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Proning in COVID-19 Acute Respiratory Distress Syndrome: Role of Paralytics

OBJECTIVES: Although proning is beneficial to acute respiratory distress syndrome, impressions vary about its efficacy. Some providers believe that paralysis is required to facilitate proning. We studied impact of paralysis on prone-induced gas exchange improvements and provider attitudes regarding paralytics.

DESIGN: Observational.

SETTING: University of California San Diego.

PATIENTS: Intubated COVID acute respiratory distress syndrome patients.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: 1) Changes in $P_{aO_2}:F_{iO_2}$ and $S_{pO_2}:F_{iO_2}$ ratios before and after proning with and without paralytics, 2) adverse events during proning with and without paralytics, and 3) nurse and physician attitudes about efficacy/safety of proning with and without paralytics. Gas-exchange improvement with proning was similar with and without paralytics (with no serious adverse events). Survey results showed similar attitudes between nurses and physicians about proning efficacy but differing attitudes about the need for paralytics with proning.

CONCLUSIONS: Findings support use of proning and may help in design of randomized trials to assess paralytics in acute respiratory distress syndrome management.

KEY WORDS: acute respiratory distress syndrome; mechanical ventilation; neuromuscular blockade; paralytics; proning

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To the Editor:

Patients with COVID-19 respiratory failure develop acute respiratory distress syndrome (ARDS), which is typically managed with lung-protective ventilation (1). Proning is one of the few proven therapies for ARDS, but implementation is inconsistent (2, 3). Guérin et al (2) showed 42% relative risk reduction for mortality with proning versus supine controls. In one recent survey, 96% of physicians reported that proning was likely to be beneficial to patients with moderate-to-severe ARDS (4); however, only 39% of ICU nurses felt it would be helpful. This disconnect between doctors and nurses offers a major opportunity to improve teamwork and communication (5).

One controversial therapy in moderate-to-severe ARDS is use of neuromuscular blockade (NMB). Of note, the proned patients in the Guérin et al (2) study routinely received NMB, leading to speculation that paralytics may be an important factor underlying the observed benefits. Data regarding benefits of NMB are conflicting, but purported benefits include patient/ventilator synchrony, improved gas exchange, and enhanced safety of proning (6, 7).

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DOI: 10.1097/CCE.0000000000000646

Based on this conceptual framework, we sought to test the hypothesis that proning could be accomplished without paralysis in people with COVID ARDS. We assessed gas exchange by comparing the Pao₂-to-Fio₂ (PF) ratio or the Spo₂-to-Fio₂ (SF) ratio in patients with ARDS during proning. We compared these ratios within the same individual when undergoing proning with and without NMB. We also determined the reported adverse events associated with proning with and without NMB to evaluate whether paralytics affected safety. Finally, we surveyed the ICU healthcare team to evaluate their comfort/confidence with proning with and without paralytics.

MATERIALS AND METHODS

We analyzed our Institutional Review Board (IRB)-approved University of California San Diego COVID Registry and Clinical Data Repository (IRB 200498). Due to the observational nature of our study, our IRB waived the need for consent. Using data from the registry and the electronic medical record (EMR), we identified 15 patients who met criteria. We enrolled intubated patients with moderate-to-severe ARDS from COVID. Patients also must have undergone two or more sessions of proning, including at least one session while receiving paralytics and one session without paralytics. This within-subject comparison was performed to maximize statistical power. Age, gender, body mass index, race/ethnicity, etiology of ARDS, and important comorbidities were recorded.

Given the retrospective nature of our study, the clinical team directed the customary best practice use of sedatives, paralytics, ventilator settings, and timing of prone versus supine positioning as well as blood draws, including arterial blood gas (ABG) measurements. Paralytics were titrated to ventilator synchrony. Sedation was assessed by means of the Richmond Agitation-Sedation Scale with a target score of -4 or -5 prior to starting paralytics. ABG values were collected from the EMR; however, there was considerable variation in the timing of ABG in relation to position change, ranging from 15 minutes to 9 hours after proning. Therefore, Spo₂ data were also obtained, and the SF ratio was used as a surrogate for the PF ratio.

Adverse safety outcomes (self-extubation, abrupt cardiopulmonary deterioration, loss of indwelling catheters, skin/soft-tissue injury, and ventilator disconnect) were reviewed.

In addition to gathering objective clinical data regarding patient characteristics, outcomes, and gas exchange, anonymous surveys regarding the healthcare team's impressions about the safety and efficacy of proning were collected from September to November 2020. All respondents worked in the ICU during the COVID pandemic. The survey included demographic questions, role in the ICU (e.g., nurse, resident, fellow, or attending physician), and the respondent's impression of proning with and without paralytics. Finally, open-ended questions were posed regarding each respondent's experience with adverse events related to proning.

We examined oxygenation changes between supine and prone comparing individual patients with and without the use of NMB. Changes in PF and SF ratio were reported as both absolute and relative differences. Due to a small sample size increasing the risk for non-normally distributed data, a nonparametric comparison was performed between the absolute and relative differences using a Wilcoxon signed-rank test due to the paired values within each patient. These results were evaluated for goodness of fit with a Kolmogorov-Smirnov test. All data were analyzed using Statistical Package for the Social Sciences Statistics (IBM SPSS Statistics for Windows, Version 26.0; IBM, Armonk, NY). Survey data and responses were reported as percentages.

RESULTS

A total of 15 patients were included in the analysis (Table 1). For all sessions, the average duration of

TABLE 1.
Baseline Characteristics of Study Participants

Variable	Value
Age, yr, mean (sd)	65.8 (6.5)
Sex, n (%)	
Female	40 (6)
Male	60 (9)
Body mass index, mean (sd)	31.2 (5.4)
Comorbidities, n (%)	
Chronic pulmonary disease	6.7 (1)
Hypertension	53.3 (8)
Chronic kidney disease	13.3 (2)
Diabetes mellitus	66.7 (10)
Cardiovascular disease	13.3 (2)

proning was 20.2 ± 14.9 hr/d. The SF ratio was collected 30 ± 15 min before (while supine) and 60 ± 15 min after proning (8). Seven patients were initially prone without paralytics and had paralytics added later due to ventilator dyssynchrony, whereas eight patients were initially prone with paralytics and subsequently had paralytics discontinued with additional proning sessions performed thereafter. There was no significant difference in mean duration of prone position with and without NMB, 23.8 ± 20.5 versus 16.6 ± 3.1 hr, respectively ($U = 148.5$, $p = 0.137$).

As expected from previous studies, oxygenation improved during all prone sessions whether it was assessed by change in PF ratio ($M = 29.5 \pm 47.6$) or SF ratio ($M = 4.2 \pm 18.3$). The supine PF ratio was not statistically different regardless of NMB use ($z = 0.105$, $p = 0.917$). There was no significant difference in the absolute P:F or relative P:F ratio regardless of NMB use. The mean absolute change in P:F was 33.5 ± 53.3 and 25.5 ± 42.6 in the unparalyzed and paralyzed groups, respectively ($z = 0.516$, $p = 0.691$). Mean improvement in relative P:F was 24.1% (43.2) and 34.7% (48.7) in the unparalyzed and paralyzed groups, respectively ($z = -0.568$, $p = 0.570$). To control for potential ascertainment bias, the S:F ratio was also compared showing no significant difference in S:F ratio regardless of NMB use (Table 2). Mean improvement in absolute S:F was 6.6 ± 20.9 and 1.9 ± 15.7 in the unparalyzed and paralyzed groups, respectively ($z = -0.314$,

$p = 0.753$). Mean improvement in relative S:F was 6.1% (17.0) and 1.9% (11.3) in the unparalyzed and paralyzed groups, respectively ($z = 0.734$, $p = 0.463$) (Table 2). Three patients were discharged home, five were discharged to long-term care, and seven died during the index hospitalization. None of the patients required extracorporeal membrane oxygenation support.

For our survey, we had 96 respondents (Fig. 1); however, 16 were excluded due to incomplete data. Of the 80 respondents included, 47 were nurses and 33 were physicians (13 faculty intensivists, nine ICU fellows, and 13 medicine residents). Nurses and physicians agreed that a patient with moderate-to-severe ARDS would benefit from proning (97% of physicians and 91.5% of nurses). Two-thirds of nurses and 50% of physicians were comfortable/confident with proning. When asked if proning with paralytics was safe for the patient, 93.6% of nurses and 91% of physicians strongly or somewhat agreed. However, when asked if proning without paralytics was safe for the patient, only 51.1% of nurses and 69.7% of physicians strongly or somewhat agreed. At the furthest end of the spectrum, only 6.4% of nurses compared with 24.2% of physicians strongly agreed that proning without paralytics was safe for the patient (Fig. 1). There were no adverse events related to proning in the medical record or the hospital event reporting system for any of the included patients.

TABLE 2.
Response to Prone Positioning With and Without Paralysis

Variable	With Paralysis	Without Paralysis	U	p
PF results				
PF, mm Hg, mean (SD)				
Supine	119.9 7(37)	113.6 (23.8)	120.5	0.744
Prone	153.5 (61.25)	139.1 (47.2)		
PF mm Hg Δ from prone positioning	33.5 (53.3)	25.5 (42.6)	121	0.744
% change in PF, mean (SD)	34.7 (48.7)	24.1 (43.2)	129	0.512
SF results				
SF, mean (SD)				
Supine	132.7 (24.2)	137.2 (27.8)		
Prone	139.2 (26.8)	143.8 (28.3)		
SF absolute change, mean (SD)	1.9 (15.7)	6.6 (20.9)	90	0.367
% change in SF, mean (SD)	1.9 (11.3)	6.1 (17.0)	93.5	0.436

PF = P_{aO_2} -to- F_{iO_2} ratio, SF = S_{pO_2} -to- F_{iO_2} ratio.

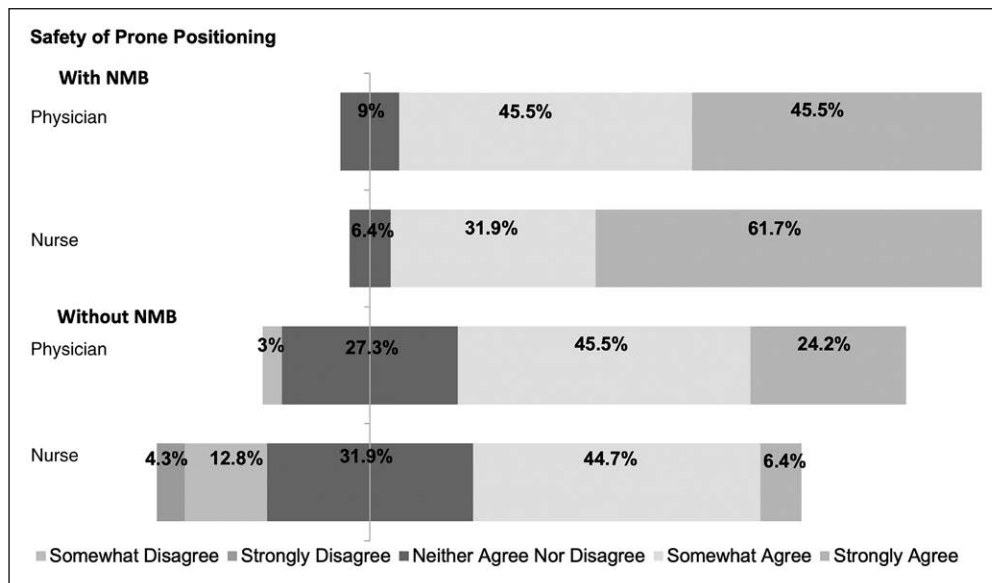


Figure 1. Physician and nurse perceptions of prone position safety with and without neuromuscular blockade. NMB = neuromuscular blockade.

DISCUSSION

Our findings add to the literature in important ways. First, we observed no significant difference in the improvement in PF or SF ratio comparing ARDS patients to themselves with or without paralytics. This finding suggests that the gas-exchange benefits of proning may be relatively independent of the use of paralytics. Second, in the absence of serious adverse events from proning without paralytics, we are reassured that paralytics are not required to prone patients safely. Third, our survey suggested some degree of variability in the experience and confidence of members of the health-care team regarding proning.

With regard to barriers to implementation of proning, a number of possibilities exist. Proning can put a major burden on the healthcare team particularly in the context of COVID when concerns about exposure are real. Another potential barrier is the concern that proning could theoretically lead to serious safety consequences such as dislodgement of endotracheal tubes and other crucial equipment. A final potential concern is the possibility that a dogma exists that heavy sedation and paralytics are required to prone patients. As a result, the potential hemodynamic and neuromuscular toxicity of these agents would have to be weighed against the possible benefits of proning. However, our findings suggest that proning can be accomplished safely in ARDS without paralytics. Indeed, experience is increasing with nonintubated proning (9), although

this approach is still being studied (10). Thus, our study provides some reassurance that serious adverse events are rare in experienced hands and that proning without paralytics can be more widely implemented.

Despite our study’s strengths, we acknowledge limitations. First, the observational nature of our study and modest sample size lead to unclear generalizability. Surrogate outcomes such as PF and SF ratio are imperfect metrics of proning benefits.

Given our within-subject design, we clearly could not use hard outcomes such as mortality or duration of mechanical ventilation. Nonetheless, we believe our findings are robust and could be used to design randomized trials. Second, because patients were not randomized, the possibility exists that some bias is present regarding timing of paralysis. Our within-subject comparison design helps to mitigate this concern such that sicker patients (e.g., those on continuous renal replacement therapy) are compared with themselves. However, we certainly support randomized trials in the future. Third, our observations may be subject to recall bias. For example, serious adverse events are typically documented, but we may have failed to capture more minor events or “near-misses” if they were not well documented. Additionally, we were unable to characterize the prevalence of ICU-acquired weakness as an adverse event due to the retrospective nature of our study and absence of consistent clinical documentation. We believe this is an important topic for future studies.

CONCLUSIONS

When implementing proning in COVID ARDS, we found no evidence to support routine use of paralytics. Safety and efficacy were similar when COVID patients were prone with or without NMB. Although nurses and physicians share similar impressions regarding proning efficacy, there are some doubts about the

safety of this intervention without paralytic medication. Further efforts can improve education and teamwork in the ICU.

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The authors have disclosed that they do not have any potential conflicts of interest.

All work performed at the University of California San Diego, La Jolla, CA.

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REFERENCES

- Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: Different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; 46:1099–1102
- Guérin C, Reignier J, Richard JC: Prone positioning in the acute respiratory distress syndrome. *N Engl J Med* 2013; 369:980–981
- Beitler JR, Shaefi S, Montesi SB, et al: Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: A meta-analysis. *Intensive Care Med* 2014; 40:332–341
- Poor AD, Acquah SO, Wells CM, et al: Implementing automated prone ventilation for acute respiratory distress syndrome via simulation-based training. *Am J Crit Care* 2020; 29:e52–e59
- Cotton SA, Roche CE, Malhotra A: Prone during COVID-19: The importance of teamwork. *Am J Crit Care* 2020; 29:418
- Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
- Moss M, Ulysse CA, Angus DC; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network: Early neuromuscular blockade in the acute respiratory distress syndrome. Reply. *N Engl J Med* 2019; 381:787–788
- Brown SM, Duggal A, Hou PC, et al; National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Prevention and Early Treatment of Acute Lung Injury (PETAL) Network: Nonlinear imputation of PaO₂/FIO₂ from SpO₂/FIO₂ among mechanically ventilated patients in the ICU: A prospective, observational study. *Crit Care Med* 2017; 45:1317–1324
- Ehrmann S, Li J, Ibarra-Estrada M, et al; Awake Prone Positioning Meta-Trial Group: Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: A randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med* 2021; 9:1387–1395
- McGuire W, Pearce A, Malhotra A: Prone in non-intubated may reduce the need for intubation in patients with severe COVID-19. *Lancet Respiratory Medicine* 2021; 9:e110