

ORIGINAL RESEARCH

PERIOPERATIVE MEDICINE

Patients self-proning with high-flow nasal cannula improves oxygenation in mild ARDS patients: a randomized clinical trial

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ABSTRACT

Background & Objective: Acute respiratory distress syndrome (ARDS) is characterized by the acute onset of tachypnea, hypoxemia, and loss of lung compliance. Clinicians have employed various means to improve oxygenation in these patients. We evaluated the effect of self-proning with a high-flow nasal cannula in patients with ARDS on oxygenation and the incidence of intubation.

Methodology: Ninety patients, aged above 18 y old, patients with BMI below 30 kg/m², from both genders, suffering from COVID-19 and mild ARDS, participated in this prospective, randomized, double-blind clinical trial at Ain Shams University hospitals. Participants were allocated into two equal groups; Group 1: Patients were subjected to HFNC with a target SpO₂ ≥ 90% with FiO₂ < 0.6. Group 2: Patients were subjected to HFNC with a target of SpO₂ > 90% with FiO₂ ≤ 0.6, and combined with self proning. Upon ICU admission, age, weight, BMI, sex, baseline P_cO₂/F_iO₂ (P/F) ratio, baseline SpO₂ and baseline heart rate were noted. During ICU stay, hemodynamic data and respiratory rate, ABG's were recorded on admission and every six hours after therapy 6, 12, 24, 48, and 96 h till the patient was discharged from ICU. CXR was obtained on admission and at 24 h, and assessed by Berlin criteria. Assuming a rate of intubation of 50% in the group without prone position setting power at 80% and alpha error at 0.05, a sample size of 45 patients per group was needed.

Results: HFNC with proning was effective in improving oxygenation of the mild ARDS patients and decreasing the incidence of intubation; 11 patients in Group 1 and 4 in Group 2 needed to be intubated. Regarding mortality 35 patients survived in Group 1 compared to 42 in Group 2. The median ICU stay was significantly shorter in Group II, 12 (10–12) days compared to Group I, 19 (18–21); P = 0.000.

Conclusion: The use of high-flow nasal cannula and proning reduced the frequency of intubation in mild ARDS patients in ICU, and also decreased the ICU stay and improved the outcome of patients with mild ARDS.

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; HFNC: High-Flow Nasal Cannula; NIV: Non-Invasive Ventilation

Key words: Acute Respiratory Distress Syndrome; COVID-19; High Flow Nasal Cannula; Proning.

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1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) was first described by Ashbaugh and colleagues in 1967. They reported a syndrome characterized by acute onset of tachypnea, hypoxemia, and loss of lung compliance. Significant atelectasis is also frequently present. ARDS can result from direct (e.g., pneumonia, aspiration) or indirect (e.g., sepsis, multiple trauma) insults to the lung and is often associated with a systemic inflammatory response.¹

Whether non-invasive ventilation should be administered in patients with acute hypoxemic respiratory failure is debated. Oxygen therapy with high-flow nasal cannula (HFNC) may offer an alternative in patients with hypoxemia,² and is associated with less mortality & more ventilator-free days than non-invasive ventilation (NIV).³

Proning is the medical term for lying on the tummy or front. Proning has proven to help with breathing in a patient with pneumonia. The prone position (pp) is associated with a decrease in mortality in patients with ARDS, as demonstrated by Guerin in 2013., and the Formal Guide to the treatment of ARDS recommended the use of the prone position for at least 16h a day when $\text{PaO}_2/\text{FiO}_2 < 150$ (moderate-severe ARDS).⁴

Prone positioning is a viable, inexpensive therapy for the treatment of severe ARDS. This maneuver consistently improves systemic oxygenation in 70% to 80% of patients with ARDS. With the utilization of a standardized protocol and a trained and dedicated critical care staff, prone positioning can be performed safely.^{5,6}

We aimed to evaluate the effect of self-proning with a high-flow nasal cannula in patients with ARDS on oxygenation and incidence of intubation.

2. METHODOLOGY

This randomized clinical research was carried out at Ain Shams University hospitals from January 2021 to December 2021. The study was registered with Pan African Clinical Trials Registry with identification code pctr202204746577792, and was approved by the research ethics committee of Ain Shams University (No. FWA00017585).

A prospective, randomized, double-blind clinical trial was conducted on 90 patients suffering from COVID-

19. Written informed consent was obtained from the patient or next of kin. The study protocol was explained to the patients before taking their informed consent. Data collection was carried out by a medical specialist in intensive care medicine.

All patients who met the following criteria were considered for inclusion in the study: aged above 18 y old, patients with BMI below 30 kg/m², from both genders, COVID-positive patients with mild ARDS according to Berlin criteria,⁷ which were confirmed clinically, with bilateral opacities on chest radiographs that were not fully explained by effusions, lobar/lung collapse, or nodules and edema not of the cardiac origin or caused by fluid overload. In the absence of risk factors for ARDS, this required objective assessment (e.g., via echocardiography) and occurrence within 1 week of a known clinical insult or worsening respiratory symptoms upon admission to ICU. While patients were excluded due to inability to collaborate with prone position (PP), agitation or refusal, moderate to severe ARDS ($\text{PaO}_2/\text{FiO}_2$ ratio less than 200), any contraindication to proning, hemodynamic instability, signs of respiratory fatigue (respiratory rate > 40/min, $\text{PaCO}_2 > 50$ mmHg/pH < 7.30, and obvious accessory respiratory muscle use, immediate need of intubation (unable to protect airway or change of mental status).

All patients were admitted to the ICU with mild ARDS and were randomized using a randomization table created by a sequential method, and then we used random allocation off-site and assigned in a 1:1 ratio to one of the following two groups: Group 1: Patients were subjected to HFNC with a target $\text{SpO}_2 \geq 90\%$ with $\text{FiO}_2 < 0.6$. Group 2: Patients were subjected to HFNC with a target of $\text{SpO}_2 > 90\%$ with $\text{FiO}_2 \leq 0.6$, and combined with self proning. At first self-proning was applied with HFNC for at least 30 min, if the patient tolerated it well, the position was maintained. The duration of the prone position was 8 h per day. If in any patient SpO_2 fell < 90%, he was managed according to hospital ICU protocols. No sedation was used with the prone position (PP).

A 20-gauge arterial catheter (Vygon Leader-Cath Arterial PE-(UK)) for ABG sampling was passed. HFNO₂ device (Germany): Servo gas humidifier with heated plate and heated wire (AIRcon gen Respiratory Humidifier WILamed), high flow nasal cannula (oxi. Plus, Nasal High Flow Kit), and Air / O₂ blender

Table 1: Comparative demographic characteristics of the studied patients

Variables		Group I N = 45	Group II N = 45	Test value	P-value
Gender	Female	19 (42.2)	13 (28.9)	C= 1.746	0.186
	Male	26 (57.8)	32 (71.1)		
Age (y)		58.47 ± 10.32	62.24 ± 15.15	t= -1.383	0.170
BMI (kg/m ²)		26.36 ± 4.03	25.09 ± 3.92	t= 1.510	0.135

Data presented as number and percentage for gender and as mean±SD for age and BMI
C: Chi-square test; t: Independent t-test; P > 0.05: non-significant

Table 2: Comparative HR, SpO₂, RR and P/F ratio on admission and during intervention

Parameter	Group I N = 45	Group II N = 45	Test value	P-value
Mean HR on admission	81.20 ± 11.10	77.91 ± 10.86	t = 1.421	0.159
Mean HR during intervention	75.78 ± 16.64	68.53 ± 15.93	t = 2.110	0.038*
Mean SpO ₂ on admission	92.13 ± 1.47	92.62 ± 1.86	t = -1.382	0.170
Mean SpO ₂ during intervention		97.56 ± 2.51	t = -3.150*	0.002**
Mean RR on admission	23.22 ± 2.49	22.24 ± 2.57	t = 1.835	0.070
Mean RR during intervention	22.51 ± 6.76	19.67 ± 5.53	t = 2.184	0.032*
Base line P/F ratio	212.67 ± 23.10	216.00 ± 20.82	t = -0.719	0.474
Mean P/F during intervention	288.64 ± 40.57	324.56 ± 39.89	t = -4.234*	0.000**

Data presented as mean ± SD
P > 0.05: Non significant; *P < 0.05: Significant; **P < 0.01: Highly significant; t: Independent t-test

(WILAmed High _ Flow AIR/O₂ blender with Flowmeter) were used.

Following data were collected;

(a) Upon ICU admission: Age, weight, BMI, sex, baseline P_cO₂/F_iO₂ (P/F) ratio, baseline SpO₂, baseline heart rate.

(b) During ICU Stay: Hemodynamic data and respiratory rate, ABG's were recorded on admission and every six hours after therapy 6, 12, 24, 48, and 96 h till the patient was discharged from ICU. CXR was obtained on admission and at 24 h, and assessed by Berlin criteria.⁷

Our primary outcome was an improvement of the patient or a worsening of his condition proceeding to intubation. While our secondary outcomes were; comparative frequency of complications of prone position and the period of ICU stay and mortality rate in the first 28 days of surgical ICU admission.

Statistical Analysis

Using Power Analysis in Sample Size (PASS) 11 program, for sample size calculation and assuming a rate of intubation of 50% in the group without prone position setting power at 80% and alpha error at 0.05, a sample size of 45 patients per group was needed.

3. RESULTS

There was no statistically significant difference between Group I and Group II regarding the gender, age, and body mass index of the studied patients (Table 1). All patients in both groups suffered from COVID-19 as a cause of their ARDS.

Heart rates on admission were statistically equivalent between Group I and Group II; but significantly lower in Group II during intervention, from 6 to 72 h. The difference was highly significant (P = 0.038) after 12 h of admission, being lower in Group II (Table 2).

SpO₂ readings on admission and at 30 h, 36 h, and 42 h were statistically not different between Group I and Group II (P = 0.170); but were highly significantly higher in Group II after intervention P = 0.002).

There was no significant difference between Group I and Group II regarding respiratory rate (RR) on admission (P = 0.070), and at 30 h, 36 h, and 42 h, while it was statistically lower in Group II after 6 h (P = 0.032).

There was no significant difference between Group I and Group II regarding the P/F ratio on admission (P = 0.474) and after 6 h of therapy and after 30 h, 36 h, and 42 h. While the difference was highly significantly higher in Group II after 12 h (P = 0.000).

Table 3: Comparison between group I and group II regarding rate of intubation, ICU and mortality rate.

Parameter	Group I N = 45	Group II N = 45	Test value	P- value
Intubation	11 (24.4)	4 (8.9)	C = 3.920	0.048*
ICU stay (days)	19 (18–21)	12 (10–12)	Z = -7.777	0.000**
Mortality rate	10 (22.2)	3 (6.7)	C = 4.406	0.036*

*Data presented as number and percentage or Median (IQR)
P > 0.05: Non significant; *P < 0.05: Significant; **P < 0.01: Highly significant
C: Chi-square test; z: Mann-Whitney test*

There was significantly lower rate of intubation in Group II (8.9%) vs. Group I (24.4%) (P = 0.048).

The ICU stay was significantly shorter in Group II, 12 (10–12) days compared to Group I, 19 (18–21); P = 0.000. Both readings given as Median (IQR) (Table 3).

There was a significantly lower mortality rate in Group II compared to Group I; 3(6.7%) vs. 10 (22.2%); P = 0.036.

Regarding complications, 77.8% of patients of Group II had no complications or tolerability problems of proning, while 10 (22.2%) of patients complained of general discomfort and back pain.

4. DISCUSSION

Coronavirus has been one of the most important causes of ARDS in the last three years which causes a rapidly progressing severe lung injury. Lung autopsies have revealed the presence of histologic patterns of diffuse alveolar damage and perivascular T-cell infiltration in the presence of the intracellular severe acute respiratory distress syndrome (ARDS). Coronavirus is known to cause immune dysfunction by activating various proinflammatory cytokines, resembling that of cytokine release syndrome.⁸ During the pandemic, sufficient number of ventilators was not available so we needed alternative ways for oxygenation. Mechanical ventilation has been associated with ventilator-associated pneumonia (VAP), ICU-acquired weakness, delirium, and cognitive impairment.⁹

HFNC offers an alternative way to administer oxygen to hypoxemic patients with ARDS which offers less mortality and more ventilator-free days than non-invasive ventilation (NIV).¹⁰ Proning is the medical term for lying on the tummy or front. The prone position is associated with a decrease in mortality in patients with ARDS. Proning favors lung recruitment, improving V/Q mismatch by decreasing shunt and this results in a more homogenous distribution of ventilation which decreases the risk of ventilator-induced lung injury which is directly related to mortality.⁹ Prone positioning in awake patients promotes better drainage

of the airway secretions and especially when combined with HFNC.¹¹

The formal guidelines to the treatment of ARDS recommend the use of the prone position for at least 16 h a day when P/F ratio < 150 (moderate–severe ARDS).¹²

Many previous studies recommended a combination of awake-prone positioning and HFNC in moderate to severe ARDS patients.^{9,11} To the best of our knowledge, no study evaluated the effect of the combination of HFNC and prone positioning in mild ARDS patients regarding oxygenation and incidence of intubation.

This study shows that SpO₂ was higher in Group II (HFNC+PP) than in Group I (HFNC), this coincides with the studies done by different researchers, who performed an observational cohort study in which they evaluated the efficacy of 4 different support methods HFNC, HFNC+PP, NIV, and NIV+PP, on improving oxygenation and the rate of intubation in moderate to severe non-intubated ARDS patients.^{11,13,14}

Tu et al. in 2021, performed a pilot study on patients diagnosed with COVID-19 on HFNC for more than 2 days and P/F ratio < 150 mmHg.¹³ They applied prone positioning with HFNC and reported an increase in mean blood oxygen saturation after proning from 90% ± 2% to 96% ± 3% and an increase in mean blood O₂ partial pressure from 69 ± 10 to 108 ± 14 mmHg. It was revealed that prone positioning combined with HFNC could improve oxygenation and potentially avoid invasive mechanical ventilation. In 2021, Solverson et al.¹⁴ assessed the tolerability of prone positioning in non-intubated COVID-19 patients with severe hypoxemia. All patients had improved oxygenation when they were in the prone position, (SpO₂ supine 91% (84–95) vs. prone 98% (92–100) with mild improvement in the median (range) of SpO₂:FiO₂ ratio after resupination compared to their baseline (before proning).

In our study, the respiratory rate was lower (more controlled) in Group II (HFNC+PP) than in Group I (HFNC) this coincides with the study done by Solverson et al. in 2021. They reported that the respiratory rate was

lower during proning of their patients [supine 28 (18–38 breath/min) vs prone 22 (15–33 breath/min)].

Our study shows that the P/F ratio was elevated more in Group II (HFNC + proning) than in Group I (HFNC), this coincides with a study done by Ding et al. in 2020.¹¹ PaO₂/FiO₂ ratio in their HFNC+PP group were significantly higher.

There was a lower rate of intubation in Group II (HFNC + PP) than in Group I (HFNC) as documented by Xu et al., in 2020.¹⁵ They performed a retrospective observational study on the effect of an early awake prone position combined with HFNC in 10 patients with severe COVID, all of them had a P/F ratio < 300 mmHg, and they reported that none of these patients required intubation or progressed to critical COVID. This also coincides with Ding et al., who concluded that early application of the prone position plus HFNC, especially in patients with moderate ARDS, may help to avoid intubation.

Our results coincide with the results by Perez-Nieto et al. who performed a multicenter observational study known as the APRONOX study (Awake *PRONe* positioning and *OXYgen* therapy in patients) in which they evaluated intubation and mortality risk in non-intubated COVID patients managed with standard awake supine positioning or with an awake prone position for at least two hours continuously.

On the other hand, Ferrando et al. compared awake prone + HFNC and awake supine patients + HFNC in severe ARDS patients and reported that there was no difference in intubation risk, which differ from our results; and it may be due to fact that their study only included patients with severe ARDS.⁹

Our study shows that ICU stay was shorter in Group II than in Group I. This means that proning with HFNC decreased days of ICU stay in mild ARDS. This was supported by the study done by Slessarev and Cheng in 2020.³ They applied proning and HFNC to patients with severe ARDS.

Also, in our study there was lower mortality rate in Group II than in Group I, as shown by Ding in 2020.¹¹ and Perez-Nieto in 2021.¹²

5. LIMITATIONS

In our study, the hospital stay was not studied; this may be considered in the future studies.

6. CONCLUSION

The results of the present study show that oxygen through a high flow nasal cannula coupled with proning succeeded in decreasing intubation rate in mild ARDS

patients in ICU, and also succeeded in decreasing ICU stay and improving the outcome of mild ARDS patients, when compared to those managed with high flow nasal cannula only.

7. Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

8. Competing interests

The authors declare that they have no competing interests.

9. Funding

No external or industry funding was involved in this study.

10. Authors' contributions

BZN: Designed the study, revised the literature, performed the analysis, followed up the patients, measured and calculated the p/f ratio of the patients, and wrote the manuscript.

MSM: Designed the study, performed the analysis, and wrote and critically revised the manuscript.

HM: Revised the literature, performed the analysis, and critically reviewed the manuscript.

NY: Revised the literature, followed up the patients, measured and calculated the P/F ratio, collected the data, performed the analysis, and critically reviewed the manuscript.

MA: Followed up the patients, measured and calculated the P/F ratio, collected the data, performed the analysis. All authors approved the final version of the manuscript.

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