Postextubation High-Flow Nasal Cannula Oxygen, Randomized Trial of an ICU Quality Improvement Intervention, and Midodrine during Recovery from Septic Shock

James M. Walter, Jacqueline M. Kruser, Paul A. Reyfman, and Peter H. S. Sporn

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Recommended Reading from the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine; Peter H. S. Sporn, M.D., Program Director

ORCID IDs: 0000-0003-3258-1869 (J.M.K.); 0000-0002-1006-9437 (P.H.S.S.).

Hernández G, et al. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. *JAMA* (1)

Reviewed by James M. Walter

Even with careful patient selection, up to 20% of patients develop post-extubation respiratory failure and require reintubation (2). Prophylactic noninvasive positive pressure ventilation after extubation has been found to improve outcomes, including all-cause mortality, although this benefit appears restricted to patients at high risk for post-extubation respiratory failure (3) and those with chronic respiratory disorders who develop hypercapnia during a trial of spontaneous breathing (4, 5).

There is increasing interest in the potential benefits of delivering humidified and heated oxygen by high-flow nasal cannula (HFNC) (6, 7). HFNC increases end-expiratory lung volume, reduces nasopharyngeal dead space, decreases work of breathing, facilitates clearance of respiratory secretions, and enhances patient comfort (8). In a recent trial, post-extubation use of HFNC in patients at high risk of post-extubation respiratory failure (identified by a $\text{PaO}_2/\text{FiO}_2$ ratio less than 300 at the end of a spontaneous breathing trial) resulted in better oxygenation than oxygen supplementation by Venturi mask and reduced the need for reintubation, although the latter was only a secondary endpoint of the study (9).

The trial by Hernández and colleagues tested whether the prophylactic use of HFNC compared with conventional oxygen therapy after extubation reduced the need for reintubation in patients at low risk of post-extubation respiratory failure (1). Ten inclusion criteria were used to identify low-risk patients, including:

age younger than 65 years; absence of heart failure as the primary indication for mechanical ventilation; absence of moderate to severe chronic obstructive pulmonary disease; Acute Physiology and Chronic Health Evaluation II score less than 12 on the day of extubation; body mass index less than 30 kg/m²; and less than 2 comorbidities. A total of 527 subjects were ultimately enrolled in the study. Immediately after extubation, subjects were randomized to either HFNC for 24 hours (with flow uptitrated at 5 L/min intervals to the point of patient discomfort) or conventional oxygen applied through a facemask or nasal cannula. The primary outcome was need for reintubation at 72 hours. The use of HFNC significantly reduced the need for reintubation at 72 hours (4.9% vs. 12.2%; $P = 0.004$), with a number needed to treat of 14 to prevent 1 reintubation. Subjects treated with HFNC also had lower rates of reintubation secondary to respiratory causes (8.3% vs. 14.4%; $P = 0.03$).

Although the results of the trial are provocative, several limitations deserve mention. Most subjects enrolled in the study had primary neurological or surgical diagnoses, whereas only a minority (16.5%) were admitted with primary respiratory failure. It was not clear that a similar benefit to HFNC would have been observed if the trial included a larger cohort of subjects with medical causes of respiratory failure. Similarly, the most common respiratory cause for reintubation with conventional oxygen therapy was the inability to clear secretions. HFNC facilitates mobilization of secretions by humidifying the airways and increasing the water content of mucus. Although this effect might be particularly important in patients with neurological injuries, it might have less impact in other patient populations. Furthermore, the inability to remove respiratory secretions is one of the more subjective of the trial's predefined criteria for reintubation. Because the trial was not blinded, this result should be interpreted with caution.

(Received in original form July 7, 2016; accepted in final form December 2, 2016)

Correspondence and requests for reprints should be addressed to Peter H. S. Sporn, M.D., Division of Pulmonary and Critical Care Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, 240 E. Huron St., McGaw M-300, Chicago, IL 60611. E-mail: p-sporn@northwestern.edu

Am J Respir Crit Care Med Vol 195, Iss 5, pp 682–684, Mar 1, 2017

Copyright © 2017 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201607-1394RR on December 2, 2016

Internet address: www.atsjournals.org

Nevertheless, this methodologically rigorous trial by Hernández and colleagues is noteworthy. It advances our understanding of how best to support patients in the tenuous period after extubation and supports the ongoing study of HFNC as a tool to prevent post-extubation respiratory failure. ■

References

1. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L, Cuenca R, Fernández R. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA* 2016;315:1354–1361.
2. Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med* 2013;187:1294–1302.
3. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med* 2006;173:164–170.
4. Ferrer M, Sellarés J, Valencia M, Carrillo A, Gonzalez G, Badia JR, Nicolas JM, Torres A. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet* 2009;374:1082–1088.
5. Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2013;12:CD004127.
6. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottreau A, et al.; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–2196.
7. Stéphane F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, Cosserant B, Flicoteaux G, Imbert A, Pilorge C, et al.; BiPOP Study Group. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015;313:2331–2339.
8. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest* 2015;148:253–261.
9. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, Montini L, De Gaetano A, Navalesi P, Antonelli M. Nasal high-flow versus Venturi mask oxygen therapy after extubation: effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med* 2014;190:282–288.

Cavalcanti AB, et al.; Writing Group for the CHECKLIST-ICU Investigators and the Brazilian Research in Intensive Care Network (BRICNet). Effect of a Quality Improvement Intervention with Daily Round Checklists, Goal Setting, and Clinician Prompting on Mortality of Critically Ill Patients: A Randomized Clinical Trial. *JAMA* (10)

Reviewed by Jacqueline M. Kruser

Quality improvement (QI) interventions in the intensive care unit (ICU) have the potential to improve processes of care and patient outcomes (11–13). The CHECKLIST-ICU study was a multicenter, cluster randomized trial in 118 Brazilian ICUs to evaluate whether a three-part QI intervention improved in-hospital mortality of ICU patients.

After baseline data collection, ICUs were randomized to the QI intervention protocol (n = 59) or continued routine care (n = 59) for 6 months. The QI intervention included daily, multidisciplinary rounds with an 11-item checklist, discussion of goals of care, and clinician prompting to complete checklist items. The investigators

found no significant difference in the primary outcome of in-hospital mortality between patients admitted to intervention ICUs (n = 3,327) and control ICUs (n = 3,434) (32.9% vs. 34.8%; odds ratio, 1.02; 95% confidence interval [CI], 0.82–1.26; *P* = 0.88). Secondary clinical outcomes (ICU mortality, nosocomial infections, duration of mechanical ventilation, and length of stay) were also not different between the control and intervention groups. However, in exploratory analyses, intervention ICUs achieved better performance on four processes of care: low tidal volume ventilation (rate ratio [RR], 1.14, 95% CI, 1.03–1.26); moderate level of patient sedation (RR, 1.19; 95% CI, 1.00–1.42), decreased use of central venous catheters (RR, 0.90; 95% CI, 0.83–0.98); and decreased use of urinary catheters (RR, 0.86; 95% CI, 0.80–0.93). The investigators found no improvement in three additional care processes: enteral or parenteral feeding, head-of-bed elevation, and venous thromboembolism prophylaxis. Although the checklist included optimization of antibiotic use, which is an important practice that has the potential to affect clinical outcomes, adherence to this item was not assessed.

Strengths of this study included the prospective randomized design, large sample, and demonstration of implementation fidelity of a three-part QI intervention across a diverse group of ICUs. However, the lack of clinical effect of the QI intervention warrants further consideration. The relationship between most of the targeted processes of care and mortality was unclear, and the population of patients likely to benefit from each individual process was a small subset of the study sample. Hence, although the study was able to show improved performance in four care processes, the QI intervention was unable to achieve a significant change in the patient-centered outcome of mortality. The 11 individual checklist items were chosen by expert consensus through a practice guideline approach, but important practices and QI interventions that have the potential to affect patient outcomes might not have been included. For example, the checklist did not explicitly encourage use of a combined, daily spontaneous awakening and breathing trial protocol, a practice that has been shown to improve mortality (14). ICUs in the study also had high baseline adherence to 3 of 11 checklist-targeted processes of care, which might have limited the impact of the intervention on clinical outcomes. This important trial demonstrated the impact of checklists, multidisciplinary goals of care discussions, and clinician prompting in the ICU, and it also highlighted the ongoing need for additional, novel strategies to improve the delivery of care. ■

References

10. Cavalcanti AB, Bozza FA, Machado FR, Salluh JI, Campagnucci VP, Vendramim P, Guimaraes HP, Normilio-Silva K, Damiani LP, Romano E, et al.; Writing Group for the CHECKLIST-ICU Investigators and the Brazilian Research in Intensive Care Network (BRICNet). Effect of a quality improvement intervention with daily round checklists, goal setting, and clinician prompting on mortality of critically ill patients: a randomized clinical trial. *JAMA* 2016;315:1480–1490.
11. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725–2732.
12. Weiss CH, Moazed F, McEvoy CA, Singer BD, Szleifer I, Amaral LA, Kwasny M, Watts CM, Persell SD, Baker DW, et al. Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. *Am J Respir Crit Care Med* 2011;184:680–686.

13. Scales DC, Dainty K, Hales B, Pinto R, Fowler RA, Adhikari NK, Zwarenstein M. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. *JAMA* 2011;305:363–372.
14. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, *et al.* Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.

Whitson MR, *et al.* Feasibility, Utility, and Safety of Midodrine during Recovery Phase from Septic Shock. *Chest* (15)

Reviewed by Paul A. Reyfman

Septic shock requiring vasopressors is an established criterion for admission to an ICU and is associated with prolonged ICU length of stay (LOS) (16, 17). Whitson and colleagues noted that the need for prolonged intravenous (IV) vasopressors might contribute to increased ICU LOS in patients with septic shock, and presented this as their rationale for investigating the potential role for oral midodrine in reducing the duration of IV vasopressor use and ICU LOS. Of note, a recent small observational trial suggested that addition of oral midodrine might accelerate IV vasopressor weaning in surgical ICU patients (18). However, this issue has not been explored in a medical ICU population.

This was a single-center retrospective study conducted at a tertiary care hospital involving 275 medical ICU patients who required at least 24 hours of IV vasopressor therapy for septic shock. The investigators compared duration of IV vasopressor use and ICU LOS in two groups: 140 patients who received only IV vasopressors and 135 patients who received IV vasopressors plus oral midodrine. Patients in the two groups had similar ages, Acute Physiology and Chronic Health Evaluation IV scores, and rates of mechanical ventilation. Patients who received only IV vasopressors required a mean of 3.8 days of IV therapy, whereas those who received IV vasopressors plus midodrine required 2.9 days of IV therapy ($P < 0.001$). Compared with patients who received IV vasopressors alone, fewer patients who received midodrine required reinstitution

of IV vasopressors after their discontinuation (5.2% vs. 15%; $P = 0.007$). ICU LOS for patients who received midodrine was shorter than for those who were treated with IV vasopressors alone (7.5 ± 5.9 days vs. 9.4 ± 6.7 days; $P = 0.017$). There was a trend toward decreased ICU mortality in patients who received midodrine, but hospital mortality was nearly identical in the two groups.

This study has received attention because it suggests the possibility that oral midodrine might be effective in reducing the duration of IV vasopressors and ICU LOS in patients with septic shock. However, there is no way to exclude the possibility that more of the patients who received midodrine were already showing signs of recovery when the drug was added and that this contributed to their shorter duration of vasopressor requirement and ICU LOS compared with patients who did not receive midodrine. In other words, selection bias might have had an important influence on the results. Other possible differences between the two groups that were not controlled for included comorbid conditions, duration of mechanical ventilation, source of infection, and causative pathogen, among others. Prospective, randomized, double-blind trials are needed to establish whether midodrine can safely decrease the duration of IV vasopressor therapy and improve clinical outcomes in patients recovering from septic shock before this approach can be recommended in routine clinical practice. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

15. Whitson MR, Mo E, Nabi T, Healy L, Koenig S, Narasimhan M, Mayo PH. Feasibility, utility, and safety of midodrine during recovery phase from septic shock. *Chest* 2016;149:1380–1383.
16. Smith G, Nielsen M. ABC of intensive care: criteria for admission. *BMJ* 1999;318:1544–1547.
17. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, Davies A, Delaney A, Harrison DA, Holdgate A, *et al.* A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMiSe Investigators. *Intensive Care Med* 2015;41:1549–1560.
18. Levine AR, Meyer MJ, Bittner EA, Berg S, Kalman R, Stanislaus AB, Ryan C, Ball SA, Eikermann M. Oral midodrine treatment accelerates the liberation of intensive care unit patients from intravenous vasopressor infusions. *J Crit Care* 2013;28:756–762.