As the COVID-19 pandemic spread around the world and intensive care units became overwhelmed with an influx of critically ill patients, clinicians struggled to determine effective treatment options for this new disease. Prone positioning has emerged as a treatment option for the care of patients with COVID-19. In this issue of JAMA Internal Medicine, Qian et al1 report results from a nonrandomized controlled trial of awake prone positioning compared with usual care among 501 nonintubated patients with COVID-19 and acute hypoxic respiratory failure. The extent of respiratory failure and the application of other COVID-19–specific therapies varied, with 66.3% of patients requiring standard nasal cannula and 79.6% receiving dexamethasone. Patients in the prone positioning arm spent an estimated median of 4.2 hours (IQR, 1.8-6.7 hours) per day in the prone position during the first 5 study days. The primary outcome was the odds of a worsening outcome based on the World Health Organization ordinal scale at study day 5. This scale describes the severity of disease from 0 (asymptomatic) to 8 (dead), with intermediate levels of 3 (hospitalization), 4 (standard nasal cannula), 5 (heated high-flow nasal cannula or noninvasive ventilation), and 6 (mechanical ventilation). The authors report a significant worsening in score at day 5 in the prone positioning arm (adjusted odds ratio, 1.63; 95% credibility interval, 1.16-2.31). This difference in the World Health Organization ordinal scale score did not persist at days 14 and 28. Moreover, there was no clinical difference in mortality, hospital length of stay, ventilator-free days, or progression to mechanical ventilation between groups, although patients in the prone positioning arm required a higher estimated fraction of inspired oxygen than those in the usual care arm.

Although acute respiratory distress syndrome (ARDS) has been a focus of research for more than 50 years, few therapies have been proven to improve patient outcomes. Low tidal volume ventilation, prone positioning, and a fluid-restrictive strategy reduce mortality or duration of mechanical ventilation, but many other interventions (eg, continuous neuromuscular blockade, albuterol, ketocoazole, statin, and steroid therapies) have not consistently demonstrated benefit.2-7 Moreover, no therapies have prevented the development of ARDS in at-risk patients. With limited resources and treatment options, investigators extrapolated from the existing ARDS literature and tried using ARDS-specific therapies for critically ill patients with COVID-19. Shortly after the onset of the pandemic, there was also considerable concern about not having enough mechanical ventilators to support patients with COVID-19 and hypoxia. Therefore, interventions known to increase oxygenation were also considered for the treatment of COVID-19 (eg, continuous positive airway pressure masks, high-flow nasal cannula, and prone positioning). The potential benefit of these oxygen delivery devices was initially weighed against the potential concern of aerosolizing the virus and infecting health care professionals.

As demonstrated in the PROSEVA (Effect of Prone Positioning on Mortality in Patients With Severe and Persistent Acute Respiratory Distress Syndrome) clinical trial,2 which was conducted in the pre–COVID-19 era, prone positioning improves oxygenation in patients with hypoxic respiratory failure and reduces mortality in patients with moderate to severe ARDS when used early and for prolonged periods. Prone positioning improves gas exchange through the recruitment of dependent atelectatic lung regions that are inferior to the heart and the dorsal portion of the diaphragm in the supine position. The increased aeration and recruitment of these dorsal regions outweigh the derecruitment of the non-dependent ventral regions, thereby reducing shunt and improving ventilation-perfusion matching and oxygenation when in the prone position. However, improved mortality is unlikely to be due to improved oxygenation alone but rather to reduced ventilator-induced lung injury (VILI).4 Because of several anatomical differences, the gravitational gradient of transpulmonary pressures is equalized in the dorsal-ventral axis when in the prone position, thereby reducing both hyperinflation of the nondependent alveoli and atelectasis in the dependent alveoli. These prone positioning–related physiological changes reduce VILI independent of any changes in oxygenation.5

Before the PROSEVA study, several randomized clinical trials6-7 of prone positioning among intubated patients with ARDS consistently demonstrated improvements in oxygenation. Only the PROSEVA clinical trial showed a statistically significant decrease in 90-day mortality among those in the prone positioning arm vs the control arm (41.0% vs 23.6%). These earlier studies6-7 may have been limited by enrollment of patients with less severe ARDS and the use of prone positioning for shorter periods (6-8 hours vs >16 hours). Notably, the PROSEVA clinical trial demonstrated a mortality benefit among patients early in the disease course (<24 hours) of moderate to severe ARDS (ratio of arterial oxygen partial pressure to fraction of inspired oxygen of <150) who were in the prone position for longer than 16 hours per day.3

The work of Qian et al1 differs in important ways from previous prone positioning studies of patients with ARDS. The first and most important difference was that patients were not intubated. Although patients were potentially at risk of patient self-inflicted lung injury from repetitively receiving large tidal volumes on their own, they clearly could not develop VILI. However, they could develop ventilation-induced lung injury. Therefore, the only way prone positioning could have prevented VILI was if it
Prone Positioning for Nonintubated Patients With COVID-19

Invited Commentary

Prone positioning for nonintubated patients with COVID-19 may be a useful strategy for the management of patients with acute hypoxemic respiratory failure, particularly those with early acute respiratory distress syndrome (ARDS). Several observational studies have suggested that prone positioning can improve oxygenation and reduce the need for mechanical ventilation. However, it is also possible that by temporarily stabilizing oxygenation, beneficial intubation and lung-protective mechanical ventilation were delayed, causing increased lung injury and worsening short-term outcomes. Second, the median time in the prone position was 4.2 hours, far less than in the PROSEVA trial, in which longer periods of prone positioning were necessary to generate a mortality benefit.3

Third, the outcomes of the Qian et al study differ from those of other COVID-19–specific prone positioning studies. In a meta-analysis of 25 observational studies of nonintubated patients with COVID-19, Ponnapa Reddy et al8 found a consistent increase in oxygenation between the supine and prone position. However, Qian et al1 showed that patients in the prone positioning group had increased over-all fraction of infused oxygen needs and worsening oxygenation. A collaborative meta-trial9 involving 6 randomized clinical trials comprising 1126 patients with COVID-19 receiving oxygen via heated high-flow nasal cannula who were in the prone position for a median of 5 hours per day demonstrated a reduction in the composite end point of death and intubation at 28 days (odds ratio, 0.85; 95% CI, 0.75-0.98). These results were caused by a reduction in intubation, not mortality. However, the patients in the meta-trial manifested more severe hypoxic respiratory failure at enrollment, had predefined criteria for intubation, and had multiple exclusion criteria for awake prone positioning, such as pregnancy, obesity, altered mental status, and recent abdominal surgery; the study thus selected for a more uniform population than that of Qian et al.1

Fourth, each step in the World Health Organization ordinal scale may not be equally important. Transitioning from standard nasal cannula to heated high-flow nasal cannula may have different associations with clinical outcomes than transitioning from heated high-flow nasal cannula to mechanical ventilation. Fifth, it is important to remember that interventions that improve intermediate (surrogate) outcomes do not necessarily improve clinically relevant outcomes, such as mortality. Surrogate outcomes, such as improved oxygenation, have been found to be irrelevant for clinically proven ARDS interventions, such as low tidal volume ventilation, that improve mortality.2

Although the short-term deleterious effects reported in the Qian et al study are provocative, concerns related to study design weaken the strength of their conclusions. If prone positioning is associated with improved mortality by reducing VILI in patients with moderate to severe ARDS who are in the prone position for more than 16 hours per day, we would expect that the use of prone positioning for shorter periods among patients with less severe disease would be associated with improved short-term oxygenation. However, the results of Qian et al3 suggest caution is warranted when extrapolating evidence-based interventions to different patient populations. As the Washington Post’s Pulitzer-prize winning columnist Michael Dirda stated, “science fiction is after all the art of extrapolation.”10

ARTICLE INFORMATION

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