophageal Balloon-Guided PEEP Titration Worthwhile?

In patients with acute respiratory distress syndrome, individualizing positive end-expiratory pressure didn't improve outcomes.

Patients with acute respiratory distress syndrome (ARDS) respond variably to positive end-expiratory pressure (PEEP), and we have no established way to find the "right" PEEP for an individual patient. More than a decade ago, a single-center study demonstrated improved oxygenation and lung compliance when PEEP was set through use of an esophageal balloon (*NEJM JW Emerg Med* Dec 2008 and *N Engl J Med* 2008; 359:2095). Because esophageal pressure estimates pleural pressure, this technique potentially helps avoid over- and underdistention of alveoli and mitigates lung injury.

Investigators randomized 202 patients with moderate-to-severe ARDS (partial pressure of arterial oxygen:fraction of inspired oxygen [PaO_2:FiO_2] <200) from 14 North American hospitals to either esophageal balloon titration of PEEP or an empirical algorithm for stepwise adjustment of PEEP and FiO_2. At 28 days, mortality and median number of ventilator-free days were similar in the two groups. Sixty-day and 1-year mortality, shock-free days, barotrauma, and acute kidney injury did not differ between groups.

COMMENT

Although individualized titration of PEEP using esophageal pressure makes sense physiologically, these results do not support this practice. Moreover, as has been demonstrated repeatedly in critical care, we should exercise caution in adopting a practice based solely on the results of one small single-center study. For now, sticking to standard PEEP and oxygen titration algorithms makes sense. ***— Patricia Kritek, MD***

Beitler JR et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-FIO_2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: A randomized clinical trial. **JAMA** *2019 Feb 18; [e-pub]. (https://doi.org/10.1001/jama.2019.0555)*

Cavalcanti AB et al. The elusive search for "best PEEP" and whether esophageal pressure monitoring helps. **JAMA** *2019 Feb 18; [e-pub]. (https://doi.org/10.1001/jama.2019.0267)*

No Mortality Benefit for Early Use of ECMO

A French trial was stopped early for futility, although crossover to extracorporeal membrane oxygenation was high.

To assess whether we should use early (rather than rescue) extracorporeal membrane oxygenation (ECMO) for patients with severe acute respiratory distress syndrome (ARDS), French investigators randomized patients to receive either venovenous ECMO or routine care within 7 days of intubation. All patients received low tidal volume ventilation. At enrollment, nearly two thirds of patients had been treated with prone positioning, and almost all had received neuromuscular blockade. Most patients who were randomized to ECMO (96%) were cannulated within 3 hours of enrollment.

The trial was stopped after 240 of 331 planned patients were enrolled, when an interim analysis indicated futility. Sixty-day mortality was not significantly lower in the ECMO group than in the control group (35% and 46%; P=0.09). Twenty-eight percent of control patients had crossed over to ECMO. When the data were reanalyzed for "treatment failure" (i.e., death in the ECMO group and death or crossover in the control group), investigators found significantly lower risk (0.62) in the ECMO group. ECMO patients were more likely to bleed but were less likely to receive renal replacement therapy and had more ventilator-free days.

COMMENT

This is a negative result for early use of ECMO for patients with severe ARDS; however, interpretation of the results is complex. Believers in ECMO will find the crossover and secondary outcomes data to be persuasive; doubters will focus on the primary-endpoint futility. I agree with the editorialists (Hardin et al.) who conclude that routine early ECMO is not superior to rescue use but is a reasonable option (at ECMO-proficient sites) when all other proven interventions, including neuromuscular blockade and prone positioning, have failed. However, other editorialists (Harrington et al.) express disappointment that the trial was stopped early and wonder if the results might have been positive if enrollment of patients had continued. ***— Patricia Kritek, MD***

Combes A et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. **N Engl J Med** *2018 May 24; 378:1965. (https://doi.org/10.1056/NEJMoa1800385)*

Hardin CC and Hibbert K. ECMO for severe ARDS. **N Engl J Med** *2018 May 24; 378:2032. (https://doi.org/10.1056/NEJMe1802676)*

Harrington D and Drazen JM. Learning from a trial stopped by a data and safety monitoring board. **N Engl J Med** *2018 May 24; 378:2031. (https://doi.org/10.1056/NEJMe1805123)*