Early Prone versus Supine Positioning in Moderate to Severe Coronavirus Disease 2019 Patients with Acute Respiratory Distress Syndrome

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ABSTRACT

Objectives: This study sought to determine whether early prone positioning of patients with moderate to severe COVID-19-related acute respiratory distress syndrome (ARDS) lowers the mortality rate. ***Methods***: We conducted a retrospective study using data from intensive care units of two tertiary centers in Oman. Adult patients with moderate to severe COVID-19-related ARDS with a PaO_2/FiO_2 ratio < 150 on FiO_2 of 60% or more and a positive end-expiratory pressure of at least 8 cm H_2O who were admitted between 1 May 2020 and 31 October 2020 were selected as participants. All patients were intubated and subjected to mechanical ventilation within 48 hours of admission and placed in either prone or supine position. Mortality was measured and compared between the patients from the two groups. ***Results:*** A total of 235 patients were included (120 in the prone group and 115 in the supine group). There were no significant differences in mortality (48.3% vs. 47.8%; $p = 0.938$) and discharge rates (50.8% vs. 51.3%; $p = 0.942$) between the prone and supine groups, respectively. ***Conclusions:*** Early prone positioning of patients with COVID-19-related ARDS does not result in a significant reduction in mortality.

The definition of acute respiratory distress syndrome (ARDS) has evolved since it was first described in 1967. The 2011 Berlin definition takes into consideration the timing of the acute onset, chest imaging, origin of edema, and eliminating the term acute lung injury.[1] ARDS is one of the commonest conditions encountered in intensive care worldwide and accounts for nearly 10–15% of intensive care unit (ICU) admissions.[2–5] It has been associated with a mortality rate of 40% and numerous long-term complications.[6–8] Approximately 40% of patients with COVID-19 pneumonia develop ARDS within 8–10 days following symptom onset.[9–13] Mortality rate of 26% was reported in patients with COVID-19 pneumonia that got admitted to the ICU and required mechanical ventilation ranges.[10,11]

Due to diffuse alveolar damage in COVID-19 patients, hypoxemic respiratory failure develops; however, atypical changes, such as thrombosis and disseminated intravascular coagulation have also been reported.[14–17]

Prone positioning is one of the measures that has been used over the last five decades to improve the outcomes of patients with severe ARDS and refractory hypoxemia.[18–22] In 2013, the PROSEVA study showed that prone positioning improved the survival rate of moderate to severe ARDS patients with a ratio of PaO_2 to FiO_2 of < 150.[23] In addition, several meta-analyses showed favorable outcomes in patients with ARDS who are promptly placed in

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the prone position for a prolonged period.[24–30] The beneficial effects of prone positioning were attributed to improvements in gas exchange, respiratory system compliance, and lung protection.[31] Despite these benefits, studies have demonstrated that prone positioning has not been integrated into routine therapy for most ARDS patients worldwide.[32,33]

Early studies and international societies supported the use of the prone position in COVID-19-related ARDS.[34–37] However, there is insufficient evidence supporting the beneficial effect of prone positioning on moderate to severe ARDS due to COVID-19 infection. Although, most of the time, COVID pneumonia falls under the Berlin definition of ARDS, severe hypoxemia associated with near-normal respiratory system compliance was distinctively observed in COVID pneumonia, which resulted in striking non-uniformity in the course of the disease and response to management.[38] With this in mind, different COVID-19 patterns may be found at presentation that is explained by the development of a time-related disease spectrum within two primary phenotypes. The 'L-type' ARDS is characterized by low lung elasticity, weight, and lung recruitability. Meanwhile, the 'H-type' is characterized by high lung elasticity, intra-pulmonary right-to-left shunting, lung weight, and lung recruitability.[37–39] Earlier in the course of the disease, 'L-type' takes place and may remain unchanging for a period and then improve or worsen to 'H-type'. Therefore, not all COVID-19 patients benefit from higher levels of positive end-expiratory pressure (PEEP) and prone positioning. We conducted a retrospective study with the aim of determining the effect of early prone positioning on oxygenation and ultimately mortality of moderate to severe COVID-19 ARDS patients.

METHODS

This was a retrospective study involving COVID-19-related ARDS patients who were intubated and underwent mechanical ventilation with a PaO_2/FiO_2 ratio of < 150, in the respective ICUs of Khoula Hospital and Sultan Qaboos University Hospital (SQUH) between 1 May and 31 October 2020. Ethical approval was obtained from the Medical Research Ethics Committee at the SQUH (SQU-EC/328/2021) and the Research and Ethical Review and Approval Committee of the Ministry of Health Oman (MoH/CSR/20/24201). Written informed consent was not required and was waived as it was a retrospective study. Ethical approval was obtained from the ethical committees at both hospitals.

The study included patients who were 18 years old or older; had infection with COVID-19 confirmed via polymerase chain reaction within the last 15 days, were intubated and underwent mechanical ventilation in the previous 48 hours, had a PaO_2/FiO_2 ratio < 150 on FiO_2 60% or more, and PEEP of > 8 cm H_2O.

Patients were excluded if they underwent invasive mechanical ventilation for > 48 hours prior to prone positioning, had a PaO_2/FiO_2 ratio of > 150, or were re-intubated.

Categorical variables were summarized using frequencies and percentages, while differences between groups were analyzed using Pearson's χ^2 test (or Fisher's exact test for expected cells < 5). Continuous variables such as age and body mass index (BMI) were presented as means and SDs, and analyses were performed using Student's *t*-test. Continuous but abnormally distributed variables

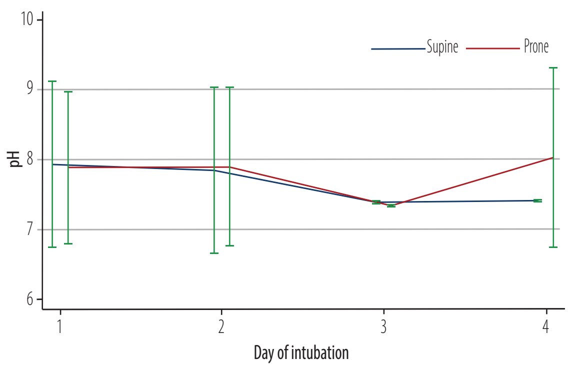

Figure 1: Arterial pH values from day one to day four of intubation, stratified by position (supine or prone) (N = 235).

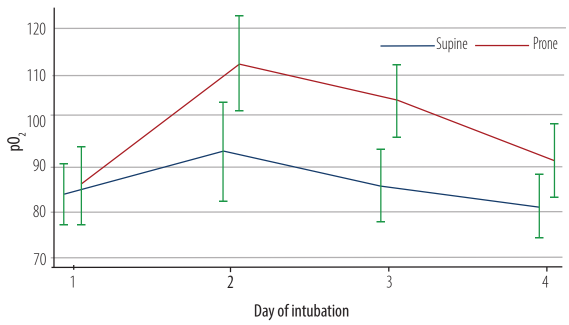

Figure 2: Arterial pO_2 values from day one to day four of intubation, stratified by position (supine or prone) (N = 235).

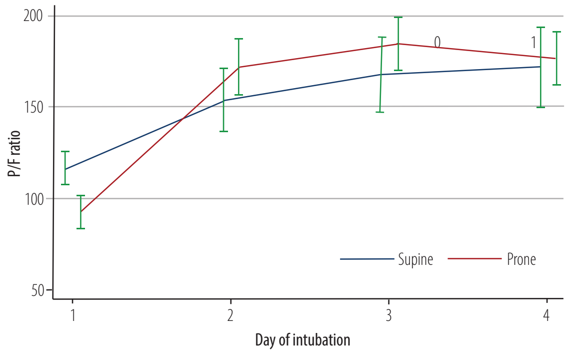

Figure 3: P/F ratio from day one to day four of intubation, stratified by position (supine or prone) (N = 235).

(assessed using the Kolmogorov-Smirnov test) such as APACHE II scores, sequential organ failure assessment (SOFA) scores, and symptoms days were presented as medians and interquartile ranges and analyzed using the Wilcoxon-Mann-Whitney test. Ventilator parameters (pH, pO_2, and P/F ratio [arterial pO_2 divided by the FiO_2]) of the patients throughout their ICU admission (days 1–4 of intubation) between supine and prone sleeping positions, as presented in Figures 1–3, were analyzed using the repeated measures analysis of variance. *P*-values (two-sided) for the differences over time were corrected using the Greenhouse-Geisser correction factor. Statistical analyses were conducted using StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.

RESULTS

A total of 310 patients were admitted to the ICUs during the six-month study. Forty-five patients were transferred to other hospitals and 17 died within 24 hours of ICU admission. A total of 248 patients were analyzed. Among them, 166 were admitted to the ICU at SQUH, and 82 were admitted to the ICU at Khoula hospital.

The demographic and clinical characteristics of the patients are listed in Table 1. The mean age was 56.0±15.0 years, 70.6% (n = 166) were male, and 13.0% (n = 30/230) were current smokers. The overall mean BMI was 31.5±7.5 kg/m^2. The most prevalent comorbidities were diabetes mellitus (55.7%; n = 131), hypertension (45.5%; n = 107), and coronary artery disease (10.6%; n = 25). The most frequent presenting symptoms were fever (81.3%; n = 191), shortness of breath (73.6%; n = 173), and cough (63.0%; n = 148). The median length of symptoms was 5 (3–8) days.

On admission, the median APACHE II and SOFA scores were 20 (13–22) and 5 (3–5), respectively. Higher APACHE II (20 vs. 13; $p < 0.001$) and SOFA (5 vs. 4; $p < 0.001$) scores were observed in patients underwent prone positioning than those who were not in the prone position. Chest radiography findings revealed bilateral lung infiltrates in most patients (91.9%; n = 216) and pulmonary edema in two patients (0.9%). A total of 70.7% (n = 164/232) and 19.0% (44/231) of the patients had vasopressor and renal replacement therapy (RRT), respectively. A quarter (25.0%) of patients who were prone-positioned also required RRT while 12.0% ($p = 0.010$) in the supine position required RRT.

Of the patients prone-positioned, 67.5% received non-invasive ventilation before intubation compared with 22.6% in the supine group. In terms of management, 96.6% (225/233) received steroids, 18.5% (43/232) received anakinra/tocilizumab, 7.4% (17/229) received convalescent plasma, and 4.4% (10/228) received remdesivir. The decision on giving this medical treatment is based on the latest updated protocol at that time, while the ventilator settings are decided by the attending physician at the time of intubation. The parameters get adjusted after repeating arterial blood gas with lung protective measures mentioned in the ARDS protocol in mind. Adjustments could be made by the primary physician, respiratory therapist, or the consultant in charge.

As shown in Table 2, no significant differences in mortality (48.3% vs. 47.8%; $p = 0.938$) and discharge rates (50.8% vs. 51.3%; $p = 0.942$) were observed between the prone and supine groups. However, patients in the prone position were associated with a longer hospital stay (19 vs. 16 days; $p = 0.041$) and more frequent tracheostomies (30.0% vs. 9.6%; $p < 0.001$) than those in the supine group, and these values of better statistical significance that may indirectly show a better outcome for patients kept in the prone position. To clarify, patients usually get tracheostomized after passing the critical stage of the disease and going into the weaning phase of mechanical ventilation, which requires longer hospital stay.

As illustrated in Figure 1, there were no significant differences in the arterial pH values between the prone and supine positions over

Table 1: Demographic and clinical characteristics of patients stratified by groups (supine or prone).

Outcomes	All (N = 235)	Groups		*p*-value
		Supine (n = 115)	Prone (n = 120)	
Demographic				
Age, mean ± SD, years (n = 234)	56.0 ± 15.0	57.0 ± 16.0	55.0 ± 15.0	0.432
Male sex	166 (70.6)	78 (67.8)	88 (73.3)	0.354
BMI, mean ± SD, kg/m^2 (n = 32)	31.5 ± 7.5	34.6 ± 10.0	30.3 ± 6.2	0.145
Current smoker (n = 230)	30 (13.0)	11 (9.6)	19 (15.8)	0.130
Clinical				
Hypertension	107 (45.5)	57 (49.6)	50 (41.7)	0.224
Diabetes mellitus	131 (55.7)	68 (59.1)	63 (52.5)	0.306
Coronary artery disease	25 (10.6)	8 (7.0)	17 (14.2)	0.073
Chronic kidney disease	19 (8.1)	7 (6.1)	12 (10.0)	0.271
Chronic lung disease	11 (4.7)	7 (6.1)	4 (3.3)	0.368
Malignancy	7 (3.0)	2 (1.7)	5 (4.2)	0.447
Symptoms at presentation				
Fever	191 (81.3)	87 (75.7)	104 (86.7)	0.030
Cough	148 (63.0)	71 (61.7)	77 (64.2)	0.700
Shortness of breath	173 (73.6)	78 (67.8)	95 (79.2)	0.049
Chest pain	17 (7.2)	10 (8.7)	7 (5.8)	0.397
Abdominal symptoms	40 (17.0)	33 (28.7)	7 (5.8)	< 0.001
Neurological symptoms	28 (11.9)	16 (13.9)	12 (10.0)	0.355
Trauma	2 (0.9)	1 (0.9)	1 (0.8)	0.976
Severity scores on admission, median (IQR)				
APACHE II scores	20 (13–22)	13 (9–20)	20 (18–22)	< 0.001
SOFA scores (n = 234)	5 (3–5)	4 (3–5)	5 (4.5–5)	< 0.001
Symptoms, days (n = 227)	5 (3–8)	5 (3–7)	5 (3–8)	0.495
Chest radiography findings (n = 231)				
Focal consolidation	13 (5.5)	11 (9.6)	2 (1.7)	0.007
Bilateral lung infiltrates	216 (91.9)	99 (86.1)	117 (987.5)	0.002
Pulmonary edema	2 (0.9)	2 (1.7)	0 (0.0)	0.234
Vasopressors (n = 232)	164 (70.7)	81 (70.4)	83 (69.2)	0.905
Renal replacement therapy	44 (19.0)	14 (12.2)	30 (25.0)	0.010
NIV before intubation	107 (45.5)	26 (22.6)	81 (67.5)	< 0.001
Laboratory investigations, mean ± SD, years				
CRP, mg/L (n = 234)	156.0 ± 108.0	167.0 ± 111.0	146.0 ± 105.0	0.137
D-dimer, ng/mL (n = 231)	7.0 ± 15.0	7.4 ± 15.0	6.7 ± 15.0	0.713
Ferritin, ng/mL (n = 232)	2643.0 ± 6806.0	2390.0 ± 6033.0	2889.0 ± 7496.0	0.578
LDH (n = 228)	620.0 ± 401.0	647.0 ± 277.0	594.0 ± 489.0	0.323
IL-6, pg/mL (n = 150)	283.0 ± 651.0	446.0 ± 903.0	141.0 ± 207.0	0.004
Management				
Steroids (n = 233)	225 (96.6)	111 (96.5)	114 (95.0)	0.970
Antivirals (remdesivir) (n = 228)	10 (4.4)	6 (5.2)	4 (3.3)	0.748
IL (anakinra/tocilizumab) (n = 232)	43 (18.5)	19 (16.5)	24 (20.0)	0.472
Convalescent plasma (n = 229)	17 (7.4)	8 (7.0)	9 (7.5)	0.815

BMI: body mass index; SOFS: sequential organ failure assessment; IQR: interquartile range; NIV: non-invasive ventilation; CRP: C-reactive protein; LDH, lactate dehydrogenase; IL: interleukin.
Data were given as n (%) unless specified otherwise.

time (days 1–4 of intubation). Figure 2 indicates the significant interaction in pO_2 values between the sleeping position and duration of intubation ($p = 0.041$). While the values were similar on day one, the pO_2 values thereafter (days 2–4) were significantly higher in patients in the prone position

Table 2: Outcome characteristics stratified by groups (supine or prone).

Outcomes	All (N = 235)	Groups		*p*-value
		Supine (n = 115)	Prone (n = 120)	
Primary				
Mortality	113 (48.1)	55 (47.8)	58 (48.3)	0.938
Discharged	120 (51.1)	59 (51.3)	61 (50.8)	0.942
Discharged to inpatient	2 (0.9)	1 (0.9)	1 (0.8)	1.000
Secondary				
LOS, median (IQR), days	17 (11–30)	16 (10–26)	19 (12–34)	0.041
ICU LOS, median (IQR), days	10 (6–20)	11 (7–20)	9 (4–20)	0.257
Tracheostomy	47 (20.0)	11 (9.6)	36 (30.0)	< 0.001

ICU: intensive care unit; LOS: length of hospital; IQR: interquartile range.
ICU and hospital LOS were missing on one (234/235) and two (233/235) occasions, respectively.
Data were given as n (%) unless specified otherwise.

than in those in the supine position ($p < 0.001$). Furthermore, as shown in Figure 3, there was also a significant interaction between the position and the duration of intubation ($p < 0.001$). Patients in the prone position had a significantly lower PaO_2/FiO_2 ratio on day 1. However, their PaO_2/FiO_2 values surpassed those of patients in the supine position on days 2 and 3 ($p < 0.001$). The PaO_2/FiO_2 values of both groups were reduced to similar values on day 4.

With these *p*-values in mind, it is safe to say that prone position led to better oxygenation in early stages of the prone position with great statistical significance. Data were collected for four days, but the duration of prone position might extend to 8–12 days depending on many factors, including responsiveness to the prone position and hemodynamics. On the other hand, the data collected do not necessary correspond to four consecutive days.

DISCUSSION

In this retrospective analysis, there was a significant improvement in oxygenation of the prone group, compared to the supine group. This finding supported the hypothesis that prone positioning improved ventilation-perfusion mismatch in ARDS patients.[40,41] However, this did not improve the mortality rate. The mortality was 48.0% in both groups with poor statistical significance and the results are contrasting with what has been reported in non-COVID patients.

Previous studies in non-COVID-19 patients have reported the benefits of early prone positioning in ICU patients with a pO_2/FiO_2 ratio < 150, despite lung-protective ventilation and adequate PEEP.[23] A recent meta-analysis showed that the PaO_2/FiO_2 ratio and oxygen saturation of COVID-19 patients improved with prone positioning, which resemble our findings.[42] Another meta-analysis demonstrated that awake and non-intubated patients that underwent prone positioning had improved respiratory and intubation rates, compared to patients in the supine position.[43]

There were some limitations to our study. First, the sample size was small. Second, this was a retrospective study; therefore, selection bias may be present. Third, prone positioning was performed mainly in one hospital, while supine positioning was conducted primarily in the other hospital. Although the disease severity, degree of ARDS, and the number of involved organs were specified, other significantly different variables such as nurse-patient ratio, availability of consultant services and experience of prone positioning between the two hospitals may have been present. Fourth, lung-protective ventilation was applied according to the ideal body weight, and BMI was not recorded in all patients. Therefore, the results of this study may not be generalizable to other hospitals and other countries.

Further studies are required to compare the effects of early prone and supine positioning on moderate to severe ARDS in intubated COVID-19 pneumonia patients.

CONCLUSION

The findings of this retrospective study show that early prone position in COVID-19-related ARDS does not result in significant mortality benefit compared to the supine position. More research and randomized clinical trials are required in this regard.

Disclosure

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