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A randomised clinical trial of awake prone positioning in COVID-19 suspects with acute hypoxemic respiratory failure

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ABSTRACT

Background: Awake prone position (APP) has been reported to improve oxygenation in patients with COVID-19 disease and to reduce the requirement for invasive mechanical ventilation for patients requiring support with high flow nasal cannula. There is conflicting data for patients requiring lower-level oxygen support.
Research question: Does APP reduce escalation of oxygen support in COVID-19 patients requiring supplementary oxygen?The primary outcome was defined as an escalation of oxygen support from simple supplementary oxygen (NP, HM, NRB) ***to*** NIV (CPAP or BiPAP), HFNC or IMV; **OR** from NIV (CPAP or BiPAP) or HFNC ***to*** IMV by day30.
Study design: Two center, prospective, non-blind, randomised controlled trial. Patients with confirmed or suspected COVID-19 pneumonia requiring $\geq$ 5 liters/min oxygen to maintain saturations $\geq$ 94 % were randomised to either APP or control group. The APP group received a 3-h APP session three times per day for three days.
Results: Between 9 May and July 13, 2021, 89 adults were screened and 61 enrolled, 31 to awake prone position and 30 controls. There was no difference in the primary outcome, 7 (22.6 %) patients randomised to APP and 9 (30.0 %) controls required escalation of oxygen support (OR 0.68 (0.22–2.14), $P = 0.51$). There were no differences in any secondary outcomes, in APP did not improve oxygenation.
Interpretation: In COVID-19 patients, the use of APP did not prevent escalation of oxygen support from supplementary to invasive or non-invasive ventilation or improve patient respiratory physiology.
Trial registration: NCT04853979 (clinicaltrials.gov).

1. Introduction

Approximately 15 % of patients with COVID-19 require hospital admission (variant dependent) and around 5 % admission to an intensive care unit (ICU), with the most common therapy being supplementary oxygen [1–3].

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Awake Prone positioning is a cheap, non-invasive intervention that results in a more uniform alveolar size throughout the lung, improved matching of conformation lung to chest cavity, reduces compressive effects of the diaphragm and heart, reduces regional hyperinflation and facilitates alveolar recruitment with little effect on pulmonary perfusion, so improving oxygenation [4,5]. High-quality evidence supports prone positioning combined with lung-protective ventilation in the treatment of patients with severe acute respiratory distress syndrome (ARDS) who require invasive mechanical ventilation (IMV) [6]. Pathological and clinical similarities between COVID-19 pneumonia and ARDS have triggered interest in using awake prone positioning (APP) in non-intubated patients. Small, single-center studies reported early in the pandemic using variable prone positioning duration and not including control groups suggested improved oxygenation for patients with COVID-19 pneumonia [7–9]. More recent, larger observational studies and randomised trials have described using APP improved oxygenation and reduced requirements for IMV in patients requiring respiratory support with high flow nasal cannula (HFNC) but data is conflicting for patients requiring lower levels of oxygen support, with possible harm [7, 10–13]. There is a potential for harm from APP if this transient increase in oxygenation provides clinicians with false reassurance and delays escalation of care, particularly to intubation. A recent best practice guideline recommended APP for patients with COVID-19 who required oxygen therapy with HFNC or noninvasive ventilation (NIV) but found insufficient evidence to make recommendations for patients requiring lower levels of oxygen support [14]. We conducted a randomised clinical trial for patients admitted to hospital with COVID19 pneumonia requiring $\geq$ 5 L per minute oxygen supplementation by nasal prongs (NP), Hudson masks (HM) *or* noninvasive ventilation (NIV) with FiO_2<0.4 to achieve a saturation of >94 % to assess if early and consistent use of APP would reduce the need for escalation of care.

2. Methods

2.1. Trial design

We conducted a randomised, non-blinded, superiority trial in two designated COVID-19 hospitals following local guidelines, the 1964 declaration of Helsinki, and Consolidated Standards of Reporting Trials (CONSORT) guidelines (registered on clinicaltrials.gov on April 22, 2021, NCT04853979). Ethical approval was obtained from the HMC institutional review board through the Medical Research Center at Hamad Medical Corporation, Qatar (IRB approval MRC-01-20-1227). The trial was overseen by a dedicated trial steering committee and an independent data safety monitoring board (DSMB).

2.2. Participants

Adults ($\geq$ 18 years) with suspected or confirmed COVID-19 pneumonia were recruited within 24 h of hospital admission. All patients underwent a SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) test. Inclusion and exclusion criteria are described in Table 1. Participants were recruited from two similarly resourced, dedicated.

COVID-19 hospitals both offering treatment along national guidelines (Hazem Mebaireek General Hospital and The Cuban Hospital, Qatar).

2.3. Randomization and masking

A computer program generated block-randomization codes in blocks of four and six. Codes were concealed in opaque envelopes until consent was obtained. Allocation to the study groups were in a ratio of 1:1. Due to the nature of the study intervention participants, staff and researchers could not be blinded.

Table 1
Inclusion and exclusion criteria.

Inclusion	Exclusion
1. Adult $\geq$ 18 years with suspected or confirmed COVID 19 pneumonia 2. Patients who required $\geq$ 5L supplementary oxygen via face mask (NP, HM, NRB) *or* NFNC/NIV FiO_2 (fraction inspired oxygen) $\geq$ 0.4 and/or positive end expiratory pressure $\geq$ 5 cm of water to achieve oxygen saturation (SpO_2) measured by pulse oximetry $\geq$ 94 %. 3. Requiring oxygen therapy initiated within 24 h of hospital	1. Patients requiring immediate IMV (clinician choice, PaO_2/FiO_2<50, SpO_2/FiO_2 < 90, RR > 60 bpm) 2. Haemodynamic instability requiring vasopressors 3. Multiorgan failure 4. Confusion and unable to understand consent/instructions 5. Agitation requiring any sedation 6. Pneumothorax 7. Any fracture requiring immobilisation 8. APP may exacerbate underlying pain (for example long term back pain or impractical. 9. Pregnancy 10. Obesity (BMI >40) 11. Any abdominal or thoracic surgery <6 weeks) 12. Vulnerable participants (prisoners, unable to understand oral or written study information) 13. Patients with a do-not-resuscitate-order in place and those where the clinicians expressed concern for safety. 14. Unstable spine or pelvis 15. Any contraindication to APP expressed by treating clinical team

2.4. Interventions/protocol

Intervention arm: Patients were asked to assume APP for as long as possible up to 3 h per session with three sessions per day. Patients received nine sessions over a period equal to three study days. Each session was supervised by a research team member. From day four patients were asked to continue these APP patterns. Patients could adopt full prone (flat face down) and/or side prone (using their arm or a pillow to tilt the body one side up) positions. Assigned staff did not alter the oxygen flow rates in the initial 30 min of assuming APP unless the respiratory rate increased by > 5 bpm or the SpO_2 fell by $\geq$ 3 %.In the event of an increase in respiratory rate of $\geq$ 10 bpm or a fall in oxygen saturation by $\geq$ 10 %, the patient was referred to clinical staff for urgent review. Any such cases were reported to the DSMB.

Control group: The control group were asked to adopt their preferred, comfortable position and not advised about APP. A priori, APP could be used as rescue therapy for patients with oxygen requirements of $\geq$ 15 L/min if directed by the treating team, but this was discouraged. If this occurred, the patient would resume their usual care position in the subsequent 3 h block. Apart from APP, there were no differences in the two groups for oxygen targets, bed positioning, and medical management. Oxygen delivery devices, oxygen flow rates, and the decision for escalation to NIV, HFNC, or IMV were at the clinical team's discretion. Patients remained in the trial until they achieved SpO_2 of $\geq$ 94 % on room air > 3 h, required IMV, died, received an alternative diagnosis, or withdrew from the trial. The use of prone position was standard of care in participating hospitals for mechanically ventilated patients with COVID-19 pneumonia/ARDS and PF < 150 on FiO2 $\geq$ 0.6).

2.5. Outcomes

The primary outcome was as an escalation of oxygen support from simple, supplementary oxygen (NP, HM, NRB) ***to*** NIV (CPAP or BiPAP), HFNC or IMV; **OR** from NIV (CPAP or BiPAP) or HFNC ***to*** IMV in each group by day 30. The choice of NIV or HFNC was clinician dependent with available resources for each device in part determining use.

Secondary outcomes were changes in physiology, duration of APP, 30-day mortality, ICU- and hospital length-of-stay, the use of rescue prone, prone failures (patients with a fall in SpO_2 >5 % or increase in RR > 10 bpm or inability to maintain prone position for >60 min) and harm associated to APP. Physiology data included respiratory rate (RR), SpO2, SF ratio (SpO2 measured by co-oximetry: fraction of inspired oxygen (FiO_2)), ROX index (SF ratio: RR), pulse (P), and blood pressure (BP). Arterial blood gases were not protocolized, and the fraction inspired oxygen for SF ratio was estimated after Vincent et al. [15]. The recorded adverse effects associated to APP included skin breakdown, pressure areas, displaced medical devices, muscle/back pain requiring analgesia, nausea/vomiting, and hemodynamic instability (arrhythmia/cardiac arrest/systolic blood pressure <90 mmHg).

2.6. Data collection

The research team recorded data by directly observing the patient for nine sessions during the first three study days. Data included for each (3-h) session were duration APP, oxygen device/flow rate/ventilatory settings, and physiology 15 min pre-APP session, 30 min and 2 h post proning, and 15 min post-supination. All patients were followed on days 5, 10, 20, and 30 to collect further data on 1) WHO (World Health Organization) ordinal scale for clinical improvement [16]; 2) use and duration prone position; 3) oxygen device/flow rate/ventilatory settings and physiology.

2.7. Sample size

Local data showed an overall baseline rate of 50 % of patients (meeting trial entry criteria) would have their oxygen therapy escalated. To have 80 % power (with alpha 0.05) to detect a 20 % absolute difference (i.e. from 50 % to 30 %) n = 186 patients were required. Adding approximately 10 % for dropouts we set out to recruit 200 patients.

2.8. Statistical analysis

Normally distributed data was described with mean and SD; non-parametric data were described with median and IQR. Categorical data is presented as proportions. Proportions for the Control and the Prone groups were executed using the Pearson $\chi 2$ test. For any tables where a cell value dropped to five or below, Fisher's exact test was used. All non-parametric comparisons were performed using the Mann-Whitney test. Full analysis is included as supplementary material. The participants were analysed in the group they were randomised into. A secondary analysis was planned for treatment escalation modelled for demographics, physiology, comorbidities and treatment. An interim analysis was planned a priori at 40 patients. This early analysis point was chosen given the lack of data concerning the use of prone position in the study population. All the analyses were performed using Stata MP 14.0 (College Station, Texas).

3. Results

The trial ran 9 May to August 10, 2021 and was stopped prematurely due to declining patient numbers after screening 89 and randomizing 61 patients (31 to APP, 30 to control group, mean age 41.8 years, 88.5 % male, 40 patients recruited in hospital 1 and 21 patients in hospital 2) (CONSORT diagram, Fig. 1).

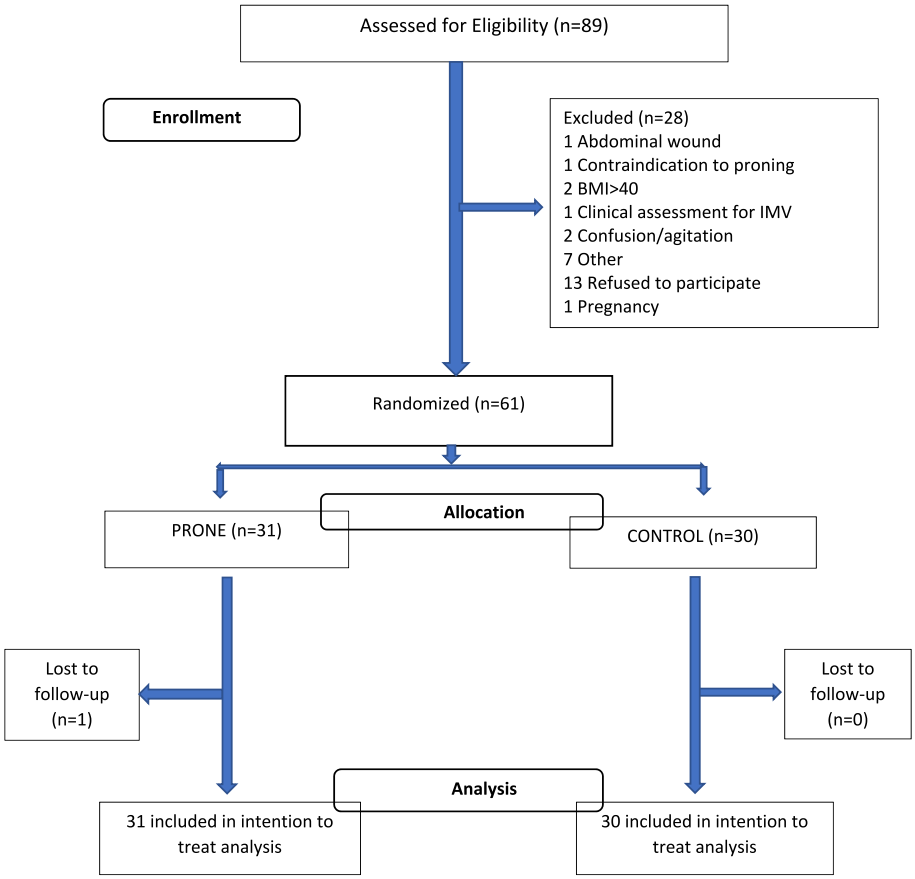

Fig. 1. Prone trial consort diagram..

3.1. Baseline characteristics of the patients

Baseline demographic data, physiology, comorbidities, oxygen support, and medications are presented in Table 2. There was a significantly higher RR in the control group at randomization. However, the SF ratio and ROX at recruitment were not significantly different between groups.

Table 2
Baseline characteristics.

Variables n (%)	Category	Intervention group		*P*-value
		Prone, n = 31 (%)	Control, n = 30 (%)	
Age (Mean ± SD), years		42.4 ± 10.9	41.2 ± 9.5	0.65
Sex, n (%)	Male	29 (93.5)	25 (83.3)	0.21
Ethnicity, n (%)	Arab and North Africa	6 (19.4)	3 (10)	0.19
	Asian	23 (74.2)	27 (90)	
	Sub-Saharan Africa	2 (6.5)	0 (0)	
BMI, kg/m2 (Mean ± SD)		28.4 ± 3.7	27.2 ± 4.6	0.29
Comorbidities, n (%)	Diabetes	14 (45.2)	10 (33.3)	0.34
	Hypertension	6 (19.4)	3 (10)	0.30
	Chronic liver disease	1 (3.2)	0 (0)	0.32
	Asthma	1 (3.2)	1 (3.3)	0.98
	Ischemic Heart Disease	1 (3.2)	2 (6.7)	0.53
	ESRF[a] on dialysis	0	0	
Vaccination, n (%)	First dose	13 (41.9)	15 (50.0)	0.52
	Both dose	12 (38.7)	12 (40.0)	0.92
PCR results, n (%)	Positive	29 (93.5)	27 (90)	0.3
	Negative	0	2 (6.7)	
	Reactive	2 (6.5)	1 (3.3)	
Drug treatment, n (%)	Tocilizumab	4 (12.9)	2 (6.7)	0.41
	Favipiravir	31 (100)	29 (96.7)	0.30
	Remdesivir	4 (12.9)	5 (16.7)	0.67
	Dexamethasone	31 (100)	30 (100)	
	Anakinra	10 (32.3)	12 (40)	0.53
	Plasma	15 (48.4)	20 (66.7)	0.15
	Antibiotic	30 (96.7)	30 (100)	0.32
Baseline parameters at randomization				
O2 device use, n (%)	Nasal prongs	8 (25.8)	8 (26.7)	0.26
	Hudson Mask	15 (48.4)	7 (23.3)	
	Non-rebreather mask	3 (9.7)	7 (23.3)	
	High-flow nasal oxygen	4 (12.9)	7 (23.3)	
	Continuous positive airway pressure (CPAP)	1 (3.2)	1 (3.3)	
Baseline physiology				
	RR (median, IQR)	22 (21–25)	26 (22–30)	0.01
	Oxygen saturation (median, IQR)	97 (96–99)	96.5 (95–98)	0.36
	Pulse (Mean ± SD)	80 ± 14.2	85 ± 11.6	0.09
	SBP (Mean ± SD)	121.8 ± 13	122.4 ± 12	0.86
	DBP (Mean ± SD)	75 ± 9.2	77.6 ± 10.3	0.31
RR/SpO2[b], Median (IQR)		0.23 (0.21–0.26)	0.27 (0.22–0.3)	0.01
SF ratio[b], Median (IQR)		196 (165–245)	196 (182–240)	0.95
ROX[b] index before intervention, Median (IQR)		9.0 (6.3–11)	7.6 (6.6–8.8)	0.14

[a] ESRF = End stage renal failure.
[b] RR = respiratory rate, SF ratio = oxygen saturation to the fraction of inspired oxygen (SpO_2/FiO_2), and ROX index = the ratio of SpO_2/FIO_2 to respiratory rate (SF/RR).

There was no significant difference in overall oxygen delivery devices at randomization. The results of RT-PCR for SARS-CoV-2 were 56 positive, 3 reactive, and 2 negative. Clinical diagnosis was COVID-19 pneumonia in all participants.

3.2. Primary outcome

The primary outcome was observed in 9/30 patients in the control group (30.0 %, 95 % CI, 14.7–49.4 %) and 7/31 in the APP group (22.6 %, 95 % CI, 9.6–41.1 %) (Table 3). There was no difference between the groups in preventing treatment escalation (OR, 0.68; 95 % CI, 0.22–2.14; $P = 00.51$).

3.3. Secondary outcomes

There were no significant differences in secondary outcomes except the WHO score at the end of Day-3 of the intervention ($P = 0.01$) and day 10 ($P = 0.05$) (Table 3). One patient died in APP group on day-20. One patient from the APP group was lost to follow up for day-30; however, their medical records did not show any death event. At randomization the ROX index was non-significantly lower in the control group (Table 3, supplementary data Tables 5 and 6). Plotting of the analysis of variance (ANOVA) interaction term between group (control *vs.* prone) and time point (from pre-proning through post-proning) is shown in Fig. 2. The plot demonstrates no statistically significant association exists between groups' ROX index over time; ROX index in control cases begins and continues to be slightly lower than ROX index in prone cases with no

Table 3
Primary and secondary outcomes.

Variables, n (%)	Intervention group		OR (95 % CI)	*P*-value
	Prone, n = 31 (%)	Control, n = 30 (%)		
Treatment escalation (primary outcome), n (%)	7 (22.6)	9 (30)	0.68 (0.22–2.14)	0.51
Intubation and invasive mechanical ventilation, n (%)	2 (6.5)	2 (6.7)	0.96 (0.13–7.33)	0.97
ROX index				
Intervention Day 1 (Pre-First session)	9.0 (6.3–11.0)	7.6 (5.6–8.8)		0.14
Intervention Day 1 (Post-First session)	10 (8.25–11.75)	7.91 (6.92–8.85)		0.04
Intervention Day 2 (Pre-First session)	10.2 (8.16–12.12)	9.27 (6.74–11.87)		0.21
Intervention Day 2 (Post-First session)	10.6 (7.46–12.25)	8.14 (6.66–11.3)		0.20
Intervention Day 3 (Pre-First session)	10.75 (6.93–12.9)	8.54 (5.66–12.5)		0.32
Intervention Day 3 (Post-First session)	11.1 (7.99–13.06)	9.74 (6.54–11.03)		0.23
ICU admission, n (%)	10 (33.3)	15 (51.7)	0.47 (0.16–1.34)	0.15
Length of ICU stay (Median, IQR), Days	0 (0–4)	2 (0–6)		0.16
Total length of stay, (Median, IQR), Days	11 (8–14)	12 (10–17)		0.45
WHO score, Median (IQR)				
End day 3	4 (3–4)	4 (4–5)		0.01
Day 5	4 (3–4)	4 (4–4)		0.07
Day 10	2 (1–3)	3 (2–4)		0.05
Day 20	1 (0–1)	0 (0–2)		0.48
Day 30	0 (0–0)	0 (0–0)		0.75
Alive at 30 days, n (%)	30 (96.7)	30 (100)	RR 0.96 (0.91–1.03)	0.32

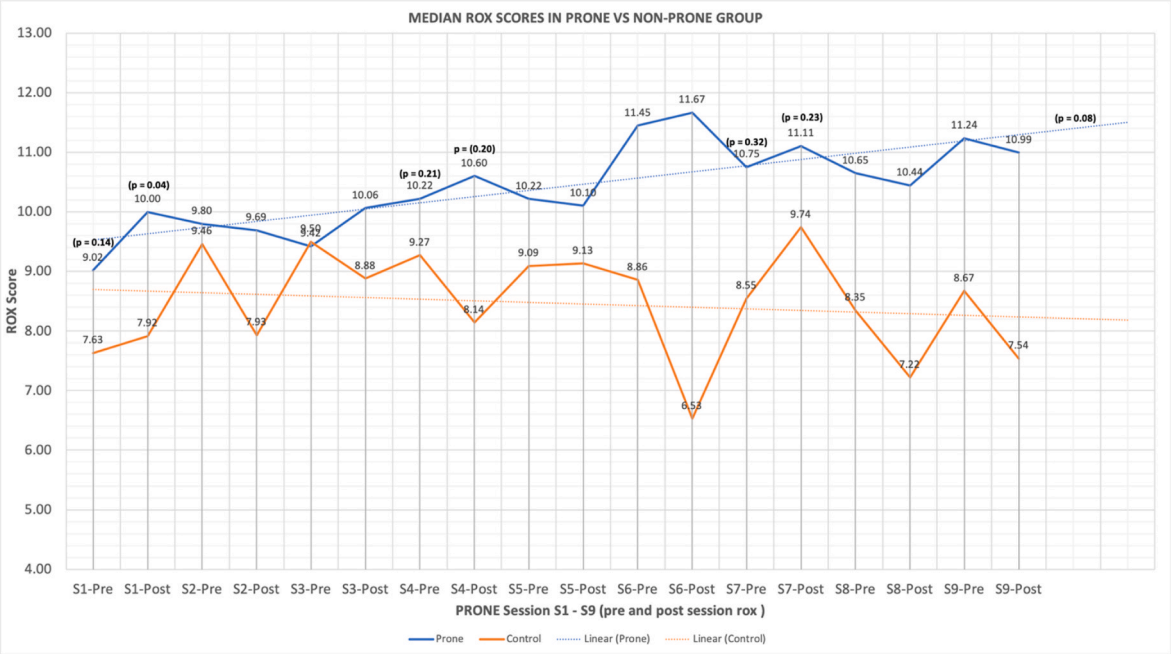

Fig. 2. Median ROX values before awake prone positioning (Pre-APP) and after awake prone positioning (post-APP) for each session for sessions 1–9 and median Pre and Post ROX at identical time points in the control (Ctl) group.
*Significant difference was only observed after the initial APP session (p = 0.04). There was no statistically significant difference between the median ROX for both groups for all APP sessions (p = 0.08).

change in this relationship over time.

3.4. Duration (dose) APP

Day 1–3 the median (IQR) total time spent in APP was 18 (10.5–20.5) hours for the APP group and 0.3 (0–5) hours for the control group (Table 4). In the control group, the treating clinician prescribed rescue prone for 11 (36.7 %) patients (median duration 0 (CI 0–2) hours), and 13 (43.3 %) participants chose to be self-prone at least once.

3.5. Secondary analyses

Comparing groups based on treatment escalation (TE) versus non-escalation (non-TE), the ROX index was 2.34 lower (95 % CI, 0.52–4.16; $P = 0.013$) for cases that ultimately required TE. There were no differences between TE and non-TE groups for age ($P = 0.47$), sex ($P = 0.36$), Indian subcontinent vs non-Indian subcontinent ($P = 0.196$), heart rate ($P = 0.24$), mean blood pressure ($P = 0.5$), and comorbid conditions (diabetes, $P = 0.31$; hypertension $P = 0.67$). The final model for TE prediction included ROX index as well as the therapeutic covariates remdesivir and anakinra. Details of variable selection and model generation are included in supplementary material. The model had acceptable discrimination and calibration. Discrimination was assessed with ROC and the AUC was 0.822. Calibration was assessed formally with the Hosmer-Lemeshow goodness-of-fit test; this test was consistent with acceptable calibration (with risk assessed in deciles): $P = 00.126$. For each 1-unit increase in ROX index the odds of treatment escalation decreased by nearly 25 % (OR, 0.758; 95 % CI, 0.592- 0.971).

3.6. Adverse events

Two patients were reported to the DSMB for meeting apriori defined safety criteria. Both we're receiving HFNC and desaturated on day 2 with improvement on de-proning, with one patient subsequently converted to CPAP. Three patients in the APP group complained of back pain, with one requiring oral analgesia.

4. Discussion

In this two-center randomised, controlled trial of 61 patients with COVID-19 pneumonia APP did not reduce the primary end point of escalation of supportive oxygen therapy from NP/HM/NRB to HFNC/NIV/CPAP/IMV *or* from HFNC/NIV/CPAP to IMV. APP was well tolerated by all but one patient with no adverse events other than musculoskeletal pain. Most patients required low and intermediate oxygen therapy (52.5 % NP/HM, 16.4 % NRB). The proportion of patients requiring HFNC/NIV/IMV was lower than local pilot (2020) data. This may reflect the rapid role out of the local vaccination program, altered clinician thresholds for initiating IMV and/or a differing population with less vulnerability to severe illness. The dominant variant in the initial wave during the pilot study was the (original) Wuhan variant, and the Alpha variant in the study period. In the largest randomised (meta) trial published to date, Ehrmann et al. recruited 1126 patients requiring HFNC support and reported a significant reduction in the composite outcome of treatment failure (requirement for IMV or death at 28 days) in the APP group (40 % vs 46 %,RR 0.86, CI 0.75–0.98), and in intubation rates alone (33 % vs 40 %) [17]. However, the reduction in IMV rates in favor of APP was driven by a single recruiting center, which had the longest duration of APP [18]. This trial recruited patients with higher levels of oxygen support than the trial reported here with consequently higher intubation and death rates. A second multicenter randomised trial recruiting 400 patients requiring oxygen $\geq$ 40 % or non-invasive ventilation reported IMV rates of 34.1 % for patients randomised to APP as compared to 40.5 % controls (hazard ratio 0.81, 95 % CI 0.59–1.12, $P = 0.2$) with no difference in 60-day mortality rates (hazard ratio 0.93, IQR 0.62–1.40, $P = 0.54$) [12]. Prespecified subgroup analysis suggested a greater reduction in IMV rates for patients with an SF ratio of >150 compared to <150. Baseline oxygen and physiology demonstrated higher oxygen requirement than in the trial reported in this journal.

These two trials recruited patients with a greater disease severity than the trial reported here, which combined with its smaller size and early termination likely accounts for the different findings. A two-

Table 4
Time in prone position.

Variables n (%)	Category	Intervention group		*P*-value
		Prone, n = 31 (%)	Control, n = 30 (%)	
Total Prone time (Intervention + rescue + self proning), hours day 1–3	Median (IQR)	18.0 (10.5–20.5)	0.3 (0–5)	<0.001
Day 1	Median (IQR)	6.2 (5.2–7.7)	0 (0–0)	<0.001
Day 2	Median (IQR)	6.3(4.2 + 7.6)	0 (0–1)	<0.001
Day 3	Median (IQR)	5.5 (0–7)	0 (0–0.5)	<0.001
Prone time per day, hours, day 1–3	Median (IQR)	6.2 (5.2–7.7)	0 (0–0.5)	<0.001
Rescue proning day 1–3, number patients	n (%)	0	11 (36.7)	
Rescue proning day 1–3, hours, control group	Median (IQR)	0	0 (0–2)	
Rescue proning day 1–3, hours per patient receiving rescue APP	Median (IQR)	0	2.5 (2–3.3)	
Total self proning time day 1–3, hours	Median (IQR)	0	0 (0–0.75)	
Continuation of allocated treatment	Median (IQR)			
	Day 5	23 (76.6)	18 (64.3)	0.30
	Day 10	22 (75.8)	24 (82.7)	0.51
	Day 20	15 (50)	26 (89.6)	<0.05
	Day 30	17 (58.6)	25 (86.2)	<0.05
Proning time post day 3, hours				
Day 4–5	Median (IQR)	3 (0–6)	0 (0–0.5)	<0.05
Day 6–10	Median (IQR)	2 (0–5)	0 (0–0)	<0.05
Day 11–20	Median (IQR)	0 (0–2)	0 (0–0)	<0.05
Day 21–30	Median (IQR)	0 (0–3)	0 (0–0)	<0.05

center, non-randomised trial of 501 patients (mean age 61.0 years) recruited a diverse group of patients by oxygen requirements, like the trial reported in this journal, with a higher proportion requiring low flow oxygen support at randomization. However, the authors reported considerably higher mortality and IMV rates. There was no difference in IMV (12.0 vs. 12.3 %) or mortality rates (23.4 vs. 21.2 %) in the APP group compared to controls and the former had potentially worse outcomes on day five as assessed using the WHO Ordinal Scale Clinical Outcomes score, and required higher levels of oxygen support [13]. A three-center, randomised trial recruited 60 patients with similar disease severity to the trial reported here ($\geq$ 4 L supplementary oxygen to achieve saturations $\geq$ 92 %) reporting a non-significantly *higher* escalation of respiratory support for patients receiving APP (20 (66.6 %) APP vs. 13 (43.3 %) controls, $P = 0.12$); with a higher proportion requiring treatment escalation than the trial reported in this journal [19].

A key strength of this trial is detailed physiological data day 1–3. At recruitment the SF ratio was similar (mean 192.2±59.4, 191.3± 59.3, $P = 0.95$) between groups. However, the RR was significantly higher (median 26 (IQR 22–30) vs. 22 (IQR 21–25) $P = 0.01$) and the mean ROX index non-significantly lower in the control group (9.0 (6.3–11.0) vs. 7.6 (5.6–8.8), $P = 0.14$). These differences were maintained at similar levels through days 1–3 suggesting APP did not improve respiratory physiology. The change in ROX index was minimal in both groups from day one to three. Previous authors have reported significantly improved oxygenation in patients receiving APP using a range of physiological parameters (lower RR, higher SF or PF ratios, higher ROX index, lower oxygen requirements); however, this data is mainly focused around the initial APP episode [7,9,17,18,20,21], indeed the trial reported here also found a significant improvement in ROX index after the initial 2 APP sessions. There is limited published data on whether these benefits are sustained over the course of the illness. In a multicenter, randomised trial of 430 patients Ibarra-Estrada reported improvements in S/F and ROX index to day 4 in patients randomised to APP. However, this trial included older (58 years), sicker patients (ROX index 5.3 at recruitment, SpO2 < 90 % 15 L NRB) with a longer duration of APP (9.4 (IQR 5.6 to 12.9) hours per day for 6 days) than the trial reported in this issue [18]. The need for higher levels of oxygen support (requiring NRB, NFNC, NIV) was greater in the control group (15 (50 %) vs. 8 (23 %), P = 0.051) at recruitment. The fact that the participants in the control group were arguably sicker than the intervention group may have biased the trial in favor of the intervention being of benefit. This data argues against a physiological benefit for APP in patients requiring low levels of oxygen support.

The dose of APP was significantly higher ($P < 0.001$) in the intervention vs. control arm during each of the first three days of the trial. The median time in APP was similar across each of the 9 sessions days 1–3. From day four onwards the time in APP and the proportion of patients using APP fell. Doses of APP are reported differently by different authors, seeing comparisons challenging. Median times in APP in published trials are 2 (IQR not published), 4.2 (IQT 1.8–6.7), 4.8 (IQR 1.8–8), 5.0 (IQR 1.6–6.8) and 8.5 (IQR 5.2–12.2) hours per day. Ibarra-Estrada et al. contributed the largest data set to the international trial with the highest number of hours in APP (9.5 per day for 6 days) and reported a dose-response effect of time in APP at 8 h[18]. Recent expert guidelines also endorse a dose response relationship, with longer periods of time in APP providing more therapeutic benefit [14]. The negative finding in the trial reported in this journal could be a consequence of lower disease severity, inadequate time in APP or the high cross over rate. The observed crossover rate (36.7 % rescue APP and 43.3 % self APP) is very high, however the duration of time in APP for the control group was very short. The total prone time, which includes the intervention/non-intervention time, rescue time and self-proning, from day one to three was a median of 18 h (CI 10.5–20.5) in the APP group as compared to 0.3 h (CI 0–5) in the control group. Although 11 (36.7 %) patients underwent rescue proning, the median time spent on rescue prone position from day one to three was 0 h (CI 0–2). During the trial 13 (43 %) patients in the control group used APP at some time. Factors influencing this may have included observation of other patients, social media, advice from friends/relatives, and potentially staff. These findings may bias the trial in favor of no benefit for APP being identified. All randomised trials published to date report similar use of APP in the control group, either because of physician directed rescue APP or patient choice, with proportions of APP in control groups varying from 11 % to 100 %.No published trial has achieved the dose of APP aimed at in the trial protocol.

5. Limitations

There are several important limitations to this trial. Firstly, it was terminated early, consequent on falling patient numbers, seeing it underpowered. The patients recruited were less unwell, requiring lower levels of oxygen support than when pilot data was gathered to assist in trial design. Patients recruited were mainly young males from the Indian subcontinent – mean age 41.8 years (other studies range mean 55–65 years [10,17,19,22,23]). APP was widely used in the recruiting hospitals and was included a priori as rescue therapy. Some patients in the control group also choose to use APP. The inadequate group separation and potential staff bias may risk type II error. Detailed APP and physiological data were collected days 1–3 by direct observation but staffing limitations allowed only daily review from day four onwards. The nature of the intervention meant the trial was unblind to patients, staff, and researchers. We randomised patients on arrival at hospital (unless admitted between 2230-0630 as the research team did not work nights).

The primary end point was not protocolized, so different clinicians may have had different criteria for commencing HFNC, CPAP, NIV or IMV. However, there were hospital guidelines in place and there was no limitation/rationing of equipment at any time. ROX index has been used mainly for patients on HFNC and may be inaccurate in patients using NP or mask oxygen delivery with FiO_2 determined by many variables such as tidal volume and inspiratory flow rates.

6. Conclusions

In this randomised clinical trial of patients with COVID-19 pneumonia requiring supplementary oxygen therapy APP did not reduce the need to escalate oxygen support or improve respiratory physiology. The trial was stopped prematurely due to a paucity of patients and is underpowered for the primary end point. The high crossover rate between groups also weakens any conclusions. Logistic regression suggested that ROX may predict treatment escalation in COVID-19 pneumonia; however, future research is required to confirm the finding.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101295.

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