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Early View

Editorial

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Prone Positioning for Non-Intubated Hypoxemic Patients with COVID-19: Cheap, Easy, and Makes Sense, but does it Work?

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Main Text

Since the 1970s, prone positioning has been proposed as an inexpensive and physiologically-justified management strategy for patients with acute respiratory distress syndrome (ARDS). The physiologic rationale for prone positioning in ARDS has been well described.[1,2] Placing a person in the prone position reduces lung compression, which facilitates better ventilation/perfusion matching and leads to improved oxygenation. However, determining whether patients receive clinically meaningful benefit from prone positioning in the form of reduced mortality or time supported on mechanical ventilation has been challenging. Early trials that used prone positioning as a "rescue" therapy or applied relatively small "doses" of prone positioning (i.e. limited duration of time in prone position) did not demonstrate improvements in mortality or ventilator-free days (VFDs).[3–5] The landmark PROSEVA trial published in 2013 enrolled patients with at least moderate ARDS (PaO_2/FiO_2 ratio < 150) who were early in their hospital course (<36 hours after intubation) and then randomized them to standard care alone (including low tidal volume ventilation) or at least 16 hours/day of prone position.[6] In contrast to prior trials, PROSEVA identified a marked reduction in mortality and VFDs in ARDS patients treated with prone positioning. There have been many proposed explanations for PROSEVA's success after repeated negative results in earlier trials of proning. However, selection of a more severe patient population early in their disease clearly differentiated PROSEVA from prior trials. A major question that remained after PROSEVA was whether there might be a broader set of patients with hypoxemic respiratory failure that might benefit from prone positioning. The onset of the COVID-19 pandemic has forced us to ask whether non-intubated hypoxemic patients infected with

SARS-CoV-2 might represent an additional group of patients that might benefit from prone positioning.

The COVID-19 pandemic has dramatically increased the number of patients with moderate-to-severe ARDS who are treated outside of intensive care units.[7] There is an urgent need to mitigate escalation in respiratory support and decrease rates of intubation, particularly in health care systems where the volume of COVID-19 patients exceeds hospital capacity. Awake prone positioning for non-intubated patients with hypoxemia and COVID-19 has been associated with improved oxygenation and decreased rates of intubation in some,[8–15] but not all reports.[16–20] None of these previously published observational studies included more than n = 200 subjects nor accounted for factors that could contribute to selection bias such as age or oxygen delivery device. A recent randomized meta-trial of COVID-19 patients supported on high-flow nasal cannula (HFNC) demonstrated decreased rates of treatment failure and subsequent intubation in patients treated with awake prone positioning vs. standard care, however there was no difference in 28-day mortality.[21] The impact of awake prone positioning on non-intubated COVID-19 patients supported on low-flow and other non-HFNC oxygen delivery devices has not been tested in an interventional trial.

In this issue of the *European Respiratory Journal*, Perez-Nieto and colleagues present findings from the APPONOX study that suggest prone positioning of awake, non-intubated, patients with hypoxemia due to COVID-19 is associated with decreased rates of subsequent intubation and mortality. This large retrospective cohort study included patients (n = 827) from 27 hospitals in Mexico and Ecuador who were infected with SARS-CoV-2 and were hypoxemic (SpO2 < 94%). Only 10% of patients were

treated with HFNC at time of enrollment, with the remainder supported on low-flow nasal cannula (49%) or non-rebreather mask (41%). The authors compared patients who were treated for greater than 2 hours of prone positioning (AP group, n = 505) vs. subjects in whom prone positioning was not attempted or were treated for less than 2 hours (AS group: awake supine, n = 322). In the AP group, the median time to initiation of proning after hospital arrival was 15 hours and patients were proned for a median time of 12 hours during their hospital course. The primary outcome for the study was rates of intubation. In order to mitigate confounding by indication, the authors performed a propensity score analysis including variables such as age, degree of hypoxemia, supplemental oxygen delivery device, comorbidities, treatment with steroids, and acuity of care. The authors found that 23.6% of AP patients were subsequently intubated vs. 40.4% of AS patients (adjusted odds ratio [OR], 0.50 [95% CI,0.36 – 0.71]; $p < 0.0001$ after propensity analysis). Mortality was also significantly lower in the AP vs. AS group (19.8% vs. 37.3%).

The major strengths of this study include the relatively large size of the cohort, the rigor of the analyses which included propensity score matching, and the diversity of the hospitals and patients included in the study. Ninety percent of patients in this study were not supported on HFNC, suggesting that awake prone positioning of non-intubated hypoxemic patients with COVID-19 might be beneficial to a broader population beyond those supported by this scare respiratory support device.[21] Indeed, as the authors note, this study was conducted at some sites that dealt with hospital strain and limited resources.[22] The findings from this study may be generalizable to institutions where

scarcity of advanced respiratory care resources has a major influence on patient outcomes.[23]

Though encouraging, the results of this study should be interpreted with caution. The authors included multiple analyses to address indication and treatment biases, however given the highly complex and rapidly evolving nature of care for hypoxemic COVID-19 patients it is not unlikely there exists some degree of residual confounding. For example, it is possible patients who did not receive awake prone positioning were too frail or had some other factors limiting appropriateness or feasibility of prone positioning, and these factors could also have increased risk for intubation. The disparity in the proportion of patients receiving HFNC and non-rebreather masks between the AP vs. AS groups could have confounded the results given the potential beneficial aspects of HFNC treatment in COVID-19.[24,25] The authors importantly adjusted for this in their analyses, and the proportion of patients receiving HFNC was only 10% in the entire cohort. Finally, although the authors found an association between awake prone positioning and decreased mortality, the safety of proning was not assessed. A recent trial of prone positioning in COVID-19 patients supported on HFNC did not demonstrate a concerning signal for harm.[21] Additional studies testing whether proning non-intubated patients might inappropriately delay initiation of invasive mechanical ventilation and lead to worse overall outcomes are currently underway (ClinicalTrials.gov, NCT04347941, NCT04344587, NCT04325906, NCT04358939, NCT04395144).[2]

In conclusion, the APPONOX study confirms that awake proning of non-intubated hypoxemic patients with COVID-19 holds promise as a cheap, easy, and effective therapy for reducing rates of intubation and mortality in hypoxemic patients with COVID-19. Reducing rates of intubation may be particularly important in healthcare systems where access to advanced respiratory care resources are scarce. There are multiple ongoing randomized controlled trials underway to confirm the findings from this study. Until the results from these studies are published, it seems reasonable to encourage non-intubated hypoxemic patients with COVID-19 to assume a prone position.

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