Awake Prone Positioning in the Management of COVID-19 Pneumonia: A Systematic Review

Geetanjali T Chilkoti, Medha Mohta, Ashok K Saxena, Zainab Ahmad, Chhavi S Sharma

ABSTRACT

Background: The aim was to investigate the efficacy of prone positioning (PP) in the management of coronavirus disease-2019 (COVID-19) pneumonia in various setups, with various modes of oxygen therapy and its optimal duration.

Materials and methods: A systematic literature search was conducted from inception until May 15, 2021. Patients with a validated diagnosis of COVID-19 and receiving PP were included. Various factors, including intensive care unit (ICU) or non-ICU setup, mode of oxygen therapy, outcome, duration of proning, and limitations, were noted.

Results: We retrieved 36 articles with a total of 1,385 patients for qualitative analysis. Out of 36 articles, there were 17 original articles, 09 case series, and 10 case reports. Out of 1,385 participants, 78.9% (n = 1,093) and 21.0% (n = 292) of patients were managed in ICU and non-ICU setup, respectively. Awake PP with high flow nasal cannula (HFNC) was found to be a promising technique; however, the result was inconclusive with helmet continuous positive airway pressure (CPAP). No study has evaluated the optimal duration of awake PP and the associated long-term outcomes.

Conclusion: We encourage the use of early awake self-proning in the management of COVID-19 disease. However, the evidence in terms of its use in non-ICU setup, the optimal duration of PP and various oxygenation devices are insufficient, thereby mandating further well-designed multicentric studies to evaluate its efficacy as an adjunct in the management of COVID-19 pneumonia in context to the aforementioned factor.

Keywords: COVID-19 pneumonia, Management, Prone positioning.

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INTRODUCTION

Prone positioning (PP) has been an established technique for improving oxygenation in severe acute respiratory distress syndrome (ARDS). Considering the proven benefits of PP in intubated patients, physiologically, it was also assumed to benefit awake, nonintubated patients with acute hypoxemic respiratory failure. With the recent coronavirus disease-2019 (COVID-19) surge, awake self-PP has been practiced widely in the treatment of moderate to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It is a low-risk intervention requiring minimal assistance and, therefore, has also been applied outside the intensive care unit (ICU). Recently, the UK Intensive Care Society has also advocated awake PP as a standard of care for suspected or confirmed COVID-19 patients requiring a FiO2 ≥28%. However, Chad et al. in a review implicated this short-term improvement in oxygenation with PP to be simply a “recruitment maneuver,” which could have been efficacious in only patients with less severe disease. In addition, the patient population assessed in various studies evaluating awake PP in SARS-CoV-2 is heterogeneous in terms of the severity of illness, mode of oxygen therapy, ventilatory status, treatment protocol, mean duration of proning, and the setting, that is, ICU or non-ICU.

As COVID-19 is a novel viral disease, and the evidence available so far to support the efficacy of awake PP is limited; this systematic review was conducted to investigate its efficacy in both awake and intubated patients as an adjunct along with different modes of oxygen therapy or respiratory support, its performance in different setups, that is, ICU or non-ICU, and also the optimal duration of PP.

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LITERATURE SEARCH AND DATA SOURCE

We conducted a comprehensive literature search using PubMed, MEDLINE, Embase, and Google Scholar from December 2019 to May 15, 2020. In PubMed, the following search strategy was used: “COVID-19 OR Novel Coronavirus–Infected Pneumonia OR 2019 novel coronavirus OR SARS-CoV-2) AND (prone oxygenation OR awake prone position OR self proning).” The strategy was then further adapted for other databases. The titles and abstracts were reviewed to evaluate their relevance to our study. Full-text articles were retrieved for further consideration for inclusion. Two authors (G.T.C. and M.M.) read all the articles, and any inconsistencies were resolved by consensus with the third author (A.K.S.).

Study Selection—For study selection, we followed PICO framework: participants, who had a validated diagnosis of COVID-19, irrespective of stage or severity of disease; intervention, oxygen therapy or respiratory support in awake self-PP; comparison, patients not receiving prone oxygenation,
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—No language restriction was imposed, in order to include maximum articles and minimize language bias. For each article, we extracted data regarding authors, year of publication, the period of observation, patient selection, ICU or non-ICU setting, duration of PP, outcomes assessed, conclusion, and limitations, if any. For the present systematic review, due to the novel nature of the disease, all kinds of publications, that is, case report, case series, editorials, letters, and reviews in addition to original articles providing evidence toward the efficacy of awake PP in the improvement of oxygenation in COVID-19 disease, were included.

RESULTS

Flowchart 1 shows the PRISMA flowchart depicting the qualitative synthesis of evidence from the literature search. Following the screening of titles, abstracts, and removal of duplicates, finally, we included 36 articles with a total of 1,385 patients for qualitative analysis. Out of 36, 17 were original articles, 6–22 nine case series, 23–31 and 10 case reports. In addition, there were seven protocols, 32–38 seven reviews, 39–45 two commentaries, 46,47 and four editorial.48–51 The 17 original articles were included in the qualitative assessment of risk of bias. All the included articles were published from the inception of COVID-19 till May 15, 2021.

Table 1 shows the characteristics of all the clinical studies evaluating PP in COVID-19 pneumonia.

Awake PP in COVID-19 Pneumonia in Non-ICU Setup

Out of all the articles, six studies have evaluated awake PP used outside the ICU for COVID-19 pneumonia. 6,7,10,14,15,22 Caputo et al. applied PP to 50 COVID-19 patients in the Emergency Department and showed a significant improvement in oxygenation. A one-day cross-sectional, before-after study was conducted by Sartini et al. on 15 awake non-ICU patients on noninvasive ventilation (NIV) irrespective of the day. They recorded SpO2, PaO2/FiO2, respiratory rate (RR), and patients’ comfort at three designated time points while receiving NIV in PP, that is, before starting NIV, 60 minutes after the start of PP, and 60 minutes after the end of NIV. A significant improvement in SpO2 and PaO2/FiO2 from 100 (IQR, 60–112) to 122 (IQR, 118–122) (p <0.001 for both) along with a decrease in RR during NIV in PP was observed. On follow-up at day 14, nine patients were discharged, one improved, one was intubated, and one died.10

On the contrary, Elharrar et al. in a single-center, before-after study, in patients receiving NIV, observed that out of 24, PaO2 improved in only six patients, that is, merely 25% with PP, whereas four patients did not tolerate PP for more than an hour and required intubation.7

Awake PP in COVID-19 Pneumonia in ICU Setup

Out of all the studies conducted in ICU, only Zang et al.13 had incorporated a control group and compared the oxygenation status of patients receiving PP with the ones who did not receive it. The oxygenation parameters used were SpO2, RR, and ROX index. They did not compare the PaO2/FiO2 ratio, and also the number of patients with severe diseases was limited in their study.

In another study, Tu et al. exclusively enrolled nine patients with COVID-19 on flow nasal cannula (HFNC) for more than 2 days and having PaO2/FiO2 <150 mm Hg. Prone position was found to be efficacious in improving oxygenation in patients on HFNC.8 Similarly, Coppo et al.,7 in a prospective cohort study, assessed the feasibility of PP in 56 patients receiving NIV or conventional oxygen therapy (COT) and found it to be feasible in 83.9% of patients (n = 47). Oxygenation improved PaO2/FiO2 ratio from 180.5 to 285.5 mm Hg (112.9) in PP (p <0.0001). Oxygenation following resupination was maintained in only 23 patients (50%). It was concluded that PP was feasible and effective in improving oxygenation in awake patients with COVID-19; however, the effect was sustained in only 50% of patients.

Thompson et al.11 in a cohort study on 25 patients also observed the efficacy of PP in improving the oxygenation and its effects on intubation rate. They observed that 1 hour after

Flowchart 1: PRISMA flowchart depicting the steps of qualitative synthesis of evidence from the literature
Table 1: Characteristics of the published clinical studies evaluating PP in patients with COVID-19 pneumonia

| Authors            | Type of study | Set-up         | N (number of patients) | Age (years) | Initiation of therapy/ mode of oxygen therapy | Outcome                                                                 | Duration of proning | Conclusion                                                                 | Limitations                                                                 |
|--------------------|---------------|----------------|------------------------|-------------|----------------------------------------------|-------------------------------------------------------------------------|---------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Caputo et al.      | Observational cohort | Non-ICU | 50                     | 59 (IQR 50–68) | SpO2<90% and NRB or nasal cannula             | Change in median SpO2 after 5 min of PP; rate of intubation in patients who were prone | Parameters evaluated after 5 min of PP | Median SpO2 increased to 94% from 84% (IQR, 75–90%) after 5 min of PP; 24% (n = 13) required intubation | None experimental sequential case series; Treatment protocols were not controlled; single centric study |
| Bharr et al.       | Prospective, single center before and after study | Non-ICU | 24                     | 66.1 (10.2)  | Requiring oxygen supplementation and CT scan suggestive of COVID-19 | Proportion of patients showing increase in PaO2 by ≥20% after PP; feasibility, that is, proportion of patients sustaining PP ≥1 hr and ≥3 hr | 1–3 hr | 63% able to tolerate PP beyond 3 hr; 21% tolerated it 1–3 hr and 17% tolerated <1 hr | Small sample size; short follow-ups; clinical outcomes were not assessed |
| Tu et al.          | Pilot study   | ICU            | 9                      | 51 ± 11     | Patients on HFNC for >2 days with PaO2/FiO2 <150 mm Hg | Improvement in SpO2; mean PaO2 | 2 hr (IQR, 1–4 hr) | SpO2 increased from 90 ± 2 to 96 ± 3% (p < 0.001), mean PaO2 increased from 69 ± 10 to 108 ± 14%, and PaCO2 decreased from 47 ± 7 to 39 ± 5 mm Hg (p = 0.007) | Small sample size; lack of control group |
| Coppo et al.       | Single center, prospective cohort, feasibility study | ICU    | 56                     | 57.4 (7.4)  | Patients on either NIV or COT PaO2/FiO2 at 10 min after PP and 1 hr after resupination; safety, feasibility, PaCO2 | 3 hr | PaO2/FiO2 ratio increased after PP; and improved oxygenation was maintained in 23 patients (50%) patients after resupination. PP was feasible (ie., PP maintained for at least 3 hr) in 47 patients (83.9%) | Lack of control group; selection bias; single-center data |
| Sartini et al.     | Cross-sectional, before after study   | Non-ICU | 15                     | 59 (6.5)    | Patients on NIV SpO2, PaO2/FiO2, RR, and patients' comfort were assessed at three time points while on NIV in PP that is, baseline, at 60 min after starting NIV, and 60 min of end of NIV session | Median number of NIV cycles in the PP was 2 (IQR, 1–3 cycles) for a total duration of 3 hr (IQR, 1–6 hr) | Significant reduction in RR during and after pronation (p <0.001 for both); significant improvement in SpO2, and PaO2/FiO2 during pronation (p<0.001 for both); improvement in SpO2, and PaO2/FiO2, after pronation in 12 patients (80%); unchanged in 2 (13.3%); and worsened in 1 (6.7%) | Small sample size; short duration of NIV in prone; no control group |
| Thompson et al.    | Single-center cohort study  | ICU    | 29 eligible, but PP in 25 patients | 67 (45–71) and Nonintubated 66.0 (53–87) | Severe hypoxemic ARF on either nasal cannula or NRB | At least one session in a day of more than 1 hr | Improvement in SpO2 from supine to 1 hr postpronning was 1–34% (median [SE], 7% [12%]; 95% CI, 4.6–9.4%); the mean difference in intubation rate among patients with SpO2 of 95% or greater vs SpO2 less than 95% 1 hr after initiation of PP was 46% (95% CI, 10–88%) | Small sample size; no control group |
| Retucci et al.     | Pilot, observational, prospective study | ICU    | 26                     | 62 (IQR, 56–69) | Patients on helmet CPAP treatment with PaO2/FiO2 ratio <250 for more than 48 hr | A decrease in the A-a O2 gradient of at least 20%; equal or reduced RR and dyspnea ≥50 mm Hg | 1 hr | Among trials conducted in PP, 33% less; 41.7% showed decreased A-a O2 (<20%), and 25% failed. Among trials conducted in lateral positioning, 8% succeeded; 52% showed decreased A-a O2 (<20%), and 40% failed. High failure rate was reported. | Did not assess the clinical outcome; evaluation of both response and tolerance to both post-tomings conducted only after 1 hr |
| Zang et al.        | Single center cohort study  | ICU    | 60 patients enrolled. PP—23 and Non-PP—37 | 62          | Moderate hypoxemia and on High FiO2 reservoir mask with SpO2 <93% | SpO2, RR, ROX index at 10 min and 30 min after PP | Mean duration of PP per patient was 13 hr | Significant difference in SpO2 10 min, ROX10 min, SpO2 30 min, RR30 min, and ROX index30 min between the two groups (p < 0.01). On 90 days follow-up, 43.5 and 76% in PP and non-PP group died, respectively | PaO2/FiO2 was not analyzed; limited number of severe disease patients were enrolled |
| Authors          | Study Type                                | Setting | n   | Intubation rate, mortality | P/F ratio, SpO₂ | Intubation rate, mortality | P/F ratio, SpO₂ | Intubation rate, mortality | P/F ratio, SpO₂ |
|------------------|-------------------------------------------|---------|-----|---------------------------|----------------|---------------------------|----------------|---------------------------|----------------|
| Jagan et al.     | Retrospective study                       | Non-ICU | 105 | 56.0 ± 14.4               | Nonintubated patients | Intubation rate, mortality >1 hr for 5 times/day | 38.1% required intubation, lower mortality |
| Hallifax et al.  | Retrospective study                       | ICU     | 48  | 69 (54–80)                | Patients on CPAP/HFNC | Intubation rate, mortality >2 hr, twice daily for at least 2 days | 22.9% discharge, 22.9% ICU admission, 62.5% of patients on CPAP tolerated awake PP |
| Singh et al.     | Retrospective study                       | ICU     | 95  | 51.5                      | Patients with SpO₂ >90% through simple face mask, NRBM, NIV | P/F ratio, SpO₂ | Intubation rate, mortality 10–12 hr/day | Marked increase in P/F ratio and SpO₂ |
| Khanum et al.    | Observational study                       | ICU     | 23  | 54.5 (11.7)               | Oxygen therapy with or without NIV | Avoidance of intubation, mortality | No prefixed targeted duration but >1 day | Only one patient required intubation, rest 22 improved |
| Sryma et al.     | Prospective interventional study          | ICU     | 45 cases = 30 Control = 15 | 53.1 (11) | All patients with room air saturation <93% | Intubation rate and ROX index at 30 min, 12 hr | 7.5 hr on day 1 | Increased intubation rate in control group (33.1 vs 6.7%) ROX index increased in cases (10.7 [3.8] vs 6.7 [2.6], p <0.001) |
| Kharat et al.    | Cluster RCT                               | Non-ICU | 27 Control = 17, cases = 10 | 58 ± 12 | Patients on low flow oxygen therapy | Oxygen flow requirement | 12 hr/day | Oxygen flow requirement was less in PP group [1 (0.1–2.9) L/min vs 2.0 (0.5–3) L/min] |
| Tonelli et al.   | Retrospective multicentric cohort study   | ICU     | 114 | PP = 61 (standard treatment = 76 PP = 38) | Patients on NIV | Intubation rate | 3 hr (1–4 sessions/day) | Reduced intubation rate with PP (18 vs 39.5%) |
| Nauka et al.     | Nested case matched control analysis      | ICU     | 600 (200 cases 400 control) | Comparable between two groups | All nonintubated patients | Rate of IMV or mortality | Cases were maintained on nonintubated proning for less time (time difference was 39.2 hr (IQR, 0–88.9 hr)) | Nonintubated proning did not alter intubation rate but temporarily improved hypoxemia |
| Dubosh et al.    | Prospective, observational cohort study   | Non-ICU | 22  | 61 (IQR: 50, 65) | Patients on oxygen via nasal cannula or NRBM | SpO₂/FiO₂ ratio, RR | SpO₂/FiO₂ ratio increased with PP (median: 298 (IQR: 263–352) vs 295 (IQR: 276–350), p = 0.01) | Small sample size |

N, number of patients; PP, prone positioning; NRBM, non-rebreathing mask; HFNC, high flow nasal cannula; A-a gradient, alveolar–arterial gradient; RR, respiratory rate; SBP, systolic blood pressure; CPAP, continuous positive airway pressure; COT, conventional oxygen therapy; NIV, noninvasive ventilation; RR, respiratory rate; VV-ECMO, Veno-venous extracorporeal membrane oxygenation; ROX index, ratio of SpO₂/FiO₂ to respiratory rate; R/I ratio, recruitment-to-inflation ratio
PP, the range of improvement in SpO\textsubscript{2} was from 1 to 34%, and the mean difference in intubation rates between patients with SpO\textsubscript{2} higher than 95% compared to those with less than 95% at 1 hour after PP was 46%.

Retucci et al.\textsuperscript{12} in an observational study evaluated PP and lateral positioning in 26 patients on helmet continuous positive airway pressure (CPAP) and observed a high failure rate.

Table 2 shows the characteristics of the case series evaluating PP in patients with COVID-19, and all had used awake PP.\textsuperscript{23-31} The mean age of all 69 patients included in the case series was 58.0 years. The mean duration of single-PP session extended from 2 hours till 16 hours/day. The PaO\textsubscript{2}/FiO\textsubscript{2} ratio, SpO\textsubscript{2}, clinical improvement, and oxygen requirements were the most commonly used clinical outcomes.

Four case series involving 43 patients evaluating awake PP in SARS-CoV-2 were conducted in non-ICU areas,\textsuperscript{24,25,28,29} out of which, few were conducted among patients receiving helmet NIV.\textsuperscript{28-30} Ripollo-Gallardo et al.\textsuperscript{28} and Bastoni et al.\textsuperscript{29} in their retrospective series of 13 and 10 patients evaluated PP among patients on helmet NIV in the general ward and Emergency Department, respectively. Both studies showed improved oxygenation with PP; however, the latter in addition conducted lung ultrasonography (USG) and did not observe any change in recruitability with the PP. As far as the feasibility of PP with helmet NIV is concerned, it was reported as 92.3% by Ripollo-Gallardo et al.\textsuperscript{28} and 60% by Bastoni et al.\textsuperscript{29}

Ng et al.\textsuperscript{25} evaluated PP in 10 patients in the general ward with the FiO\textsubscript{2} requirement <0.5; three patients were later shifted to ICU where one died. The rest seven patients showed improvement in clinical symptoms. No PaO\textsubscript{2}/FiO\textsubscript{2} ratio could be assessed due to the setting of the study. Out of five case series that were conducted in the ICU setup, three were conducted among patients receiving HFNC,\textsuperscript{23,26,27} one with helmet CPAP,\textsuperscript{30} and one on non-rebreathing mask (NRBM).\textsuperscript{31}

Table 3 shows the details of various case reports in this context.\textsuperscript{32-41} The mean duration of PP in these case reports ranged from 1 hour till 16–18 hours/day (Table 3).

**Specific Subpopulation**

**Awake PP in ICU and Non-ICU Setups**

Out of all 1,385 participants, 78.9% (n = 1,093) received awake PP in ICU and 21.0% (n = 292) received it in non-ICU areas, including emergency areas, wards, etc.

**Awake PP in Pregnant Patient and Morbidly Obese**

There has been little evidence regarding the use of PP in pregnant women with COVID-19. The only reported use of PP in pregnant patients with COVID-19 was found to be efficacious when combined with HFNC. However, the practical applicability or use of PP in the pregnant patient was a concern.\textsuperscript{28} Recently, Paul et al. reported a morbidly obese (body mass index, 65 kg/m\textsuperscript{2}) COVID-19 patient with obstructive sleep apnea and reported notable improvement in FiO\textsubscript{2} requirements titrated down to 0.4 within 1 hour of proning, which persisted even on return to supine position.\textsuperscript{29}

**Awake PP along with HFNC**

Nine articles that include two clinical studies,\textsuperscript{8,15} three case series,\textsuperscript{23,26,27} and five case reports\textsuperscript{34,36-39} including a total of 90 patients have evaluated awake PP along with HFNC in the management of COVID-19 pneumonia. This combination was found to be feasible, helpful, and efficacious in terms of various oxygenation outcomes, for example, PaO\textsubscript{2}/FiO\textsubscript{2}, RR, SpO\textsubscript{2}, and other clinical parameters, and also in a single case report on a pregnant patient with COVID-19 pneumonia.\textsuperscript{36} However, there has been a lack of well-designed studies to validate this finding.

**Awake PP with Helmet CPAP**

Only one clinical study\textsuperscript{22} and three case series\textsuperscript{28-30} including 59 patients have evaluated PP along with helmet CPAP. Retucci et al. observed a high failure rate with PP and lateral positioning in patients receiving helmet CPAP.\textsuperscript{12} On the contrary, all the three case series found PP with helmet CPAP to be feasible and efficacious,\textsuperscript{28-30} however, the sustained improvement in oxygenation even after 12 hours of PP was documented only by Golestani et al.\textsuperscript{30}

**Risk of Bias (Quality) Assessment**

In order to assess the risk of bias of the included studies, the Cochrane Collaboration tool, namely ROBINS-I (“Risk of Bias In Non-randomized Studies—of Interventions”), was used. It is a tool for evaluating the risk of bias from nonrandomized studies utilizing interventions.\textsuperscript{61} The ROBINS-I assesses the risk of bias in seven domains: (1) bias due to confounding, (2) bias due to selection of participants, (3) bias in classification of interventions, (4) bias due to deviation from intended intervention, (5) bias due to missing data, (6) bias in the measurement of outcomes, and (7) bias in the selection of the reported result. Each aforementioned parameter of bias in each study will be scored as having low, medium, high, or unclear risk. The study with lower risk is deemed as a high-quality study. The risk of bias was independently assessed by GCT and ZA, and disagreements were resolved through discussion with MM. The overall judgment on the bias assessment following assessment of each domain of the included studies in the present systematic review as per the ROBINS-I tool has been found to have moderate to serious risk.\textsuperscript{61} The risk of bias was variable among different included studies. The weighted summary plot of different aforementioned biases among all nonrandomized studies\textsuperscript{6-22} was designed using robvis web app (Fig. 1).\textsuperscript{62}

**Discussion**

The present review has summarized the current evidence of awake PP in patients with SARS-CoV-2, out of a total of 1,385 patients in whom awake PP was evaluated. Overall, the technique was found to be efficacious in terms of improvement in oxygenation in 78.9% (n = 1,093) of patients in ICU and 21.0% (n = 292) in non-ICU areas, including emergency areas, wards, etc. Awake PP along with HFNC was used in 90 patients and was found to be efficacious in all the cases. Awake PP was used in patients with helmet CPAP in 59 cases with inconclusive results. However, none of the studies have evaluated the optimal duration of awake PP; in the majority, the oxygenation parameters were evaluated within few minutes to only a few hours after PP, and no long-term outcomes were assessed.

PP reverses the compression atelectasis of the dorsal lungs due to heart and mediastinum and helps alveolar recruitment in the dorsal lung (now nondependent) by increasing the transpulmonary pressure leading to the homogenous distribution of ventilation across the lung.\textsuperscript{2,2} However, perfusion remains higher in the dorsal region due to higher production of nitric oxide (a potent vasodilator) in the endothelium of the dorsal lung leading to a
Table 2: Characteristics of the case series evaluating PP for COVID-19 pneumonia\textsuperscript{23-31}

| Authors           | N/Gender | Age (yrs) | Setup       | Initiation of therapy/ mode of oxygen therapy | Awake proning/ prone ventilation | Duration of proning | Outcome | Conclusion |
|-------------------|----------|-----------|-------------|-----------------------------------------------|---------------------------------|---------------------|---------|------------|
| Xu et al.         | 10 (50% males) | 50.2   | ICU         | Severe hypoxemia on HFNC                     | Awake proning                  | Approx. 16 h/day    | Median PaCO\textsubscript{2}: PaO\textsubscript{2}/FiO\textsubscript{2} ratio | Median PaCO\textsubscript{2} increased slightly (32.3[29.3–34.0] mm Hg vs 29.7 [28.0–32.0] mm Hg (p <0.001)) and significant increase in PaO\textsubscript{2}/FiO\textsubscript{2} after PP |
| Moghadam et al.  | 10 (70% males) | 41     | Non-ICU     | Random selection                             | Awake proning                  | —                   | Clinical dyspnea; SpO\textsubscript{2} before and after PP | Dyspnea decreased by 40% and SpO\textsubscript{2} improved to 95.9% from 85.6% with PP |
| Ng et al.         | 10 (80% males) | 60     | General ward | Patients requiring FiO\textsubscript{2} <0.5 | Awake proning                  | 5 sessions/ day with 1 hr/ session, each spaced 3 hr during the waking hours | Clinical symptoms; Weaning off oxygen; intubation | Low risk, low cost, and improvement in clinical symptoms reported with PP |
| Despreset et al. | 06 (100% males) | 60     | ICU         | Patients on either HFNC (n = 3) or COT (n = 3) | Awake proning                  | 8.3 hr              | PaO\textsubscript{2}/FiO\textsubscript{2} | A total of nine PP sessions in six patients. PP + HFNC in four sessions and PP + COT in five sessions. PaO\textsubscript{2}/FiO\textsubscript{2} ratio improved after four sessions, including three sessions with HFNC and one session with COT; intubation avoided in 50% patients |
| Damarla et al.   | 10 (70% males) | 56 (range, 40–80) | ICU | HFNC (n = 4) and nasal cannula (n = 5) | Awake proning                  | 2 hr prone and supine alternately | Change in SpO\textsubscript{2} and RR before and 1 hr after PP; intubation within 2 weeks | Median SpO\textsubscript{2} increased from 94% (IQR, 91–95%) to 98% (IQR, 97–99%), median RR reduced from 31 (IQR, 28–39) to 22 (IQR, 18–25) breaths/min; 8 out of 10 did not require intubation |
| Ripoll-Gallardo et al. | 13 (85% males) | 66     | General ward | Patients on helmet NIV CPAP                  | Awake proning                  | Maintained as long as patient tolerated | PaO\textsubscript{2}/FiO\textsubscript{2}: RR | Improved PaO\textsubscript{2}/FiO\textsubscript{2} compared to baseline in 12 patients (p = 0.003); no difference was found in the RR before and after PP (p = 0.20) |
| Bastoni et al.   | 10 (80% males) | 73     | Emergency department | Patients on helmet NIV CPAP with no clinical improvement | Awake proning                  | 1 hr                 | PaO\textsubscript{2}/FiO\textsubscript{2}: Lung USG | In 4 out of 10 patients, the attempt of PP failed; an improvement in PaO\textsubscript{2}/FiO\textsubscript{2} ratio from 68 ± 5 to 97 ± 8 mm Hg after 1 hr of PP in all; No change in B-line quantity and distribution in lung USG after 1 hr |
| Golestani et al. | 10 — | — | ICU | Patients with PaO\textsubscript{2}/FiO\textsubscript{2} ratio <150 and on helmet NIV | Awake proning                  | 9 hr                 | PaO\textsubscript{2}/FiO\textsubscript{2} ratio after 1 and 12 hr of PP | 60% patients had sustained improvement in PaO\textsubscript{2}/FiO\textsubscript{2} ratio after 1 hr; 30% of patients had delayed positive result, and one patient was intubated |
| Eragini et al.   | 24 54   | ICU | SpO\textsubscript{2} <90% on NRBM, PaO\textsubscript{2}/FiO\textsubscript{2} ratio <200 on ABG | Awake proning                  | —                   | Intubation rate      | 37.5% failed trials of awake proning and required intubation | 55.5% of these patients were successfully extubated simplest, most resource-effective method for improving oxygenation |

\textit{N}, number of patients; PP, prone positioning; NRBM, non-rebreathing mask; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; COT, conventional oxygen therapy; NIV, noninvasive ventilation; RR, respiratory rate; USG, ultrasonography
Table 3: Summary of the case reports evaluating PP for the management of COVID-19 pneumonia

| Authors          | N   | Set-up          | Age (yrs)/gender | Initiation of therapy/mode of oxygen therapy | Awake proning/prone ventilation | Duration of proning | Outcome                                                                                                                                          | Conclusion                                                                                                                                                                                                 |
|------------------|-----|-----------------|------------------|----------------------------------------------|---------------------------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sztanjbok et al. | 32  | ICU             | 43 and 37 (both males) | On NRBM                                      | Awake proning                  | 8–10 hr            | Need of oxygen (L/min), improvement in clinical symptoms, PaO₂/FiO₂ ratio                                                                          | Decrease in need of oxygen from 10 to 5 L/min; improvement in clinical symptoms and PaO₂/FiO₂                                                                                                             |
| Elkattawys et al.| 33  | Emergency department | 36, male          | Severe hypoxemia and on nasal cannula         | Awake proning                  | At least 6–8 hr on nasal cannula (approx. 12 hr/day) | SpO₂ on rest and on ambulation                                                                                                             | After approx. 12 hr of PP, patient was taken off of nasal cannula with SpO₂ >95% at rest and 90% on ambulation; however, tachycardia continued                                                                 |
| Slessarev et al. | 34  | ICU             | 68, male          | Patient on HFNC                               | Awake proning                  | 16–18 hr/day including 8–10 hr in sleep           | Clinical improvement                                                                                                                        | HFNC with self-proning leads to improvement in symptoms and oxygenation                                                                                                                                   |
| Cohen et al.     | 35  | Non-ICU         | 52, female and 40, male | Profound hypoxemia on oxygen via nasal cannula | Awake proning                  | 2–5 hr/day                                    | Improvement in SpO₂ and RR with PP                                                                                                           | Improvement in SpO₂ and reduction in RR observed between 10 min and 30 min after PP in both the cases                                                                                                     |
| Vibert et al.    | 36  | ICU             | 21 pregnant patient | 23 weeks of gestation, on HFNC               | Awake proning                  | Lateralized for 2 hr period, that is, PP right lateral, left lateral | Hemodynamic and ABG parameters before, during, and after PP                                                                                   | SpO₂ and ABG parameters improved with PP; patient was weaned off HFNC and intermittent NIV and was discharged on day 24 after symptoms onset                                                                 |
| Paul et al.      | 02  | ICU             | 42, male and 35, male | First patient had severe hypoxemia on HFNC Second patient was morbidly obese | Early awake proning in first patient and late awake self-proning in second patient after extubation | 2–3 hr/session          | SpO₂, and oxygen requirement                                                                                                                     | Within few hours of proning, the SpO₂ improved and FiO₂ requirement reduced to 0.4–0.5; obesity should not be a contraindication to PP                                                                 |
| Huang et al.     | 03  | ICU             | 55, male; 61, female; 61, male | Patients on HFNC                             | Awake proning                  | 4 sessions a day of 2 hr each                      | ROX index                                                                                                                                    | The first two required 5 and 2 days of PP + HFNC, while the third patient was intubated after 4 days                                                                                            |
| Taboda et al.    | 01  | Non-ICU         | 71, female        | Severe hypoxemia and on HFNC                 | Awake proning                  | CT scan in prone and supine position, duration of PP not mentioned | CT finding and PaO₂/FiO₂                                                                                                                    | CT findings suggestive of recruitment of alveoli along with a moderate decrease in the attenuation of the lesions in the lower lobes. PaO₂/FiO₂ increased from 130 to 238 mm Hg with PP                                  |
| Alseoudy et al.  | male | ICU             | Following extubation for ARDS                  | Awake PP                           | 4 hr prone followed by 1 hr supine, these cycles for 4 days | Oxygen saturation | The trial of PP resulted in a dramatic increase in peripheral oxygen saturations to 97% and decreased work of breathing |                                                                                                                                                                                                          |
| Whittenmore et al.| Male | ICU            | On low flow oxygen therapy                    | Awake PP                           | >18 hr/day                                      | Oxygen saturation | Significantly improves oxygenation in COVID-19 pneumonia                                                                                          |                                                                                                                                                                                                          |

N, number of patients; PP, prone positioning; HFNC, high flow nasal cannula; NRBM, non-rebreathing mask; CPAP, continuous positive airway pressure; COT, conventional oxygen therapy; NIV, noninvasive ventilation; ECMO, extracorporeal membrane oxygenation; RR, respiratory rate; V/Q scanning, ventilation/perfusion scanning; ET, endotracheal
significant reduction in the relative shunt fraction along with the improvement in $\text{PaO}_2/\text{FiO}_2$. The role of prone ventilation in intubated ARDS patients has been established since the last few years.\textsuperscript{12,13} Extrapolating the evidence of PP in mechanically ventilated non-ARDS ARDS patients, recently, even the Surviving Sepsis Campaign panel has advocated a trial of PP in mechanically ventilated COVID-19 patients with moderate to severe ARDS for a period of 12–16 hours.\textsuperscript{14}

In the present COVID-19 pandemic, the use of PP has been widely extended to awake patients in both ICU and non-ICU areas. Awake PP is an important adjuvant for improving oxygenation in ARDS along with other factors like FiO$_2$ delivered, mode of oxygen therapy, and other treatment protocols. HFNC has been known to increase the ventilator-free days and decrease the mortality in ICU patients. In the present systematic review, we observed a striking improvement in oxygenation with PP in patients who were receiving HFNC. We are also looking forward to the results of the ongoing meta-trial to investigate awake PP in COVID-19 patients undergoing HFNC.\textsuperscript{15} However, with helmet NIV, its efficacy has been found to be contentious.

There have been concrete evidences regarding the optimal duration of prone ventilation in non-ARDS\textsuperscript{2,3}, however, no study has assessed the optimal duration of awake PP since its inception has gained momentum in COVID-19 pandemic. The majority of the clinical studies evaluating awake PP in COVID-19 pneumonia have assessed the oxygenation as early as 5 minutes to the maximum of 1 to 3 hours after PP.\textsuperscript{6,9,11–13} The sustained improvement in oxygenation as assessed in a single study by Golestani et al. after 12 hours was observed in only 30% of patients.\textsuperscript{16} In addition, only a few studies have utilized control group for the evaluation of awake PP.\textsuperscript{13,18,19} In all these studies, the assessment for improved oxygenation was undertaken as early as 1 hour\textsuperscript{13,18} till the end of day one.\textsuperscript{17} These studies’ results highlighting the improvement in oxygenation following such a short duration of awake PP could possibly be implicated to the transient lung recruitment.\textsuperscript{18} This mandates the need to determine the optimal duration of awake PP along with the assessment of long-term clinical outcomes, for example, intubation rates and mortality.

The present systematic literature review is dealt with few limitations. Firstly, the studies included had small sample sizes and single centric data.

Secondly, except for one,\textsuperscript{13} all studies lacked the control group. Thirdly, considering the fact that early use of awake PP may improve the overall prognosis, the evidence regarding the efficacy and safety of the institution of PP in outside ICU setups has been found to be insufficient. Interestingly, a clinical study by Sartini et al.\textsuperscript{19} and two case series\textsuperscript{18,20} have evaluated PP in severely hypoxemic patients receiving NIV and helmet CPAP in non-ICU areas, a finding which cannot be related in developing countries with limited facilities during this pandemic times. Fourthly, there was a heterogeneous patient population in terms of the mode of oxygen therapy or respiratory support, duration of proning, treatment protocol, and severity of illness at the time of initiation of PP. Also, few studies displayed incomplete data, particularly the mode of oxygen therapy and duration of proning.

In conclusion, the literature available so far encourages the use of early awake self-proning in addition to its use in intubated patients in the management of SARS-CoV-2 infection. The short-term improvement in the oxygenation as reported in various trials could simply be a “recruitment maneuver” as the majority of the oxygenation outcome parameters were assessed between few minutes to 3 hours after PP in various studies. The overall evidence pertaining to the use of awake proning in the management of COVID-19 disease is not sufficient as there has been a lack of randomized controlled trial, and therefore, further well-designed multicentric studies with larger sample size and preferably with a control group are warranted to evaluate the PP as an adjunct in the management of COVID-19 pneumonia in terms of its safety, optimal duration of proning, and efficacy in improving oxygenation with individual modes of oxygen therapy.

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