Short communication

# Predictive factors for success of awake proning in hypoxemic respiratory failure secondary to COVID-19: A retrospective cohort study

Sujith V. Cherian [a,*], Chang Li [b], Brad Roche [b], Stephan A. Reyes [b], Siddharth Karanth [a], Aditya P. Lal [b], Gabriel M. Aisenberg [b], Rosa M. Estrada-Y- Martin [a]

[a] Department of Internal Medicine, Divisions of Critical Care, Pulmonary and Sleep Medicine, University of Texas Health Science Center at Houston, McGovern Medical School, TX, 77030, USA
[b] Department of Internal Medicine, University of Texas Health Science Center at Houston, McGovern Medical School, TX, 77030, USA

## ARTICLE INFO

## ABSTRACT

*Background:* Awake prone positioning has been recommended as an adjunctive measure in spontaneously breathing patients with hypoxemic respiratory failure during the COVID-19 pandemic. It remains uncertain as to how long this should be implemented, what variables to follow and who would be the ideal candidates for this adjunctive therapy.

*Methods:* A retrospective chart review of patients admitted from April to August 2020 within our institution with multifocal pneumonia and hypoxemic respiratory failure secondary to COVID-19 who underwent awake-proning for at least 3 hours was conducted.

*Results:* Improvement in respiratory parameters including ROX (SpO2/Fio2/ Respiratory Rate) indices and inflammatory markers within 4 days of institution of awake proning predicted a higher chance for success of this strategy in preventing need for mechanical ventilation. Moreover, benefits of awake proning were limited to patients with mild to moderate ARDS.

*Conclusions:* Awake prone positioning can be safely performed with improvement in oxygenation. However, its institution may be beneficial only in patients with mild to moderate ARDS and requires careful evaluation of respiratory parameters and serum inflammatory markers to avoid a delay in endotracheal intubation and consequent increase in mortality rates.

*To the Editor*

The COVID -19 pandemic has affected (at the time of writing) at least 190 countries worldwide, with more than 1.2 million deaths recorded. A significant proportion of patients are admitted with severe acute respiratory distress syndrome (ARDS), thus imposing a heavy burden on health care with a resultant shortage in ventilator supply. Awake-proning has been recommended as a tool to improve oxygenation in these patients, with multiple case series and observational studies attesting to these findings [1–4]. It remains unclear as to how long this should be implemented, what variables to follow, and whether it does prevent patients from needing invasive mechanical ventilation [5]. We describe the use of awake-prone positioning in a cohort of non-intubated patients with COVID-19 and their clinical outcomes. Moreover, we sought to identify differences between patients who ultimately required mechanical ventilation and those who did not within this cohort.

## 1. Methods

The study was conducted at the Lyndon Baines Johnson Hospital, Houston, Texas, which included all patients with hypoxemic respiratory failure secondary to COVID-19 who had been admitted to the intensive care units or intermediate care units and underwent awake-proning for 3 h or more in a day. Hypoxemic respiratory failure was defined as oxygen saturations less than 88% while on room air and needing supplemental oxygen, high flow oxygen nasal cannula, or non-invasive positive pressure ventilation. A confirmed case of COVID-19 was defined by a positive result on reverse-transcriptase-polymerase chain reaction assay on a nasopharyngeal swab. All patients had bilateral

alveolar multi-focal ground glass opacities on chest imaging, and were on antibiotics for community acquired pneumonia. Patients were asked to prone as soon as they were requiring high flow oxygen therapy (started when oxygen desaturations noted on supplemental oxygen with nasal prongs up to 6L/min) and for as long as tolerated, but only included within the study, if they could prone for at least 3 h in a day. Given the difficulty involved with staying prone for long sessions without sedation and benefits seen within 75 min of proning, duration of at least 3 h for the study was chosen.

This retrospective study was approved by the local institutional review board (HSC-MS-20-0794). The following variables were collected including respiratory rate, oxygen saturation/inhaled oxygen (SpO2/Fio2), ROX index ( SpO2/Fio2/ Respiratory Rate ), vital signs including blood pressure, respiratory rate and heart rate, inflammatory markers including white blood counts, C-reactive protein levels (CRP), d-dimer levels, lactate dehydrogenase (LDH) levels, and ferritin.

All patients with acute hypoxemic respiratory failure secondary to COVID-19 from April 15 to August 15, 2020, were screened in the study. Patient data were analyzed descriptively using median for continuous variables and proportions for categorical variables. The difference in characteristics among patients between those who needed mechanical ventilation and those who did not were tested using *t*-test or Wilcoxon rank-sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Multivariable logistic regression analysis was used to assess the association of study variables on endotracheal intubation by adjusting for age and hypoxemia (SpO2/FiO2 ratio at proning). All analyses were performed using Stata 15 and tests were considered significant at a P-value < 0.05.

## 2. Results

From among 64 patients who underwent awake-proning during this period, 59 patients were eventually included, as the other 5 patients could not perform awake-proning for at least 3-h/day. There were no complications related to awake proning. Table 1 demonstrates the differences in characteristics between the subgroups undergoing awake-proning who did need invasive mechanical ventilation (Group A) and did not (Group B). Thirty-six patients (61%) did not require mechanical ventilation. The decision to intubate was based on worsening hypoxemia and increased work of breathing. Underlying comorbidities such as diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, and obesity were not significantly different between both groups. High flow nasal cannula was used in the majority of patients in both groups, with a higher proportion of patients (14/23, 61%; P < 0.01) needing non-invasive positive pressure ventilation (NIPPV) due to worsening hypoxemia in Group A. The median SpO2/Fio2 ratio in Group A at initiation was lower in Group A compared to Group B (100 vs 206; P < 0.01). Although the SpO2/Fio2 ratio decreased in Day 1 and 2 to 150–160 in Group B, it subsequently improved by Day 4–207 in Group B, while it did not improve in Group A and stayed at 97 (P < 0.01). Moreover, the ROX index was higher post proning in Group B, which was statistically significant when corrected for age and degree of hypoxemia (P = 0.01). The median number of days both groups underwent awake-proning was 10 days. Within inflammatory markers, CRP levels and ferritin were high in both groups which improved by day 4; however CRP levels showed a more than 50% decrease in Group B as compared to Group A. Moreover, median LDH level was lower in Group B [532 IU (IQR: 470–682) vs 405 I.U (IQR: 341–567); P = 0.01] and decreased at day 4, which was statistically significant when compared to Group A [551 IU, (IQR: 432–601) vs 359 I.U (IQR: 307–452); P = 0.01]. D-dimer levels, although similar initially between Group A and B, stayed low by day 4 in Group B, unlike group A where it increased; which was statistically significant from Group A [4.41(IQR 1.97–10.2) vs 1.37 (IQR: 0.70–2.70); P < 0.01]. Among patients who needed to be on mechanical ventilation, mortality was high (83%).

**Table 1**
Demographic and clinical characteristics between subgroup needing (Group A) and not needing mechanical ventilation (Group B).

| Demographics | Group A (23patients) | Group B (36 patients) | P-value | P-value adjusted for age and SpO2/Fio2 at the time of proning |
|---|---|---|---|---|
| Age, median, range | 60 (52–67) | 51 (41–63) | **0.02** | |
| Gender        Male | 27.1 | 38.9 | | |
| %        Female | 11.9 | 22.1 | | |
| **Comorbidities** | | | | |
| Diabetes mellitus | 10 | 14 | 0.73 | 0.68 |
| Hypertension | 9 | 14 | 0.99 | 0.66 |
| CAD | 2 | 1 | 0.55 | 0.53 |
| Heart failure | 0 | 3 | 0.27 | |
| **BMI** | | | | |
| BMI < 30 | 8 | 14 | 0.75 | |
| BMI> 30 | 15 | 22 | 0.75 | |
| BMI: 30–34.9 | 3 | 11 | 0.21 | 0.69 |
| BMI: 35–39.9 | 6 | 4 | 0.17 | 0.10 |
| BMI: 40 and above | 6 | 7 | 0. 75 | 0.17 |
| **Medications** | | | | |
| Dexamethasone | 18 | 16 | **0.01** | **<0.01** |
| Convalescent plasma | 9 | 11 | 0.50 | 0.91 |
| Remdesivir | 19 | 18 | **0.01** | **<0.01** |
| **Respiratory support** | | | | |
| HFNC, n (%) | 21(91) | 31(86) | 0.69 | 0.95 |
| NIPPV, n (%) | 14(61) | 6(16.6) | <0.01 | **<0.01** |
| **SpO2/Fio2, median (range)** | | | | |
| At proning | 100 (95–155) | 206 (100–293) | <0.01 | |
| Four hrs post proning | 99(94–141) | 195 (100–263) | <0.01 | **0.04** |
| Day 1 | 99 (95–118) | 152(116–230) | <0.01 | **0.02** |
| Day 2 | 104(96–123) | 158(107–224) | <0.01 | **0.02** |
| Day 3 | 101(93–139) | 189(113–224) | <0.01 | **<0.01** |
| Day 4 | 97(95–100) | 211(158–267) | <0.01 | **<0.01** |
| **Respiratory rate (breaths/minute), median (range)** | | | | |
| At proning | 28 (24–35) | 25(21–31) | 0.14 | 0.08 |
| 4 h post proning | 28 (22–34) | 22(19–28) | **0.02** | **0.04** |
| **ROX index** | | | | |
| At proning | 4.00 (3.00–6.00) | 8.00 (4.00–10.00) | **<0.01** | 0.21 |
| 4 h post proning | 4.00 (3.00–6.00) | 8.00 (4.00–13.00) | <0.01 | **0.01** |
| **Serum inflammatory markers, median (range)** | | | | |
| LDH day 0, U/L | 532 (470–682) | 405(341–567) | **0.01** | |
| LDH day 4 | 551 (432–601) | 359 (307–422) | <0.01 | |
| CRP day 0,mg/dl | 20.9 (13.4–24.5) | 23.25 (14.25–39.10) | 0.15 | |
| CRP day 4 | 12.90 (8.65–22.4) | 8.1 (5.1–13.00) | **0.02** | |
| D dimer day 0, µg/ml | 1.72 (0.96–3.05) | 1.23 (0.72–1.64) | 0.06 | |
| D dimer day 4 | 4.41 (1.97–10.20) | 1.36 (0.70–2.53) | <0.01 | |
| Ferritin day 0, ng/ml | 639 (444–1068) | 712 (365–1106) | 0.96 | |
| Ferritin day 4 | 450 (347–1112) | 511 (328–1066) | 0.81 | |

Median (25th- 75th percentiles).
**LDH**: Lactate dehydrogenase; **CRP**: C-reactive protein; **HFNC**: High flow nasal cannula; **NIPPV**: Non-invasive positive pressure ventilation.
SpO2/Fio2 of 235 corresponds to PaO2/Fio2 of 200.
SpO2/Fio2 = 64 + 0.84 xPaO2/Fio2.
ROX index: SpO2/Fio2/Respiratory Rate X100.

## 3. Discussion

Our study corroborates the findings of other studies that awake-proning was clinically feasible and institution of mechanical ventilation was averted in 61% of patients irrespective of underlying comorbidities [2–4,6]. Moreover, our study suggests that adjusted for age and degree of hypoxemia; higher SpO2/Fio2 at the outset, higher ROX index [9], improvement in SpO2/Fio2 ratios and inflammatory markers within 4 days of the institution of proning may help identify patients who may succeed with awake proning without needing invasive mechanical ventilation.

Although proning in mechanically ventilated patients in ARDS has been associated with mortality benefit [7]- its role in spontaneously breathing patients in improving mortality is unclear. Other concerns include delay in endotracheal intubation with associated higher mortality [5,8,10], which patients would benefit the most, and what markers may help the clinician to decide on earlier intubation [5]. Within our study, we found that that ROX indices, persistent improvement in SpO2/Fio2 ratios within day 4 of proning; along with improvement in d-dimer and LDH (possibly due to the improvement of work of breathing and hence avoiding patient self-inflicted lung injury) should be the criteria to decide when to terminate awake proning. Furthermore, benefit may be limited to patients with mild to moderate ARDS at the outset, similar to other studies using HFNC [9].

The study has several limitations, including its retrospective design, the limited number of patients, lack of a comparator arm, and single-center implementation.

In conclusion, awake prone positioning can be safely performed and improves oxygenation. Following inflammatory markers and assessment of work of breathing along with ROX index could be valuable tools to predict failure of awake-proning within the first 4 days of institution; thus avoiding delays in endotracheal intubation in ARDS secondary to COVID-19. Thus our study has important clinical implications, and these findings should be further validated in prospective randomized trials, several of which are currently ongoing (NCT 04402879, NCT 04383613, NCT 04350723). Moreover, the role of awake-proning in patients with less severe ARDS should be tested in randomized controlled trials.

## CRediT authorship contribution statement

**Sujith V. Cherian:** Data curation, Formal analysis, Writing – original draft, Collected the data, Analyzsed the data and built the first draft, Directly involved with patient care and helped prepare the manuscript. **Chang Li:** Data curation, Collected the data. **Brad Roche:** Data curation, Collected the data. **Stephan A. Reyes:** Data curation, Collected the data. **Siddharth Karanth:** Formal analysis, Writing – original draft, Analyzsed the data and built the first draft. **Aditya P. Lal:** Directly involved with patient care and helped prepare the manuscript. **Gabriel M. Aisenberg:** Formal analysis, Writing – original draft, Analyzsed the data and built the first draft, Directly involved with patient care and helped prepare the manuscript. **Rosa M. Estrada-Y- Martin:** Directly involved with patient care and helped prepare the manuscript.

## Declaration of competing interest

The authors have no financial disclosures to declare and no conflicts of interest to report.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2021.106379.

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