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Original Article

# Effect of prone positioning and high flow nasal oxygen on oxygenation and overall outcome in spontaneously breathing awake patient with severe COVID-19 induced acute hypoxemic respiratory failure: A prospective observational study



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## ABSTRACT

*Background:* Previous studies suggest that prone positioning can increase  $PaO_2/FiO_2$  and reduce mortality in moderate to severe acute respiratory distress syndrome. Effect of prone positioning and high flow nasal oxygen has been studied individually in COVID-19 patients but their combined effect on patient's outcome is yet to be reported.

*Methods:* In this study 120 severe COVID-19 positive patients were included and placed in awake prone positioning with high flow nasal oxygen. The efficacy in improving oxygenation with prone positioning and high flow nasal oxygen were evaluated by blood gas analysis. The primary outcome was a proportion of patients requiring non-invasive ventilation or invasive ventilation. The secondary outcomes were a comparison of arterial blood gas parameters and biochemical inflammatory parameters pre proning, end of first proning and end of last prone position in these patients.

*Results:* We found only 35 patients (34.3%) required the need for non-invasive or invasive mechanical ventilation support whereas 67 patients (65.7%) were managed successfully on high flow nasal oxygen along with awake prone positioning (p = 0.001). We found there were statistically significant improvements in arterial blood gas parameters and biochemical inflammatory markers after the end of last prone positioning with high flow nasal oxygen.

Conclusions: Early application of prone positioning in combination with high flow nasal oxygen may help in avoiding mechanical ventilation by improving oxygenation and biochemical inflammatory markers. © 2021 Elsevier Ltd. All rights reserved.

## 1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 25 million cases and deaths of over 0.25 million in the India till 21 May 2021 [1]. With rising numbers of cases, more patients are getting admitted to Intensive Care Units (ICUs) with moderate to severe forms of the illness necessitating either non-invasive or invasive ventilation. Intubation and mechanical ventilation put an added strain on already overburdened ICUs in terms of manpower, resource infrastructure and diagnostic services. In addition, it increases the financial burden for healthcare systems and patients, at the same time may decrease their survival chances. Thus, strategies to prevent intubation and mechanical ventilation are urgently needed.

A syndrome like an acute respiratory distress syndrome (ARDS) is one of the main complications of COVID-19 occurring in 20-40% of patients with severe disease. Evidence has demonstrated that prone positioning can improve oxygenation and reduce the 28-day mortality from 32.8-16% (p < 0.001) in non-COVID-19 related ARDS [2]. The improvement in oxygenation in the prone position is the result of better ventilation-perfusion matching. The Surviving Sepsis Campaign COVID-19 guidelines have recommended the prone positioning to be one of the treatment options in COVID-19 related ARDS [3].

High flow nasal oxygen (HFNO) therapy provides oxygen-rich



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heated humidified gas to the patient's nose at flow rates sufficient to deliver a constant, precisely set high fraction of inspired oxygen (FiO<sub>2</sub>). HFNO washes out carbon dioxide from the dead space in the nose and mouth, decreases breathing frequency and work of breathing [4]. However, recent studies showed that in HFNO essentially no positive end-expiratory pressure exists with an open mouth [5]. HFNO is also better tolerated when compared to noninvasive ventilation (NIV) and can be applied continuously for a long period of time. In hypoxemic respiratory failure, HFNO use is associated with lower mortality, lower rates on tracheal intubation and improved oxygenation [6,7]. It has been extensively used early in the COVID-19 patients.

With the global pandemic putting a strain on many countries' resources, awake prone positioning combined with HFNO therapy seems to be of low risk, easy to perform, and low-cost management strategy in non-intubated patients and to avoid intubation. So far, the combined role of early awake prone positioning along with HFNO therapy in the management of severe COVID-19 has not been widely studied and having a limited literature. Hence, we conducted an observational study to evaluate the effect of awake prone positioning along with HFNO on oxygenation in severe COVID-19 patients.

We aimed to conduct a prospective observational study to evaluate the effects of prone positioning combined with HFNO on oxygenation and biochemical inflammatory markers in COVID-19 patients and to assess whether this combination can prevent the intubation rates by improving oxygenation.

## 2. Methods

This prospective observational study was conducted in the ICU of a tertiary care teaching hospital and the largest dedicated COVID-19 care facility under the government of Delhi, India, after prior approval from the institutional ethics committee [F.1/IEC/MAMC/ (79/07/2020/No 200, dated: 24-08-2020]. This trial was registered with the Central Trial Registry India (CTRI) with reference number CTRI/2020/09/027562. Written informed consent to participate was taken from all enrolled patients or their next of kin.

The study was conducted on laboratory-confirmed SARS-CoV-2 infected patients. Infection was defined as a positive result of realtime reverse transcriptase-polymerase chain reaction (RT-PCR) from nasal and pharyngeal swabs in patients older than 12 years of age. Patients with severe COVID-19 pneumonia cases (defined as per Revised Guidelines on Clinical Management of COVID-19 by Government of India Ministry of Health & Family Welfare Directorate General of Health Services, EMR Division) with hypoxemic respiratory failure defined as respiratory rate  $\geq$  25 breaths/min and oxyhaemoglobin saturation (SpO<sub>2</sub>) <94% despite oxygen delivery devices (like 6 L/min via nasal cannula or 15 L/min via nonrebreather facemask) were included in the study. However, patients having PaO<sub>2</sub>/FiO<sub>2</sub>< 50 mmHg, altered sensorium, unstable hemodynamic status, pregnant patients, morbidly obese and those refusing to prone positioning or any other contraindication to prone positioning, like spinal instability, patients at risk of spinal instability (e.g., rheumatoid arthritis), unstable fractures (especially facial and pelvic), anterior burns, chest tubes, recent anterior abdominal surgeries, shock, pregnancy, recent tracheal surgery and raised intracranial pressure were excluded from the study.

Sample size was calculated on the basis of a study published by Despres et al. [8], taking as the primary objective to achieve a 95% confidence level and taking into consideration a 10% attrition rate. A total of 120 patients needed to be recruited for this study.

In included patients, HFNO (AIRVO<sub>2</sub>; Fisher & Paykel Healthcare Limited, Auckland, New Zealand) via a specialized nasal cannula (F&P Optiflow<sup>TM</sup>) was attached with initial settings of 50–60L/min

flow, humidified at 37°c with FiO<sub>2</sub> of 0.6–1.0 (by adjusting the flow meter of blender of AIRVO<sub>2</sub>) depending on patient status. If patients had a stable  $SpO_2 > 90\%$  on HFNO at the above settings, then patients were asked to lie down in prone positioning with the help of a nursing assistant. An arterial blood sample for arterial blood gas (ABG) parameters and venous blood sample for biochemical inflammatory markers were taken before putting the patients in prone position. All patients were asked to follow the awake cyclical repositioning protocol [9]. As per this protocol, patients remained prone for 30 min to 2 h (bed flat) followed by right lateral for 30 min to 1 h (bed flat) followed by a semi sitting position  $(30-60^{\circ})$ by increasing the head end of the bed for 30 min to 1 h and then left lateral (bed flat) for 30 min to 1 h and then again in the prone position. This cycle was continued and patients were oxygenated throughout with HFNO. A nurse or assistant helped turn the patient into the prone or lateral position with the support of pillows. No sedation was given to any patients during prone positioning. A repeat sample for ABG and inflammatory biochemical markers were taken at the end of first cycle of awake prone positioning and again at the end of last cycle of prone positioning with HFNC.

At any point during prone positioning, if a patient's  $\text{SpO}_2$  dropped to less than 90% on HFNO at FiO<sub>2</sub> 1.0 and a patient became hemodynamically unstable or uncomfortable due to prone positioning then the patient was immediately changed to the supine position with HFNO at FiO<sub>2</sub> 1.0 and observed for some time. If the patients  $\text{SpO}_2$  improved and became >94% on same settings and was hemodynamically stable, we asked them to lie down again in the prone position and follow the cyclical repositioning protocol.

All patients were closely monitored. At any point if patients SpO<sub>2</sub> remained at <90% on FiO<sub>2</sub> 1.0 through HFNO, RR > 24/minute or patient's sensorium deteriorated even after making them supine, HFNO was removed and patients were either put on bilevel positive airway pressure (BiPAP) mask ventilation or if patient (a) SpO<sub>2</sub> still remained <90% even on NIV with FiO<sub>2</sub> 1.0, (b) Glasgow Coma Scale fall <8, (c) patient became hemodynamically unstable, (d) respiratory distress (respiratory rate >40/min) with hypercarbia (PaCO<sub>2</sub>) >60 mm Hg) [10] even on NIV then patients were either put on invasive ventilation. Blood samples for ABG and same biochemical markers were also withdrawn from a patient before putting the patients on BiPAP mask or invasive ventilation. Apart from awake prone positioning with HFNO, we had used pharmacotherapy in form of i/v steroids, i/v remdesivir and i/v tocilizumab in all study patients unless contraindicated as per then approved recommendations by the World Health Organisation.

The primary outcome was a proportion of patients requiring non-invasive ventilation or invasive ventilation which considered as failure of prone positioning with HFNO protocol. Secondary outcomes were the comparison of ABG parameters [PaO<sub>2</sub>/FiO<sub>2</sub>, PaCO<sub>2</sub>, P(A-a) O<sub>2</sub> gradient, pH], respiratory rate, SpO<sub>2</sub>/FiO<sub>2</sub> ratio and biochemical inflammatory markers [Interluekin-6, Lymphocytes, D-Dimer, pro-calcitonin, lactate dehydrogenase (LDH), serum ferritin] before prone positioning, end of first proning with HFNO and end of last proning with HFNO.

The criteria for stopping prone treatment were improvement in oxygenation (defined as a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of  $\geq$ 150 mm Hg, with a HFNO flow of  $\leq$ 45L/min and an FiO<sub>2</sub> of  $\leq$ 0.6; in the prone group, these criteria had to be met in the supine position at least 4 h after the end of the last prone session) or 28 days in ICU stay whichever was the earliest.

## 3. Statistics

The data was analyzed using the IBM Statistical Package for Social Science (SPSS 24.0 version, IBM Corp., Armonk, N.Y., USA). The collected data was non-normally distributed as assessed by D. Kumar, A. Kumar, A. Kohli et al.



Fig. 1. Line diagram showing trend of ABG parameters with proning (N = 67).

Shapiro-wilk test. Quantitative variables like age of the patients, duration of ICU stay, ABG parameters, respiratory rate, SpO<sub>2</sub>/FiO<sub>2</sub> ratio and values of biochemical markers were expressed as median and interquartile range (IQR) and compared using Friedman test. Qualitative variables like sex of patients, age group and number of patients requiring ventilation or intubation were expressed as frequencies and percentages. They were compared using Chi-square test or Fisher's exact test whenever appropriate. A p-value < 0.05 was considered statistically significant.

## 4. Results

From September to December 2020, we enrolled 120 patients of COVID-19 who were admitted into the ICU with acute hypoxemic respiratory failure. However, only 102 patients were included for statistical analysis as 18 patients could not tolerate prone positioning due to non-compliance to prone positioning.

In our study the median age of patients was 58.5 years (IQR: 51.0, 64.3), 37 (36.3%) patients were female. Fifty-nine (57.8%) patients were below 60 years of age, all other 43 (42.2%) were above 60 years of age. The median duration of proning was 7.8 h (IQR: 3.7–9.0). In our study only 35 patients (34.3%) required ventilatory support [NIV 11 (10.8%) and invasive 24 (23.5%)] whereas 67 patients (65.7%) were managed successfully on HFNO along with awake prone positioning. ABG parameters and inflammatory biomarkers have been compared in those 67 patients. Thirty-five (34.3%) patients who failed HFNO trial were excluded from further statistical analysis.

We compared the ABG parameters at pre-proning, at the end of first proning and at the end of last proning with HFNO and found that there was statistically significant improvement in PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, SpO<sub>2</sub>/FiO<sub>2</sub> ratio, P(A-a) O<sub>2</sub> gradient (Fig. 1) and respiratory rate (Table 1). We also compared inflammatory biochemical markers at above-mentioned time points along with HFNO (Fig. 2) and found that there was significant improvement in serum levels of IL-6, LDH, absolute lymphocytes count and Ferritin (Table 2).



**Fig. 2.** Line diagram showing trend of inflammatory makers with proning (N = 67).

#### 5. Discussion

A massive pandemic outbreak of COVID-19 occurred worldwide in 2020. About 20% of COVID-19 patients developed an acute respiratory distress like syndrome, with mortality ranging from 20% to 50%. Since the publication of the PROSEVA (Prone positioning in severe acute respiratory distress syndrome) trial [2] prone positioning has become a cornerstone of management of mechanically ventilated severe ARDS patients. Recently, prone positioning was reported to enhance oxygenation when combined with HFNO in severe non COVID-19 ARDS [9,11] and to improve lung recruitability when combined with NIV in severe COVID-19 ARDS [12]. The main strength of our study is that, we evaluated the early use of prone positioning combined with HFNO on oxygenation and overall outcome in spontaneously breathing awake patient with COVID-19 induced acute hypoxemic respiratory failure. Our study revealed that prone positioning was safe and associated with improved oxygenation in HFNO patients with severe hypoxemia. We did not observe any major adverse events, such as hemodynamic instability or aspiration. Although the results are encouraging, they should be interpreted with great caution.

In our study only 35 patients (34.3%) required the need of noninvasive or invasive mechanical ventilator support whereas, 67 patients (65.7%) managed successfully on HFNO along with awake prone positioning and discharged from ICU (p = 0.001), which indicated that prone positioning might help to avoid intubation in patients on HFNO. It is an established fact that global morbidity and mortality is certainly more in mechanically ventilated patients. Any form of ventilation not only affects the overall outcome but also adds burden to an already affected health care infrastructure, especially in resource limited settings. Thus, one should adopt all measures to prevent patients from going on to mechanical ventilation.

Ding L. et al., conducted a prospective observational cohort study on efficacy and safety of early prone positioning combined with HFNO or NIV in moderate to severe ARDS. They included 20

#### Table 1

Comparison of ABG parameters and respiratory rate of patients on HFNO at pre-proning, end of first proning and end of last proning (n = 67).

Parameters [in median (IQR)]	Pre-proning	End of first prone positioning	End of last prone positioning	p-value
pH	7.36 (7.29,7.40)	7.35 (7.28,7.41)	7.36 (7.28,7.41)	0.990
PaO <sub>2</sub> (mmHg)	87.0 (75.7, 102.0)	107.5 (85.0,146.3)	118.0 (82.8,157.8)	< <b>0.001</b>
PaO <sub>2</sub> (mmHg)	37.0 (32.0, 41.5)	37.0 (33.0,41.0)	38 (33.8,41.3)	0.996
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	106.2 (81.4,132.5)	158.1 (94.2,211.0)	251.4 (103.6,322.8)	< <b>0.001</b>
SpO <sub>2</sub> /FiO <sub>2</sub>	97.0 (92.0, 116.0)	135.4 (93.0,147.4)	150.2 (115.0,210.0)	< <b>0.001</b>
P(A-a)O <sub>2</sub> gradient (mmHg)	437.4 (411.5,570.4)	300.3 (259.5, 434.7)	167.7 (125.3,426.6)	< <b>0.001</b>
Respiratory rate (RB)/min	26 (22.28)	22 (19.28)	21 (18.30)	0.004

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#### Table-2

Com	parison of inflammator	v biomarkers of	patients on HFNO at	pre-proning, end of first	proning and end of last	proning $(n = 67)$ .

Parameters [in median (IQR)]	Pre-proning	End of first prone positioning	End of last prone positioning	p-value
Procalcitonin (ng/ml)	1.45 (0.93,2.02)	1.18 (1.00,2.00)	1.19 (0.77,2.52)	0.960
LDH (u/L)	750.0 (643.7, 900.0)	568.5 (369.0,783.3)	433.5 (232.8,860.5)	<0.001
IL-6 (pg/ml)	80.0 (49.3,130.8)	46.0 (23.0,92.8)	22.0 (10.8,87.0)	<0.001
D-Dimer (ng/ml)	986.5 (677.2,2052.3)	890.0 (660.0,1467.0)	685.0 (442.5,2000.0)	0.791
S. Ferritin (ng/ml)	481.0 (300.0,643.5)	337.5 (199.5,500.0)	304.5 (190.0,650.0)	0.011
Lymphocytes (per mm <sup>3</sup> )	1687.0 (1200.0,1912.5)	1617.0 (937.5,2082.5)	1900 (1237.5,2500.0)	<0.001

patients in which 11 patients avoided intubation and 9 patients were intubated. They concluded that early application of prone positioning with HFNO, especially in patients with moderate ARDS and baseline  $SpO_2 > 95\%$ , may help to avoid intubation [9]. These results were consistent with our study results however they had a very small sample size and their study was not conducted on COVID-19 patients.

A pilot study by Tu GW et al., on the effects of prone positioning and HFNO in COVID-19 patients with severe hypoxemia, 7 out of 9 patients successfully avoided invasive mechanical ventilation, which indicated that prone positioning along with HFNO might help in avoiding intubation [13]. However, the small sample size of the study precluded the establishment of definitive conclusions. Moreover, they had not evaluated the effect of this combination on detailed ABG parameters and inflammatory biomarkers.

In our study we found a significant increase in PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, SpO<sub>2</sub>/FiO<sub>2</sub> and P(A-a) O<sub>2</sub> gradient after awake prone positioning along with HFNO. These results were consistent with the study conducted by Ding L et al. [9] Although they had used NIV along with HFNO in ARDS patients. APRONET (ARDS Prone Position Network) study was conducted by Guerin C et al. [14] in 2018 and they concluded that prone positioning was used in 32.9% of severe ARDS and was associated with a low rate of complications, a significant increase in oxygenation (by comparing PaO<sub>2</sub>/FiO<sub>2</sub> and SpO<sub>2</sub>/FiO<sub>2</sub>), and a significant decrease in driving pressure.

In our study we also compared the effect of prone positioning along with HFNO on biochemical inflammatory markers and we found there were significant improvement in IL-6, serum ferritin, LDH and lymphocyte counts after the last proning. However, we could not find any change in D-dimer levels with our intervention, this might be due to the fact that most of our patients were already on some form of injectable anticoagulant therapy. A meta-analysis conducted by Zhang ZL et al. [15], in 2020 on laboratory findings of COVID-19 concluded that patients with COVID-19 with increased creactive protein (CRP), increased erythrocyte sedimentation rate (ESR), increased IL-6, lymphopenia, and increased LDH require proper management and if needed should be transferred to an ICU. However, we did not find any study comparing the effect of prone positioning along with HFNO on all ABG parameters along with P (A-a) O<sub>2</sub> gradient and biochemical inflammatory markers in COVID-19 acute hypoxemic patients.

The optimal timing of prone positioning initiation in severe hypoxemia patients with HFNO remains unknown. In the PROSEVA trial, Guerin et al., included ARDS patients with PaO<sub>2</sub>/FiO<sub>2</sub> less than 150 mmHg and FiO<sub>2</sub> at least 0.6 [2]. However, this enrolment criteria included already intubated patients and prone positioning was used as a "salvage therapy". It should be noted that if the invasive mechanical ventilation is inevitable and the situation is emergent, delayed intubation of patients will increase, rather than decrease, the mortality [16,17]. When combined with HFNO, whether prone positioning should be used as "pre-emptive strategy" or "salvage therapy" need to be further evaluated. In our study 18 patients were not able to tolerate prone positioning due to increased respiratory distress (10 patients), morbidly obese (5 patients) and discomfort due to positioning (3 patients) and these patients were excluded from the analysis.

This study has certain limitations. Primarily it is an observational study with no control group, so it may be a selection confounding factor to reach definitive conclusions. Secondly, we have included severe acute hypoxemic respiratory failure patients admitted in a COVID-19 ICU which could have attributed to some bias in assessing the efficacy of awake proning and HFNO. In addition, we have used pharmacotherapy in the form of i/v steroids, i/v remdesivir and i/v tocilizumab wherever indicated as per then approved recommendations which could have been a confounding factor in inflammatory biomarkers estimation.

In conclusion, our study revealed hints that the early institution of prone positioning along with high flow nasal oxygen in spontaneously breathing awake COVID-19 patients has a positive impact on oxygenation thus preventing invasive mechanical ventilation in resource limited settings during the pandemic and also improves biochemical inflammatory markers.

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Nil.

#### **CRediT** authorship contribution statement

**Deepak Kumar:** Conceptualization, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing, Query replies. **Abhijit Kumar:** Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing, Query replies. **Amit Kohli:** Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing, Query replies. **Rahil Singh:** Project administration. **Raman Karthik:** Writing – review & editing.

#### **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.

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