ORIGINAL CLINICAL RESEARCH REPORT

Effectiveness of Prone Positioning in Nonintubated Intensive Care Unit Patients With Moderate to Severe Acute Respiratory Distress Syndrome by Coronavirus Disease 2019

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BACKGROUND: In the treatment for severe acute respiratory distress syndrome (ARDS) from coronavirus disease 2019 (COVID-19), the World Health Organization (WHO) recommends prone positioning (PP) during mechanical ventilation for periods of 12–16 h/d to potentially improve oxygenation and survival. In this prospective observational study, we evaluated the ability of long PP sessions to improve oxygenation in awake intensive care unit (ICU) patients with moderate or severe ARDS due to COVID-19.

METHODS: The study was approved by the ethics committee of Galicia (code No. 2020-188), and all patients provided informed consent. In this case series, awake patients with moderate or severe ARDS by COVID-19 admitted to the ICU at University Hospital of Santiago from March 21 to April 5, 2020 were prospectively analyzed. Patients were instructed to remain in PP as long as possible until the patient felt too tired to maintain that position. Light sedation was administered with dexmedetomidine. The following information was collected: number and duration of PP sessions; tissue O_2 saturation (Sto_2) and blood gases before, during, and following a PP session; need of mechanical ventilation; duration of ICU admission; and ICU outcome. Linear mixed-effects models (LMM) were fit to estimate changes from baseline with a random effect for patient.

RESULTS: Seven patients with moderate or severe ARDS by COVID-19 were included. All patients received at least 1 PP session. A total of 16 PP sessions were performed in the 7 patients during the period study. The median duration of PP sessions was 10 hours. Dexmedetomidine was used in all PP sessions. Oxygenation increased in all 16 sessions performed in the 7 patients. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (Pao_2/Fio_2) significantly increased during PP (change from baseline 110 with 97.5% confidence interval [CI], 19-202) and, after PP, albeit not significantly (change from baseline 38 with 97.5% CI, −9.2 to 85) compared with previous supine position. Similarly, tissue oxygenation underwent a small improvement during PP (change from baseline 2.6% with 97.5% CI, 0.69-4.6) without significant changes after PP. Two patients required intubation. All patients were discharged from the ICU.

CONCLUSIONS: We found that PP improved oxygenation in ICU patients with COVID-19 and moderate or severe ARDS. PP was relatively well tolerated in our patients and may be a simple strategy to improve oxygenation trying to reduce the number of patients in mechanical ventilation and the length of stay in the ICU, especially in COVID-19 pandemic. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Can prone positioning improve oxygenation and avoid intubation in nonintubated intensive care unit (ICU) patients with moderate or severe acute respiratory distress syndrome (ARDS) by coronavirus disease 2019 (COVID-19)?
- **Findings:** In this prospective observational study including 7 nonintubated patients admitted to the ICU with COVID-19 and moderate or severe ARDS, prone positioning improved oxygenation in all patients and intubation was avoided in 5 of them.
- **Meaning:** Prone positioning (PP) may be a possible economic and simple strategy to improve oxygenation trying to reduce patients in mechanical ventilation and the length of stay in the ICU, especially in COVID-19 pandemic.

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GLOSSARY

APACHE II = Acute Physiology and Chronic Health Evaluation II; **ARDS** = acute respiratory distress syndrome; **CI** = confidence interval; **COVID-19** = Coronavirus Disease 2019; **FFP3** = filtering face pieces; **F_{IO_2}** = fractional inspired oxygen; **ICU** = intensive care unit; **IQR** = interquartile range; **LMM** = linear mixed-effects models; **P_{aCO_2}** = partial pressure of carbon dioxide; **P_{aO_2}** = arterial partial pressure of oxygen; **P_{aO_2}/F_{IO_2}** = ratio arterial partial pressure of oxygen/fraction of inspired oxygen; **POST** = postprone positioning; **PP** = prone positioning; **PRE** = previous to prone positioning; **PRONE** = during prone positioning; **SAOS** = sleep apnea obstructive syndrome; **SARS-CoV-2** = XXX; **S_{tO_2}** = tissue O2 saturation; **WHO** = World Health Organization

Since the emergence of the 2019 novel coronavirus (SARS-CoV-2) infection in December 2019, the coronavirus disease 2019 (COVID-19) has rapidly spread across the globe. The clinical spectrum of patients with COVID-19 ranges from asymptomatic or mild symptoms to critical disease with a high risk of mortality. In particular, of the incidence of acute respiratory distress syndrome (ARDS) in patients hospitalized with COVID-19 can range from 17% to 30% (1–2). Some of these patients with ARDS (20%–30%) may develop respiratory failure 10–11 days after the onset of symptoms requiring intensive care unit (ICU) admission and mechanical ventilation.[1,2]

In treatment for severe ARDS associated with COVID-19, 1 option is prone positioning (PP) during mechanical ventilation. The World Health Organization (WHO) recommends its use for periods of 12–16 h/d because it may improve oxygenation and survival.[3,4]

The objective of this prospective observational study was to evaluate the effectiveness of the PP sessions to improve oxygenation and assess the incidence of tracheal intubation and mechanical ventilation in patients with moderate or severe ARDS by COVID-19.

METHODS

We prospectively evaluated patients with laboratory-confirmed COVID-19 disease who had moderate or severe ARDS and were admitted to the ICU at Clinical University Hospital Santiago of Compostela from March 21 to April 5. The study protocol was approved by the ethics committee of Galicia (code No. 2020-188), and all participating subjects provided informed consent.

Patients were enrolled if they met the following criteria: ≥18 years of age, ability to self-prone, and moderate or severe ARDS as defined by the WHO (moderate ARDS: 100 mm Hg < arterial oxygen partial pressure (P_{aO_2})/fractional inspired oxygen (F_{IO_2}) ≤ 200 mm Hg; severe ARDS: P_{aO_2}/F_{IO_2} ≤ 100 mm Hg).

Exclusion criteria were inability to collaborate with PP or refusal, unstable hemodynamic status, patients with moderate or severe ARDS needing intubation, and mechanical ventilation. We considered that patients needed intubation when they had signs of respiratory fatigue (respiratory rate >30, partial pressure of carbon dioxide (P_{aCO_2}) > 60 mm Hg, pH < 7.3, and obvious accessory respiratory muscle use), unstable hemodynamic status, lethargy, or unconsciousness.

All patients were monitored with continuous electrocardiogram, oxygen saturation, and invasive arterial blood pressure. All physicians caring for patients wore standard personal protective equipment (filtering face pieces [FFP3] mask, surgical cap, goggles, surgical gown, and double gloves). Patients were instructed to remain in PP until they felt too tired to maintain that position. If the patient needed it, light sedation with dexmedetomidine 0.2–0.8 µg/kg/h was administered. The following information was collected: age; sex; coexisting disorders; Acute Physiology and Chronic Health Evaluation II score (APACHE II); treatments (eg, oxygen therapy, antibiotics, antivirals, corticosteroids); tissue O_2 saturation (S_{tO_2}); and blood gases (P_{aO_2}, P_{aO_2}/F_{IO_2}, P_{aCO_2}) in ICU admission; number and duration of PP sessions; S_{tO_2} and blood gases before, during, and following a PP session; need of mechanical ventilation; duration of ICU admission; and ICU outcome.

Data consisted of several 1–4 prone procedures per patient and several measurements per procedure. Linear mixed-effects models (LMM) were fit to estimate changes from baseline to account for the inherent within-patient correlation across the multiple measurements of the outcome. The outcome variables for the 6 models were P_{aO_2}, P_{aO_2}/F_{IO_2}, and S_{tO_2}. The 2 fixed effects for each outcome were either preprone versus prone status or preprone versus postprone status. We included a random effect for patient. To protect type I error at least within outcome, results were penalized using a Bonferroni correction for having 2 comparisons of interest for each outcome. The baseline significance level was 0.05 for each outcome, and significance criterion (after Bonferroni correction for 2 comparisons per

versions of this article on the journal's website (www.anesthesia-analgesia.org).

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outcome) was 0.05/2 = 0.025. Therefore, the variables reported for the LMM were the change from baseline estimates and 97.5% confidence intervals (CIs). *P* values were obtained from each LMM using the function anova from the stats package in R.

The interpretation of the CI ranges depends on whether the values of the CI, 97.5% crossed zero (nonsignificant) and were both positive (significant increase) or both negative (significant decrease). Descriptive results were presented as median and interquartile range (IQR).

To assess study viability in a setting of high workload during the pandemic peak, sample size was estimated beforehand of the study for a simple, binary outcome of improvement versus nonimprovement in Pao_2/Fio_2. We estimated that 12 pairs of measurements would be needed to detect a 70% minimum increase and a 5% maximum decrease (up to 5% of all patients) in Pao_2/Fio_2 from preprone to PP, of at least 30 mm Hg, with an error α of 5% and an 80% power (2-tailed) using a McNemar χ^2 test. After data collection, the main outcome measure was later modified as the change in Pao_2/Fio_2 from baseline to PP and from baseline to postprone to account for within-patient correlation in a mixed-effects model with random effects.

All analyses were conducted in Rv.3.6 6 (R Core Team, Vienna, Austria) using the longpower (Donohue 2020), lme4 (Bates 2015), lmerTest (Kuznetsova 2020), and dplyr (Wickham 2020) packages.

RESULTS

Seven awake patients with moderate or severe ARDS by COVID-19 were included during the period study. Four were women, and the mean age was 65 years. Patients' characteristics and clinical ICU course of the 7 patients are summarized in Table 1 and Figure.

All patients were treated with lopinavir/ritonavir, hydroxychloroquine, azithromycin, and supportive therapies. Four patients received tocilizumab, and 4 patients received corticosteroids. All patients received at least 1 PP session. A total of 16 awake PP sessions were performed in the 7 patients during the period study (Figure; Supplemental Digital Content, Table S1, http://links.lww.com/AA/D215). The median duration of PP sessions was 10 hours. Sedation with dexmedetomidine (0.2–0.8 µg/kg/h) was used in all patients.

PP improved oxygenation during all 16 sessions performed in the 7 patients (Table 2; Supplemental Digital Content, Table S1, http://links.lww.com/AA/D215). Pao_2/Fio_2 increased during PP (207 [181–226] compared with previous supine position (114 [89–165]). The change from baseline and 97.5% CI was 110 and 19-202, respectively.

Pao_2/Fio_2 also increased after PP (160 [101–204]) compared with previous supine position (114 [89; 165]). The change from baseline (38) and 97.5% CI (−9.2 to 85) was not significant. Similarly, tissue oxygenation underwent a small improvement after PP (change from baseline 2.63% with 97.5% CI, 0.69-4.6) without significant changes in pre-PP versus post-PP (change from baseline 0.59% with 97.5% CI, −1.8 to 3).

Two patients required intubation 2 hours after a PP session due to respiratory fatigue, tachypnea, and accessory respiratory muscle use. After intubation, PP for long periods of time (>16 hours) was used in these 2 patients (Figure). Figure provides representative information of outcomes for individual patients

Table 1. Clinical Characteristics of 7 ICU Patients With Moderate or Severe Distress by COVID-19 Where PP Awake Sessions Were Used

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Characteristics							
Age, y	53	70	49	67	73	77	58
Sex	Female	Male	Male	Female	Female	Male	Female
APACHE II score	12	10	11	19	21	16	10
Pao_2/Fio_2 in ICU admission, mm Hg	73	158	155	110	120	185	167
Pao_2 in ICU admission, mm Hg	65	63	62	55	61	65	53
Sto_2 in ICU admission (%)	93	93	92	90	85	85	84
Chronic medical illness	Hypothyroidism Dyslipidemia	Hypertension Obesity SAOS	Hypertension Obesity	Obesity	No	Hypertension Diabetes	Asthma
Additional therapy							
Tocilizumab	Yes	Yes	Yes	Yes	No	No	No
Glucocorticoids	Yes	Yes	No	No	No	Yes	Yes
Clinical ICU course							
No. of PP sessions	3	4	2	2	1	2	2
Median duration of PP sessions, h	13	6	12	9	12	12	4
Longest duration of PP session	15	9	15	13	12	12	4
Need of mechanical ventilation, d	Yes (8 d)	No	No	No	Yes (6 d)	No	No
Duration of ICU admission, d	13	10	7	6	10	6	4
ICU outcome	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; COVID-19, coronavirus disease 2019; Fio_2, fractional inspired oxygen; ICU, intensive care unit; Pao_2, arterial oxygen partial pressure; PP, prone positioning; SAOS, sleep apnea obstructive syndrome; Sto_2, tissue O_2 saturation.

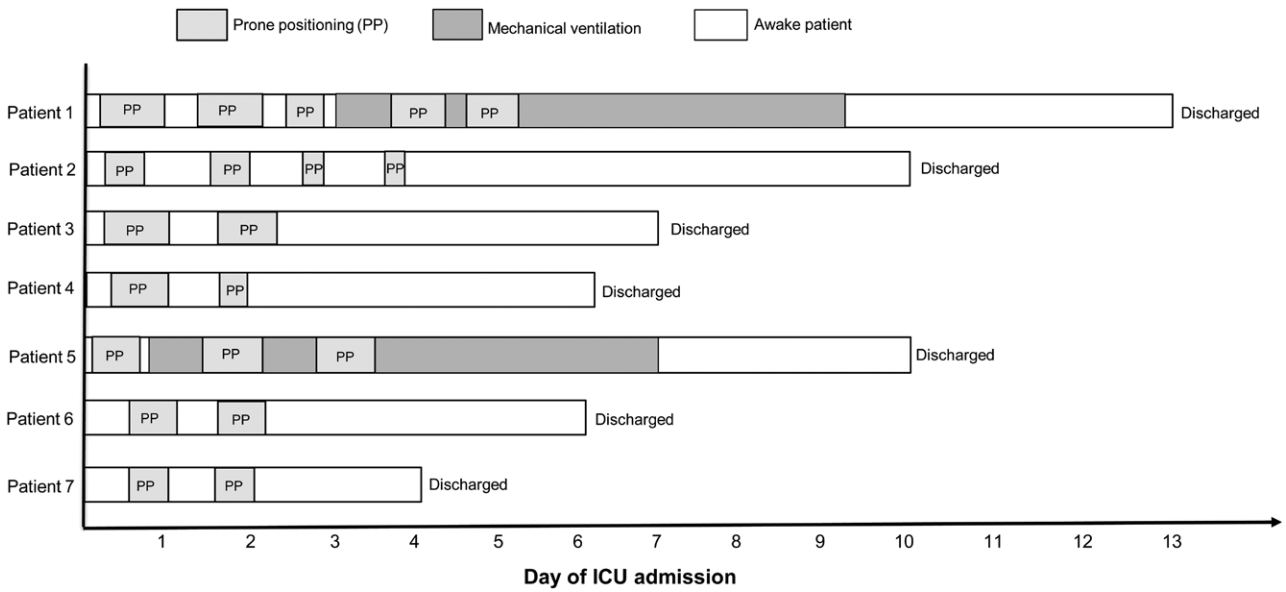

Figure. Outcomes for individual patients included in the case series. ICU indicates intensive care unit; PP, prone positioning.

Table 2. Arterial Blood Gas Analyses During the Different Study Periods

Variable	PRE (n = 16)	PRONE (n = 16)	POST (n = 16)	LMM Change [97.5% CI]	*P*
Sto_2	96 [94–96]	98 [97–99]		2.6 [0.69 to 4.6]	.0045
Sto_2	96 [94–96]		96 [95.3–98]	0.59 [−1.8 to 3]	.6
Pao_2, mm Hg	81 [67–84]	115 [104–185]		68 [19 to 118]	.0049
Pao_2, mm Hg	81 [66–84]		84 [80–92]	7.40 [−3.2 to 18]	.11
Pao_2/Fio_2	114 [89–165]	207 [181–226]		110 [19 to 202]	.0094
Pao_2/Fio_2	114 [89–165]		160 [101–204]	38 [−9.2 to 85]	.08

Data in columns 2–4 presented as median and [interquartile range]. After adjusting for within-patient correlation, the increase in Sto_2 ranged from 1.4% to 3.9%, with a point estimate of 2.6%. LMM change [97.5% CI]: change from baseline after linear mixed-effects modeling with random effects, to account for within-patient correlation. The median Sto_2 was 96% preprone.

Abbreviations: CI, confidence interval; Fio_2, fractional inspired oxygen; LMM, linear mixed-effects model; Pao_2, arterial oxygen partial pressure; POST, postprone positioning; PRE, previous to prone positioning; PRONE, during prone positioning; Sto_2, tissue O_2 saturation.

included in the study. All 7 patients were discharged from the ICU.

DISCUSSION

The WHO recommends the use of prone ventilation for 12–16 h/d in the management of intubated patients with severe ARDS due to COVID-19.[3] PP is an adjunct strategy in patients with ARDS and may improve oxygenation and survival.[4] Potential explications for this improved oxygenation are reduction of ventilation/perfusion mismatch, a more homogeneous distribution of transpulmonary pressure along the ventral-to-dorsal axis in PP compared with supine position, and recruitment of nonaerated dorsal lung regions of the lung.[4–8] In theory, many of the mechanisms that would explain an improvement of oxygenation with PP in intubated patients would also apply to awake patients with ARDS.[9–11] Ding et al[11] observed that early application of PP combined with noninvasive ventilation or high-flow nasal cannula in nonintubated patients with moderate to severe ARDS and Sto_2 >95% may avoid the need for intubation. Similarly, Scaravilli et al[9] observed, in a retrospective study of 15 nonintubated ICU patients with hypoxemic acute respiratory failure, that PP improved oxygenation. The duration of PP in these 2 studies lasted between 2 and 3 hours. In the present investigation, we observed that PP improved oxygenation in awake ICU patients with COVID-19 and moderate to severe ARDS. Patients tolerated long periods of PP (10 hours) relatively well with only light sedation with dexmedetomidine. Such an approach would be particularly useful in COVID-19 due to concern regarding ventilator adequacy.[12] PP in awake ICU patients with ARDS may be a potential strategy to improve oxygenation and allow patients time to recover lung function. Unlike PP in intubated patients with mechanical ventilation, which is complex and requires several operators to perform it safely, the PP in awake ICU patients is easier. The patient may turn themselves prone or with the help of 1 operator. Recently, Sun et al[13] described their experience in managing COVID-19. They also attempted awake PP observing significant effects in improving oxygenation. According to our

experience, we recommend it if the patient has no signs of respiratory fatigue or was not hemodynamically stable.

The present study has some limitations. First, the study was performed in a single center; however, it is easily utilized in other centers. Second, although we observed an improvement in oxygenation during the PP sessions, we were not able to determine the optimal duration and frequency of PP. We assume that similarly to mechanically ventilated patients with severe ARDS from COVID-19 where 12–16 hours of PP are suggested, in an awake patient with moderate or severe ARDS, a longer duration may likewise improve oxygenation. Third, the small sample size does not permit the evaluation of the effect of PP on important clinical outcomes such as intubation or mortality. We hope that our results can contribute meaningful information to clinical teams, to design and conduct further randomized assessment of this intervention, facilitating its routine use if proven beneficial.

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DISCLOSURES

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