Effectiveness of early awake self-proning strategy in non-intubated patients with moderate COVID-19 hypoxemia: an open-labelled randomized clinical trial from Jodhpur, India

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Ethics approval: the study was approved by Institute Ethics Committee (AIIMS/IEC/2020-21/2040 dated June 6th, 2020). All patients provided written informed consent to participate. Trial was registered at Clinical trial registry of India, CTRI/2020/06/025804 and is accessible from WHO's International Clinical Trials Registry Platform (ICTRP) at https://trialsearch.who.int

Availability of data and materials: the research protocol for the trial is available as supplement and on the trial registration website. De-identified data will be available after article publication to researchers who provide a methodologically sound and ethically approved proposal, for any purpose of analysis.

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Abstract

Awake self-proning is being used widely as respiratory support in COVID-19 hypoxemia, in resource-limited settings. We aimed to investigate the effectiveness of early awake self-proning in preventing mortality and the need for intubation in adults with moderate COVID-19 hypoxemia. In this randomized clinical trial with intention-to-treat analysis, we enrolled eligible adults with COVID-19 hypoxemia (SpO_2 <94%), requiring supplemental oxygen via nasal prongs or facemask from a tertiary-care setting in Jodhpur, India between June 15 to December 24, 2020. Awake proning comprised of 4-hour cycles with prone position maintained 2 h per cycle. The control group did not maintain any specific position. All participants received standard care. The primary outcomes were 30-day mortality and requirement for mechanical ventilation. Of 502 participants included, mean (SD) age was 59.7 (12.7) years with 124 women (24.6%); 257 were randomized to awake-proning, 245 to control group and all 502 were included for follow-up mortality analysis. Mortality at follow-up was 16.3% in the awake-prone and 15.1% in the control group [OR:1.10 (0.68-1.78), p=0.703). The requirement of mechanical ventilation was 10% in both groups (p=0.974). Survival time (in days) was not significantly different between the groups [Log-rank test, HR: 1.08 (95% CI, 0.70-1.68), p=0.726]. Likewise, time to intubation was comparable (Log-rank test, HR: 0.93 (95% CI, 0.56-1.70), p=0.974). Hence, awake self-proning did not improve survival or requirement of mechanical-ventilation in non-intubated patients with mild to moderate COVID-19 hypoxemia. Trial Registration: Clinical trial registry of India, ID: CTRI/2020/06/025804.

Introduction

Hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) are life-threatening complications of COVID-19 resulting in mechanical ventilation and deaths [1,2] The optimal initial support for COVID-19 hypoxemia to prevent adverse outcomes are unclear. Different approaches explored including awake self-proning, helmet ventilation, non-invasive ventilation (NIV), high flow nasal oxygen (HFNO) and mechanical ventilation [3-6].

Prone-positioning has been used in ARDS, but evidence for

awake-proning for non-intubated patients remains limited [7,8]. Awake-proning appeared low-risk and safe for self-administration, hence, widely recommended as an adjunctive intervention for mild-to-moderate COVID-19 hypoxemia [9-11]. Several observational studies reported improvement in oxygenation [12,13]. Few randomised trials are available till date which show conflicting results [14-17]. Whether awake prone positioning offers meaningful clinical benefits in all settings and patient populations remains to be clearly established [18] A recent systematic review concluded that there is a need for randomised trials to determine the impact of awake proning on mortality, mechanical ventilation, and length of hospital stay [19]- This open-label randomized clinical trial aimed to assess the effects of early awake-proning strategy on mortality and requirement for mechanical ventilation in non-intubated patients with moderate COVID-19 hypoxemia.

Methods

This was an investigator-initiated, parallel-arm, open-label, pragmatic randomized clinical trial conducted at intensive care and high dependency units (HDUs) in a tertiary care centre, India between June 15th 2020, and December 24th 2020; and follow-up was completed by February 15th, 2021. The study was conducted in two phases: pilot study (phase 1) with a crossover design to explore feasibility and effect of awake proning on hypoxemia and a phase 2 trial to determine the effect of awake proning on mortality, and requirement and time to mechanical ventilation.

Ethics statement

The study was approved by the Institute Ethics Committee (AIIMS/IEC/2020-21/2040 dated June 6th, 2020). All patients provided written informed consent to participate. The trial was registered at the Clinical Trial Registry of India, CTRI/2020/06/025804 and is accessible from WHO's International Clinical Trials Registry Platform (ICTRP) at https://trialsearch.who.int

Participants

All consecutive adult patients (>18 years) admitted with a molecular diagnosis of COVID-19 by RT-PCR for viral RNA from nasopharyngeal or oral swabs were screened for inclusion. The criteria for enrollment were peripheral oxygen saturation (SpO_2) < 94% on room air (measured using finger probe pulse oximetry) or requiring oxygen support by nasal prongs/facemask for maintaining SpO_2 >94% and being able to communicate and self-prone. These inclusion criteria were kept pragmatic in view of early recruitment of patients during the pandemic without the need for blood gas analysis. Those with blood pressure (BP) <90/60 mmHg or on inotrope support, deep venous thrombosis in the past 3 months, morbid obesity, pregnancy, Glasgow Coma Scale (GCS) <11, seizures, psychiatric diagnosis, stroke, or limb paralysis precluding self-proning, massive hemoptysis in the 48 h (>500 mL/requiring transfusion) and patients at high risk of requiring defibrillation were excluded. Patients who had received non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO) at the time of screening were also excluded as all these patients were offered proning as part of routine clinical care.

Phase 1 trial (Pilot study)

A proof-of-concept cross-over design randomized trial was planned to demonstrate feasibility with a sample size of 20 patients. All patients underwent both prone and supine positioning. Ten patients underwent early prone positioning (prone followed by left-lateral, right lateral) and supine/sitting positioning, while the remaining 10 followed the reverse sequence of positions. If saturation dropped or patient was unable to maintain the position, the next position was initiated. Oxygen saturation was noted at 0, 10, 20, 30 and 40 min for each position (total cycle: 40 min). A paired *t*-test was used to compare improvement in saturation level and oxygen saturation and saturation/fraction of inspired oxygen ratio (S/F) in prone as compared to supine were determined.

Phase 2 trial

The phase 2 trial was planned as a parallel-arm, open-label, pragmatic randomized clinical trial to assess the effect of awake proning on mortality, and requirement and time for mechanical ventilation. In this mortality was considered as the primary outcome.

Sample size calculation

With 80% power and a two-sided α of 0.05, we assumed that the risk of mortality with COVID-19 would be 24.5% [20]. With the goal of detecting a 10% reduction in mortality (primary outcome) and our total estimated sample size is 488 with 244 in each group. We expected 1.5% attrition or crossover, and the final sample size was calculated as 502.

Randomization and allocation concealment

An investigator not involved in patient recruitment generated the allocation sequence. Patients were assigned to either early awake-prone group or control group using a 1:1 computer-generated sequence. If found eligible, the resident doctor on duty contacted the designated investigator over the phone for group allocation. Allocation was concealed from the nursing staff, physicians, and the patient prior to that time.

Study intervention in Phase 2

Proning was initiated within 4 h from enrollment in those allocated to awake-prone group. Patients performed awake proning as per recommended guidelines. *(Supplementary 1*, *Figures S1*, *S2*, *Supplementary 4*). Prone-position was maintained for at least 30 min and up to 2 h followed by left-lateral position for 30 min, right-lateral for 30 min and supine or sitting for 30 min [21]. The total cycle duration aimed at 4h. All patients aimed for 6-8h of awake-proning (3-4 cycles) per day and were encouraged to sleep prone. The prone cycle was based on the Ministry of Health and Family Welfare guidelines in India (*Supplementary 4*) [22]. Supplemental oxygen by nasal prongs or facemask was adjusted to maintain a target SpO2 ≥94%. One trained person was designated per prone cycle/patient for assistance, monitoring, adjusting oxygen flow and encouraging efforts. Patients in the control group were not asked to maintain any specific position [23,24].

Standard care

In both groups, standard care was delivered according to the then clinical-practice guidelines of Ministry of Health and Family Welfare [22]. Accordingly, patients received dexamethasone (6 mg intravenous for 10 days), remdesivir (200 mg intravenously on day 1, 100 mg daily for the following 9 days) and subcutaneous prophylactic dose of low molecular weight heparin (enoxaparin 40 mg per day) if no contraindications were present.

Tolerance/intervention failure

Tolerance was monitored using heart rate, blood pressure and respiratory rate at 10, 30, and 120 min (if prone) (*Supplementary 1*) and supplementary oxygen was titrated to maintain Spo_2 ≥94%. The decision to escalate support to HFNO, NIV or intubation was made by the managing physician based on national guidelines (*Supplementary 1*). Proning was terminated if patient required endotracheal intubation, NIV/HFNO support; (as all these patients were then offered proning), death or till hospital discharge. Patients developing systolic BP <90 mm Hg, GCS <12 or seizures discontinued proning.

Measurements

Patient demographic characteristics, oxygen requirement, S/F ratio, arterial blood gases (when feasible) and baseline blood investigations were collected at study entry. (Table 1). The need for mechanical ventilation and all-cause mortality at hospital discharge and at least 30 days after randomization were recorded. All patients were contacted telephonically for mortality follow-up. Further monthly follow-up was done monthly for all patients till the trial ended (Feb 2021).

Outcomes

The outcome in the proof-of-concept phase was S/F ratio in prone as compared to supine position. The primary outcome in the Phase 2 study was 30-day mortality. Secondary outcomes included requirement for mechanical ventilation and time-to-intubation. Additionally, we evaluated in-hospital mortality, hospital length of stay, and need for HFNO/NIV. Safety endpoints included events leading to emergency intubation, rates of pressure sores, musculoskeletal injury, or falls due to proning. Other exploratory outcomes: improvements in S/F ratio at 2h of proning and 30 minutes after resumption of supine position, improvements in P/F ratios (the arterial pO_2 divided by the fraction of inspired oxygen expressed as a decimal) at baseline and 2 h of awake proning where arterial blood gases were available *post-hoc*.

Table 1. Baseline characteristics of both the groups (n=502).

Characteristic	Awake proning group (n=257)	Control group (n=245)
Age (year) mean (SD)	58.2 (12.2)	61.3 (13.0)
Sex-n (%)		
Female	55 (21.4)	67 (27.3)
Male	202 (78.6)	178 (72.7)
Comorbidities-n (%)		
Diabetes	99 (38.5)	98 (40.0)
Hypertension	100 (38.9)	106 (43.2)
COPD/asthma	32 (12.4)	37 (15.1)
Heart disease	28 (10.9)	38 (15.5)
Hypothyroidism	9 (3.5)	9 (3.6)
Cancer	1 (0.3)	5 (0.2)
CKD	3 (1.1)	7 (2.9)
No comorbidity	85 (33.1)	73 (29.8)
Systolic blood pressure (mm Hg), median (IQR)	124 (114-132)	126 (118-138)
FiO_2 requirement at enrollment, median (IQR)	0.32 (24-40)	0.32 (24-40)
Median (IQR) oxygen saturation, SpO_2%	94 (92-95)	94 (93-96)
S/F ratio, baseline Median (IQR)	287 (223-376)	286 (224-378)
P/F ratio, baseline mean (SD) (n=168)	197.3 (70.3)	221.7 (89.3)
Concomitant medications, n (%)		
Dexamethasone	232 (90.3)	230 (93.8)
Low molecular weight heparin (prophylactic)	192 (75.0)	186 (75.9)
Remdesivir	164 (63.8)	158 (64.5)
Convalescent plasma	19 (7.4)	17 (6.9)
Tocilizumab	7 (2.7)	9 (3.7)
Mode of oxygen delivery, n (%)		
No oxygen support	39 (15.4)	43 (17.5)
Nasal prongs	110 (43.5)	98 (40)
Face mask	76 (29.6)	74 (30.2)
Non-rebreather mask	32 (12.5)	30 (12.2)
Laboratory parameters		
Hs CRP (n=303)	34±60.03	37±62.31
Serum IL-6 (n=303)	16.50±40.23	28.4±89.95
D-dimer (n=303)	0.39±1.64	0.28±0.67

SpO_2, oxygen saturation; FiO_2, fraction of inspired oxygen ratio; IL-6, interleukin 6; S/F ratio, ratio of saturation of oxygen to fraction of inspired oxygen; P/F ratio, ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HsCRP, high sensitivity C-reactive protein; IQR, interquartile range.

Statistical analysis

Data are expressed as number of events (percentage), mean (standard deviation) or median (interquartile rage). Data are tabulated descriptively by study group and analysed for all randomized patients in the primary intention-to-treat analysis. A per-protocol analysis (*post-hoc*) was conducted after excluding those who showed major protocol deviations, defined as crossover between intervention protocols and assigned intervention not followed due to any reason. Normally distributed quantitative variables were assessed with the *t*-test. Kaplan-Meier curves are displayed for mortality and time-to-intubation with graphical representation and analysed using a Cox proportional hazards model. There was some missing data for the follow-up mortality but no missing data for other outcomes. There were missing data in the exploratory endpoints. Because data were not missing at random, we did not perform multiple imputation and excluded missing values from analysis. All results are expressed with odds ratio and confidence intervals while those with 2-sided p-value ≤0.05 are considered statistically significant. Statistical analysis was performed with SPSS ver.22.0 (IBM, Armonk, NY, USA).

Results

Phase 1: Proof-of-concept trial

Twenty patients were randomized within 24 hours of confirmation of COVID-19. Of these, 8 required oxygen support at admission and 4 eventually required mechanical ventilation. There was a minimal improvement of mean oxygen saturation (1.75% *versus* 0.25%; two-tailed p=0.128, on paired *t*-test; a net improvement of 1.5%, 95% CI 0.47-3.47); and mean improvement of S/F ratio (6.28 *versus* 1.40, two-tailed p=0.194; and net difference of 4.87, 95% CI - 2.70 to 12.45) (*Figure S3*) in prone phase as compared to supine phase.

Phase 2 trial

Between June 15, 2020, and December 24, 2020, a total of 841 patients were screened and 502 underwent randomization (Figure 1). Two hundred and fifty-seven patients were assigned to awake-prone group and 245 to control group. All 502 patients were included in the primary intention-to-treat analysis. Sixty (23.3%) patients could not perform prone positioning for at least 2 h/day according to protocol despite being assigned to the awake-prone group while 6 patients (2.4%) assigned to control group attempted prone positioning as a choice >2 h/day on their own volition. Hence, 436 patients were included in the per-protocol analysis. The follow-up period ranged from 8-294 days. A total of 44 patients were (8.7%) lost to follow-up (19 in awake-prone and 25 in control group). Mean age (SD) was 59.7 (2.7) years and 24.6% were females. The mean oxygen requirement at admission was 3.6 L/min (FiO_2:0.35). The baseline characteristics of the patients are displayed in Table 1.

Primary outcome

There was no significant difference in 30 day mortality between awake-prone and control groups in the intention to treat or per-protocol analysis (Table 2). In intention-to-treat analysis, in-hospital mortality was 12.1% in the awake-prone group and

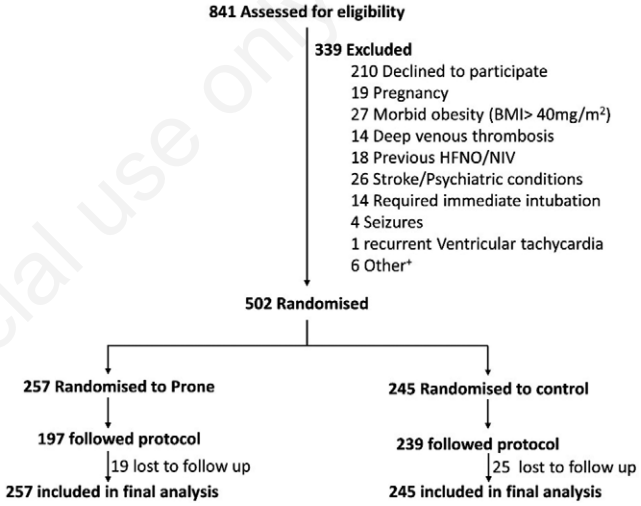


Figure 1. CONSORT diagram depicting enrollment, randomization, and follow-up of trial participants. BMI, body mass index; HFNO/NIV, high flow nasal oxygen, non-invasive ventilation. *Other reasons for exclusion were persistent vomiting, femoral dialysis catheter, treating physician's decision to exclusion.

Table 2. Comparison of primary outcomes of in-hospital mortality, mortality including follow-up period and need for mechanical ventilation between the awake proning and control groups.

Outcome	Awake proning group, n/total (%)	Control group n/total (%)	Odds ratio (95% CI)	p-value
Intention to treat analysis				
30-day mortality (follow-up)	42/257 (16.3)	37/245 (15.1)	1.10 (0.68-1.78)	0.703
In-hospital mortality	31/257 (12.1)	26/245 (10.6)	1.16 (0.66-2.01)	0.609
Requirement for mechanical ventilation	26/257 (10.1)	25/245 (10.2)	0.99 (0.56-1.77)	0.974
Requirement for HFNO/NIV	30/257 (11.7)	27/245 (11.0)	1.07 (0.61-1.85)	0.818
Per protocol analysis				
30-day mortality (follow up)	20/197 (10.2)	36/239 (15.1)	0.64 (0.36-1.14)	0.129
In-hospital mortality	15/197 (7.6)	25/239 (10.5)	0.71 (0.36-1.38)	0.307
Requirement for mechanical ventilation	14/197 (7.1)	24/239 (10.0)	0.69 (0.34-1.36)	0.282
Requirement for HFNO/NIV	16/197 (8.1)	25/239 (10.5)	0.76 (0.39-1.46)	0.406

HFNO, high flow nasal oxygen; NIV, non-invasive ventilation.

10.6% in the control group (p=0. 609). In per-protocol analysis, mortality including follow-up period was 10.2% in the awake-prone group and 15.1% in the control group (p=0.129). Mortality including the longest follow-up period was 16.3% in the awake-prone and 15.1% in the control group (p=0.703). Survival time (in days) since randomization, did not show any significant difference between awake-prone and control groups in intention-to treat [Log-rank test, HR: 1.10 (95%CI, 0.70-1.70), p=0.689] or per protocol analysis (Log-rank test, HR: 0.65 (95%CI, 0.38-0.20, p=0.120) (Figure 2 A,B).

Secondary and other outcomes

Requirement for mechanical ventilation was 10% in both groups (p=0. 974). Likewise, there was no significant difference in time-to-intubation between the groups was observed in intention-to-treat [log-rank test, HR: 1.00 (95%CI, 0.58-1.74), p=0.997] or per protocol analysis [log-rank test, HR: 0.65 (95%CI, 0.33-1.28), p=0.203] (Figure 3 A,B). There was no difference in progression to HFNO/NIV in both groups (Table 2). There was no significant difference in the duration of hospital stay between awake-prone and control group [11.0 (±6.3) *vs* 11.4 (±6.9) days; p=0.583, Independent sample *t*-test]. In the awake-prone group, the mean prone duration was 4.3h (± 2.96), only 83 (32.2%) patients maintained prone positioning for >6 h/day (Figure 4). Mortality was not significantly different among groups with different duration of proning (p=0.256, Kruskal Wallis test). In the awake-prone group, the improvement in S/F ratio after 2 h of proning was significant (mean change: 12.2±34.0, p<0.0001, paired sample *t*-test). This was not sustained after 30 min of resuming supine position (mean change -2.97±64.6, p=0.55, paired sample *t*-test) (Figure 5). P/F ratio at baseline was 197.26 (±70.3) in awake-prone (n=81), and 221.67 (±89.3) in control group (n=85). Paired arterial blood gases at randomization and 2 h of proning were available for 36 patients (16 awake-prone and 20 control group). The P/F ratio was 230.92 (±84.16) in awake-prone and 216.86 (±84.79) in control group which was not significantly different (p=0.623, independent sample *t*-test). The mean improvement after 2 h of proning in the awake-prone group was also not statistically significant (p=0.08, paired sample *t*-test).

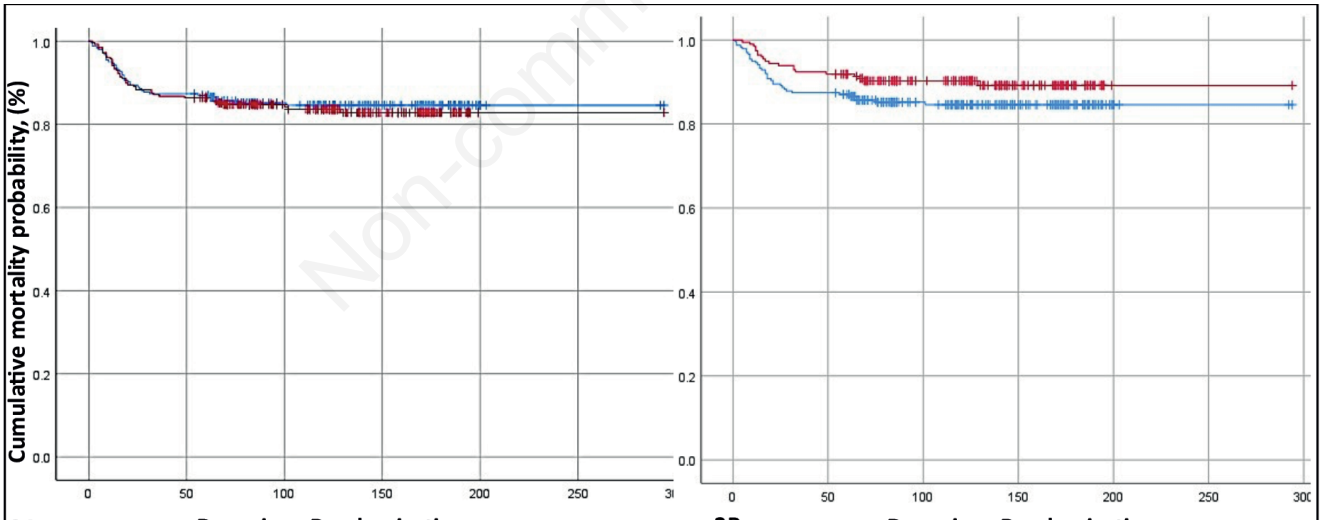
Safety outcomes

None of the participants experienced any proning-related adverse events, pressure sores or injuries. There were 3 emergency intubations in the prone group (one for stroke and worsening GCS and 2 for worsening hypoxemia) and 4 emergency intubations in the control group (one for pulmonary embolism and others for hypoxemia).

Discussion

In this single-center, randomized, open-label clinical trial of patients with moderate COVID-19 hypoxemia, early awake self-proning did not improve 30-day mortality, requirement for intubation or time to intubation. Recommendations for awake proning in COVID-19 have been supported by several clinical practice guidelines [11,25-27]. Awake proning has also been proposed as a low-cost intervention COVID-19 hypoxemia in low and middle-income countries [10,28,29].

Initial studies exploring proning, reported significant improve-

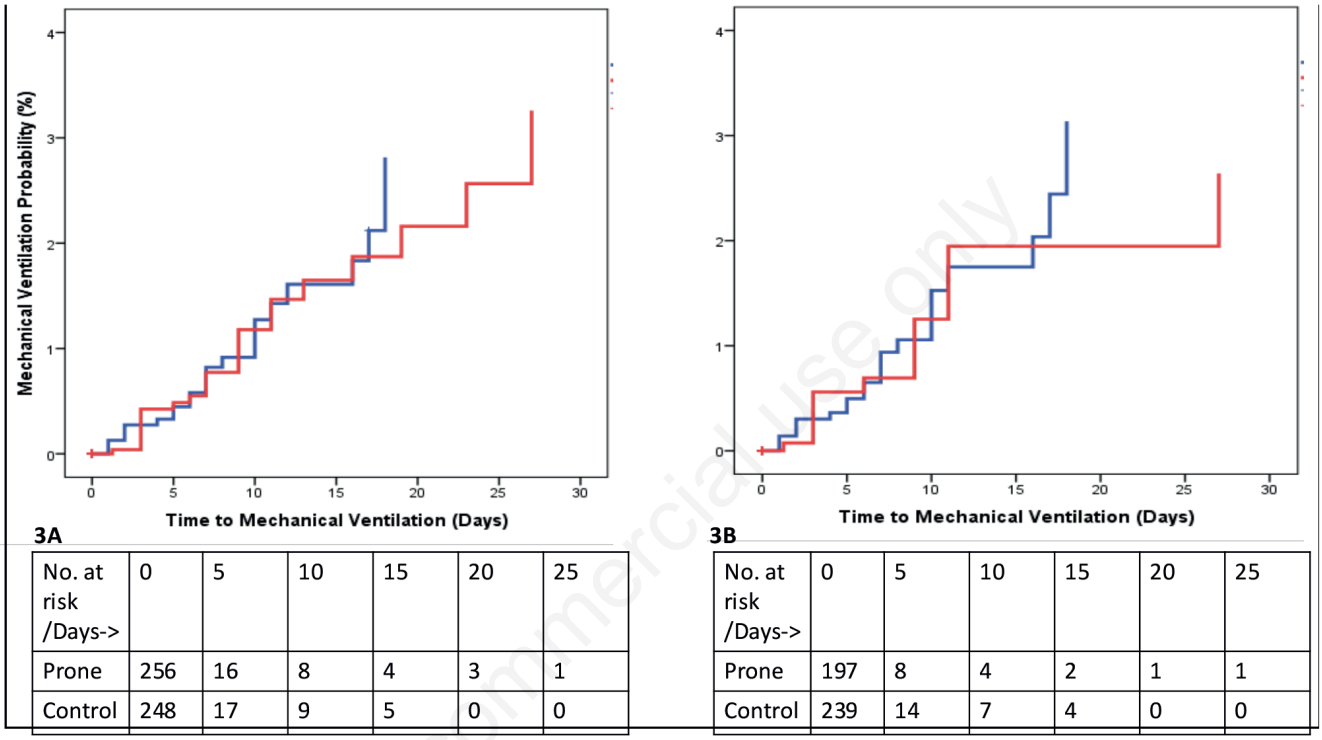


Days No. at risk	0	50	100	150	200	250
Prone	257	222	148	75	1	1
Control	245	213	143	78	7	2

Days No. at risk	0	50	100	150	200
Prone	197	181	120	55	1
Control	239	209	138	88	7

Figure 2. Kaplan-Meier probabilities, estimates population over 30 days after enrollment. A) Probability of survival in ITT. B) Probability of survival per protocol analysis. Red, intervention; blue, control group.

ments in oxygenation in COVID-19 hypoxemia [9,30,31]. In terms of clinically relevant outcomes, a multicentre retrospective observational APRONOX study suggested benefits in mortality and reducing mechanical ventilation, while feasibility trials with sample sizes of 75 and 60 each failed to demonstrate any difference in oxygenation or other outcomes [6,23,24]. A meta-trial (including 6 trials) by Ehrmann *et al*., which included patients on HFNO concluded that there was no difference in mortality between awake proning and standard care groups [16]. However, their results suggested that awake proning reduced the need for intubation [16]. A multicenter trial by Fralick *et al.* reported that awake-proning in non-intubated patients (SPO_2 >90% on nasal prongs) did not improve mortality or intubation rates [14]. Another recent study by Alhazzani *et al*. [17], concluded that awake proning did not significantly reduce endotracheal intubation at 30 days, hence it is unclear whether prone positioning may have some potential benefit as the effect sizes were imprecise. Several explanations maybe possible for these contrasting results.



3A

No. at risk /Days->	0	5	10	15	20	25
Prone	256	16	8	4	3	1
Control	248	17	9	5	0	0

3B

No. at risk /Days->	0	5	10	15	20	25
Prone	197	8	4	2	1	1
Control	239	14	7	4	0	0

Figure 3. Kaplan-Meier probabilities, estimates population over 30 days after enrollment. A) Probability of mechanical ventilation in ITT. B) Probability of mechanical ventilation per protocol analysis. Red, intervention; blue, control group.

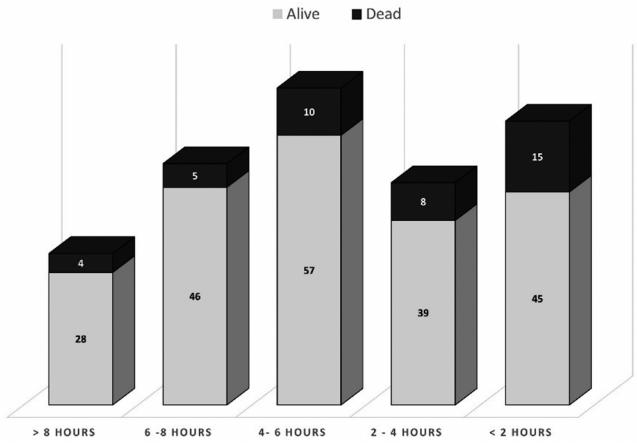


Figure 4. Daily mean duration of prone positioning and mortality in the intervention group (n=257).

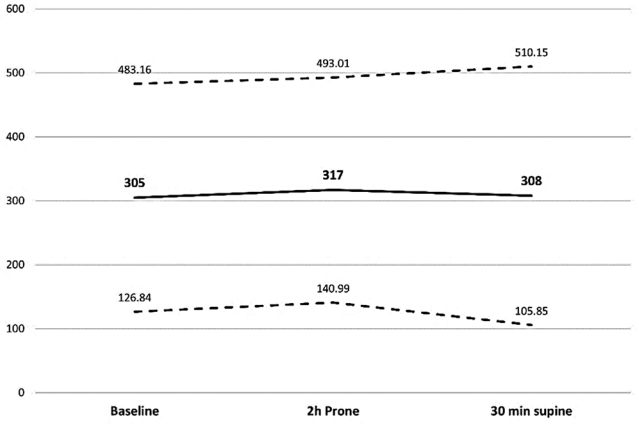


Figure 5. Mean (95%CI) S/F at baseline, 2 h after prone position and 30 min after resuming supine position in the intervention group (n=168).

The median duration of proning in Ehrmann *et al*. [16] and Alhazzani *et al*. [17], was 5 h/day, while it was 4 h/day in our trial and 2.5 h/day in trial by Fralick *et al*. [14]. Even though the results of meta-trial suggested reduction in intubations, the results were driven by one large trial (in Mexico) where the median proning duration was higher (9 h/day) compared to other sites (5 h/day) [16,32]. Indeed, they specifically reported that prone-duration >8 h/day was likely to yield favorable outcomes. Fralick *et al*. [14] and Alhazzani *et al*. [17], did not report significant improvements in any of their outcomes. It appears reasonable to assume that optimal "dose" of proning for sustained benefits may be 8-9 h/day. This was not discernible in our trial as only 12.6% could maintain proning >8 h/day.

Fralick *et al*., suggest several strategies to improve prone adherence including better nurse: patient ratio or presence of ICU physician, to address limitations of their trial [14]. Despite both the above strategies being factored in the current study with a dedicated prone team, adherence was only marginally better- 63% of our patients maintained prone position for at least 2 h/day. Johnson *et al*. explored patient-directed awake proning without support or motivation, and established that protocol adherence was poor [24]. Another trial reported low adherence to proning and large differences between physician-recommended and patient-tolerated prone durations [33]. The emerging evidence highlighting challenges in prone-adherence implies that proning requires greater investments in manpower, time, training and efforts which are limited in supply during pandemic surge in resource-constrained settings [29,34,35]. Patient self-induced lung injury (P-SILI) is hypothesized to be due to focal atelectasis causing force generated by diaphragm to remain localized. Thus, a pressure gradient displaces air preferentially to dependent areas [36]. In awake patients, proning aids uniform distribution of tidal volume and reduces P-SILI.

We hypothesize that in -moderate hypoxemia, P-SILI due to muscle fatigue or work of breathing may not be significant compared to severe hypoxemia. Consequently, the role of prone positioning for lung protection in patients with moderate disease may be limited. In fact, comparing Ehrmann *et al.* [16] and Alhazzani *et al*. [17] (median S/F<150, median FiO_2 0.6 and 0.7, respectively), Fralick *et al*. [14] (S/F: 303, FiO_2: 0.3) and our trial, (S/F 287, FiO_2 0.3), it appears that our trial and Fralick *et al*., enrolling those with less severe hypoxemia did not find proning beneficial. A non-randomized trial concluded that awake-proning might possibly harm patients on nasal prongs and may worsen disease progression- which appears to support our findings [15]. It is possible that proning may benefit patients who have severe hypoxemia or must be initiated when patients worsen rather than early initiation. Thus, optimal timing for initiating proning needs serious exploration in future studies.

Our strengths were having an adequately powered large sample size clinical trial in real-world resource-limited settings, efforts made to encourage prone adherence and good follow-up at 30 days and beyond.

Our study has several limitations. It was a single-centre study. Despite employing the optimal support available in our settings, prone adherence remained a challenge. All patients did not have blood gas analysis before randomization owing to resource constraints.

In conclusion, awake self-proning did not improve survival, mechanical ventilation requirement or time to intubation in patients with moderate COVID-19 hypoxemia. As evidence appears limited, the recommendations to apply it widely in non-intubated patients need to be seriously reconsidered.

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Contributions:

DK, NKC, NK, SM ,VN, provided critical inputs at the design stage; DK, GB, NK, were involved in planning the study; DK, GB, NC, NK, VN, recruitment and data collection; VN, NK, NC, SM, revised the draft manuscript with critical intellectual inputs. All authors read and approved the final manuscript.

Online supplementary material:

1A. Awake prone procedure.

Table S1. Data collection and monitoring proforma used in intervention group.

Figure S1. Schematic diagram of awake prone cycle used in intervention group.

Figure S2. Patient photographs showing prone cycle.

Figure S3. Improvement of SpO_2/FiO_2 ratio in prone phase as compared to supine phase in the proof-of-concept trial.