Effect of proning in patients with COVID-19 acute hypoxemic respiratory failure receiving noninvasive oxygen therapy

PB Sryma1, Saurabh Mittal1, Anant Mohan1, Karan Madan1, Pawan Tiwari1, Sushma Bhatnagar2, Anjan Trikha1, Ravi Dosi2, Shweta Bhopale2, Renjith Viswanath3, Vijay Hadda1, Randeep Guleria1, Bhuya Baldua1

1Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences, New Delhi, India, 2Department of Onco-Anaesthesia and Palliative Medicine, All India Institute of Medical Sciences, New Delhi, India, 3Department of Anesthesiology and Pain Medicine, All India Institute of Medical Sciences, New Delhi, India, 4Department of Pulmonary Medicine, Motherhood Hospital, Indore, Madhya Pradesh, India

ABSTRACT

Background: Novel coronavirus (SARS-CoV-2) infection is associated with hypoxemic respiratory failure. Mechanical ventilation (MV) is reported to have high mortality in SARS-CoV-2 acute respiratory distress syndrome. We aimed to investigate whether awake prone positioning (PP) can improve oxygenation and prevent intubation when employed early.

Methods: This prospective interventional study included proven coronavirus disease 2019 (COVID-19) patients with room air saturation 93% or less. The primary outcome was the rate of intubation between the two groups. The secondary outcomes included ROX index (SpO2/FiO2%/respiratory rate, breaths/min) at 30 min following the intervention, ROX index at 12 h, time to recovery of hypoxemia, and mortality.

Results: A total of 45 subjects were included (30 cases and 15 controls) with a mean (standard deviation [SD]) age of 53.1 (11.0) years. The age, comorbidities, and baseline ROX index were similar between the two groups. The median duration of PP achieved was 7.5 h on the 1st day. The need for MV was higher in the control group (5/15; 33.3%) versus prone group (2/30; 6.7%). At 30 min, there was a statistically significant improvement in the mean (SD) ROX index of cases compared with that of the controls (10.7 [3.8] vs. 6.7 [2.6], \( P < 0.001 \)). No significant adverse effects related to intervention were noted.

Conclusion: Awake PP is associated with significant improvement in oxygenation and may reduce the need for MV in subjects with COVID-19.

KEY WORDS: Awake proning, COVID-19, prone positioning, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has resulted in a significant number of critically ill patients requiring intensive unit care admissions. A systematic review of intensive care unit mortality of COVID-19 reported mortality of 31.1%–79.0% among patients on invasive mechanical ventilation (MV).[1] Among intubated patients...
with severe acute respiratory distress syndrome (ARDS), prolonged prone positioning (PP) for at least 12–16 h/day, is associated with significant improvement in oxygenation and mortality.[2] During this pandemic, there is a pressing need to conserve essential resources, and awake PP may be useful to improve oxygenation and reduce the need for MV.[3] There is emerging data on the same, but most studies lack a control group to provide information about the definite utility of this intervention. This study aimed to determine whether the early use of PP combined with noninvasive modalities of oxygen therapy can improve oxygenation and avoid the need for intubation in patients with hypoxemic respiratory failure due to COVID-19.

**METHODS**

This prospective, interventional study was conducted in Delhi, India, after obtaining approval from the institutional ethics board (IEC-308/27.04.2020, AA-4/08.05.2020). Subjects with nasopharyngeal swab RT-PCR-confirmed COVID-19, having room air pulse oxygen saturation (SpO₂) <94%, were included in the study. We excluded subjects with hypercapnic respiratory failure, hemodynamic instability, altered sensorium; those requiring immediate tracheal intubation; those with duration of hypoxia or hospitalization for more than 12 h; those with obesity with body mass index (BMI) >30 kg/m²; those with PaO₂/FiO₂ <100 on noninvasive ventilation (NIV)/high-flow nasal cannula (HFNC); and having an intolerance to PP. All consecutive subjects admitted with hypoxemic respiratory failure were screened. The treating team decided the mode of oxygen delivery among conventional oxygen therapy, NIV, or HFNC as per the availability. Subjects who did not allow for PP underwent standard treatment and were included as controls for study purpose. Baseline variables, including age, comorbidities, radiological involvement, symptom duration, and severity of illness, were recorded. The severity of pneumonia was assessed by chest X-ray severity scoring.[4] On chest X-ray, divided into three zones in each lung, a severity score was assigned based on the presence or absence of opacity in each zone (maximum score 6, minimum 0).

The protocol followed for proning has been previously published.[3] Patients undergoing PP were assisted in changing positions. Proning was made comfortable by the use of multiple pillows over pressure points to avoid pain. Prone position was maintained for a minimum of 2 h per session and with a target duration of 8 h/day. A reverse Trendelenburg position of the bed was used to help increase comfort. The PP was stopped if there were patient intolerance, worsening of hypoxia, or the patient has recovered from respiratory failure. In case of any worsening hypoxia with respiratory distress, technical problems were checked and corrected, and prone position was withdrawn. Any respiratory distress with increased work of breathing was monitored, and MV was employed as per the discretion of the treating team. There was no protocolized transition to other noninvasive methods of oxygen delivery so as to avoid any delay in instituting MV. Recovery was defined as sustained improvement in oxygenation defined as more than 93% saturation in room air for at least 2 h following supination. Patients were followed up until hospital discharge or death.

The primary outcome was the rate of intubation between the two groups. The secondary outcomes included ROX index at 30 min from the start of the intervention, ROX index at 12 h, days to the recovery of hypoxia (defined as room air SpO₂ >93%), and mortality.

**RESULTS**

Among 78 subjects with COVID-19-related hypoxemic respiratory failure, 45 were enrolled following the inclusion and exclusion criteria. Among the 45 subjects included in the study, 30 patients received PP, while 15 were in the control group [Figure 1]. The mean (SD) age was 53.1 (11.0) years, with the majority being males. Age, comorbidities, and radiological severity were similar between the two groups [Table 1]. Medical management of both the groups included hydroxychloroquine (83% in cases and 73% in controls, P = 0.45) and corticosteroids (methylprednisolone 40 mg twice daily, 86.7% of both cases and controls) for 5 days. Baseline oxygenation, as measured by the ROX index, was similar in both the groups. The median duration of PP on the 1st day was 7.5 h (range, 4–12 h). The need for MV was higher in the control group (5/15; 33.3%) versus prone group (2/30; 6.7%). At 30 min from the initiation of proning, there was a statistically significant difference in the ROX index between cases and controls (10.7 ± 3.8 in cases vs. 6.7 ± 2.6 in controls, P < 0.001). At 12 h, both respiratory rate per minute (23.8 ± 3.4 among cases vs. 27.5 ± 4.6 among controls, P = 0.004) and ROX index (12.4 ± 4.5 among cases vs. 6.4 ± 3.0 among controls, P < 0.001) were significantly different between the two groups. The time to resolution of hypoxia as well as the mortality rate was not different. Adverse events associated with proning were mild and included backache (6.6%)...
and bloating sensation (6.6%). There were no episodes of desaturation or hemodynamic worsening. Among cases, the ROX index improved statistically significantly from 8.5 ± 2.3 at baseline to 10.7 ± 3.8 at 30 min (P < 0.001). There was also an improvement in heart rate, respiratory rate, and saturation at 30 min and 12 h [Table 2].

**DISCUSSION**

In this study of COVID-19 patients with hypoxic respiratory failure, there was a lower rate of need for MV as well as a significant improvement in the oxygenation parameters with awake PP as compared to that of the control group.
Proning in COVID-19 hypoxemic respiratory failure has been shown to result in improved oxygenation in multiple small studies.\[^{[7-11]}\] PP can improve oxygenation by multiple mechanisms, resulting in improved ventilation-perfusion matching. Most studies have demonstrated an improvement in PaO\(_2\)/FiO\(_2\) ratio and the respiratory rate among patients who tolerated a session of PP. The prone sessions reported in these studies were short, partly because of limited patient tolerance. The effects were transient, and respiratory rates and oxygenation parameters often returned to baseline after supination.\[^{[9]}\] Most of these studies were limited by their retrospective design and lacked a control group. Our study stands apart as we included a comparison group, though in a nonrandomized fashion. We were able to achieve a longer duration of PP, with a median of 7 h/day.

The ROX index was used as it reflects an objective measure of work of breathing. ROX index was validated for identifying patients requiring intubation in hypoxic respiratory failure treated with HFNC.\[^{[12]}\] ROX at 4 h of starting noninvasive oxygen therapy ≥5.37 was significantly associated with a lower risk for intubation in COVID-19 hypoxic respiratory failure in intensive care admitted patients from a retrospective single-center study.\[^{[13]}\]

Caution against early intubation has been raised in COVID-19 ARDS, and assessment of work of breathing is an essential determinant of the same.\[^{[14]}\] We included patients early during the respiratory failure as this subgroup of patients are likely to benefit most from PP. Due to the limited sample size, we cannot conclude on the minimum duration of proning, which may be beneficial for crucial clinical outcomes. We also did not find any harm associated with the intervention in terms of mortality or recovery of hypoxia. The reported mortality rate in another prospective study of awake proning in COVID-19 was 43.5%, which may be beneficial for crucial clinical outcomes. We also did not find any harm associated with the intervention in terms of mortality or recovery of hypoxia. The reported mortality rate in another prospective study of awake proning in COVID-19 was 43.5% in the prone position group, compared with 28 (75.7%) COVID-19 patients in the nonprone position group.\[^{[13]}\]

There are several limitations to our study. It was a nonrandomized study and is subjected to bias. The tolerance of patients to PP was not measured as we excluded patients, not tolerating PP. We did not perform regular ABG, which is considered best to assess oxygenation and used noninvasive surrogates. All patients included were hemodynamically stable and had a similar baseline oxygenation index (ROX), which suggests homogeneity between cases and controls with respect to the severity of hypoxia. The mean ROX index in our study was 8.1, which suggests a milder form of hypoxic respiratory failure in the included population. Computed tomography depiction of lung involvement has been used in some studies to predict the underlying physiology and determine the utility of PP; however, this was not done in our study due to feasibility issues.\[^{[15,16]}\]

### CONCLUSION

We conclude that awake PP, when employed early, for patients with COVID-19-associated hypoxic respiratory failure, improves oxygenation, and may obviate the need for MV. Further randomized controlled trials are needed to assess its effect on mortality, although it may be difficult to perform in such a pandemic situation.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

### REFERENCES

1. Quah P, Li A, Phua J. Mortality rates of patients with COVID-19 in the intensive care unit: A systematic review of the emerging literature. Crit Care 2020;24:285.
2. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, et al. Prone position for acute respiratory distress syndrome: A systematic review and meta-analysis. Ann Am Thorac Soc 2017;14:5280-8.
3. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: Experience from Jiangsu Province. Ann Intensive Care 2020;10:33.
4. Toussie D, Voutsinas N, Finkelstein M, Cedillo MA, Manna S, Maron SZ, et al. Clinical and chest radiography features determine patient outcomes in young and middle age adults with COVID-19. Radiology 2020;29:201754.
5. Sryma PB, Mittal S, Madan K, Mohan A, Hadda V, Tiwari P, et al. Reinventing the wheel in ARDS: Awake proning in COVID-19. Arch Bronconeumol 2020;56:747-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7312953/. [Last accessed on 2020 Jul 22].
6. Hill NS, Rutnazer R. Predicting outcomes of high-flow nasal cannula for acute respiratory distress syndrome: An index that ROX. Am J Respir Crit Care Med 2019;199:1300-2.
7. Despres C, Brunin Y, Berthier F, Pili-Floury S, Besch G. Prone positioning combined with high-flow nasal or conventional oxygen therapy in severe Covid-19 patients. Critical Care 2020;24:256.
8. Coppel A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): A prospective cohort study. Lancet Respir Med 2020;8:765-74.
9. Elharrar X, Trigui Y, Dols A-M, Touchon F, Martinez S, Prud’homme E, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxic acute respiratory failure. JAMA 2020;323:2336-8. Available from: https://jamanetwork.com/journals/jama/fullarticle/2766292. [Last accessed on 2020 May 22].

---

**Table 2: Baseline, 30 min, and 12 h postintervention parameters among cases (n=30)**

| Parameter                          | Baseline | 30 min postprone | 12 h postprone |
|------------------------------------|----------|-----------------|---------------|
| Heart rate (beats/min), mean±SD    | 105.9±11.6 | 102±12.3         | 92.8±11.7     |
| Respiratory rate (breaths/min), mean±SD | 28.9±3.6 | 27.1±3.4        | 23.8±3.4     |
| Pulse oxygen saturation (%)        | 92.4 (2.8) | 94.8 (1.7)      | 95.3 (2.3)    |
| ROX index                          | 8.5 (2.3) | 10.7 (3.8)      | 12.4 (4.5)    |

*Compared to baseline. SD: Standard deviation, SpO\(_2\): Oxygen saturation
10. Sartini C, Tresoldi M, Scarpellini P, Tettamanti A, Carcò F, Landoni G, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA 2020;323:2338-40. Available from: https://jamanetwork.com/journals/jama/fullarticle/2766291. [Last accessed on 2020 May 22].

11. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: A single ED’s experience during the COVID-19 pandemic. Acad Emerg Med 2020;27:375-8. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/acem.13994. [Last accessed on 2020 Apr 30].

12. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med 2019;199:1368-76.

13. Zucman N, Mullaert J, Roux D, Roca O, Ricard JD, Contributors. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. Intensive Care Med 2020;46:1924-6.

14. Tobin MJ, Laghi F, Jurban A. Caution about early intubation and mechanical ventilation in COVID-19. Ann Intensive Care 2020;10:78.

15. COVID-19 Early Prone Position Study Group, Zang X, Wang Q, Zhou H, Liu S, Xue X. Efficacy of early prone position for COVID-19 patients with severe hypoxia: A single-center prospective cohort study. Intensive Care Med 2020;46:1927-9. Available From: http://link.springer.com/10.1007/s00134-020-06182-4. [Last accessed on 2020 Aug 01].

16. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a “Typical” acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201:1299-300.