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Prone positioning in the management of spontaneously breathing non intubated covid-19 patients on oxygen therapy: A prospective observational study

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Abstract

Background: There are various studies that suggest that short term and early prone positioning can increase PaO_2/FiO_2 in moderate to severe acute respiratory distress syndrome (ARDS). The aim of our study was to observe the effect of prone position on oxygenation status in spontaneously breathing non intubated covid19 patients on either non rebreathing mask (NRBM) or on noninvasive ventilation (NIV).
Aims: To observe the effect of prone position along with oxygen therapy (NIV or NRBM) on oxygenation in spontaneously breathing none intubated covid19 patient.
Material and Methods: This prospective observational study was performed in a covid19 intensive care unit (ICU) at tertiary care hospital for the period of two months. Non-intubated confirmed RTPCR (Reverse transcription polymerase chain reaction) positive covid19 patients were included and observed who were placed in prone position with NIV BIPAP (Bi level positive airway pressure) or with NRBM by ICU consultant. Primary outcome was oxygenation status from Pao2/fio2 ratio from arterial blood gas analysis. Secondary outcome was hemodynamic parameter and any adverse effect occurred during prone positioning. Collected data were analyzed using SPSS software and P value of Pao_2/Fio_2 ratio of before and after prone position, less than 0.05 considered significant.
Results: We observed among our study participants significant improvement of PaO_2/FiO_2 ratio in both group of patients.
Conclusions: Early use of prone position improved oxygenation in majority of our patients in short periods of time in both NIV and NRBM group of patients.

Keywords: Covid-19, Acute respiratory distress syndrome (ARDS), Prone positioning (PP), Intensive care unit (ICU), Non-invasive ventilation (NIV), Bi-level positive airway pressure (BIPAP) non rebreathing mask (NRBM)

Introduction

Sudden outbreak of covid19 disease found in Wuhan, China in December 2019. Within short span of time, it spreads to more than one continents. It causes severe hypoxemia due to loss of lung perfusion regulation and hypoxic pulmonary vasoconstriction [1] lower pulmonary compliance followed by edema formation [2] leading to large ventilation perfusion mismatch. Ultimately, it become greater challenges for all medical resources.

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Clustering onset of this 2019 nCov results into severe and fatal respiratory diseases such as ARDS [3]. Indian guideline for management of covid19 patients suggest supplemental oxygen therapy through nasal cannula, simple face mask and NRBM [4]. Insufficiency of conventional oxygen therapy due to disease evolution needing extra respiratory supports in forms of HFNC (high flow nasal cannula), NIV, Invasive ventilation or ECMO(extra corporal membrane oxygenation) in case of refractory hypoxemia. NIV-BIPAP or NRBM are routinely used in our institute as per patient's requirement.

Guideline issued by Mohfw (Ministry of health and family welfare) by Government of India and WHO (World health organization) suggested prone position could be applied in critically ill covid19 patient for 12-16 hrs [4, 5]. It improves oxygenation by optimizing lung recruitment and ventilation perfusion matching and reduces mortality in ARDS patient [6, 7].

There is a limited data in the literature on the prone position for short duration in spontaneous ventilated Covid19 patients with oxygen therapy with or without pressure support. Based on this potential beneficial mechanism of prone position, we performed prospective observational study with aim to observe the effect of prone position along with oxygen therapy (NIV or NRBM) on oxygenation in spontaneously breathing non intubated covid19 patient.

Subjects and Methods

This prospective observational study was performed in a covid19 intensive care unit (ICU) at tertiary care hospital for the period of two months (August-Sept 2020).

The study was approved by the ethics committees of our institution (GMCS/STU/ETHICS/APPROVAL/10617/20). This study was also registered prospectively online under clinical trial registry of India (CTRI/2020/07/026797).

Patient's selection

The inclusion criteria were patients of both sex, aged between 18 to 60 years of confirmed RTPCR positive non intubated spontaneously breathing covid19 patients on oxygen therapy with NIV or NRBM.

Exclusion criteria were patients refusal, signs of respiratory fatigue (RR>40/min, PH<7.2, $Paco_2$>50mmHg, obvious use of accessory muscle), Immediate need for intubation, hemodynamically unstable patients, patients with abdominal surgery and lumber lordosis.

Sample size

The sample size and power of the study analysis were performed to estimate the total number of patients required to be included in our study. It was estimated that a minimum of 111 patients would be required to ensure with a 95% confidence level and a confidence interval of 4, to estimate 80+/-5% outcome factor based on previous studies [8].

In Covid19 ICU, patients full filling the inclusion criteria were in supine position but planned to give prone position by ICU consultant were included in our study within 36 hours of admission.

These patients were turned to prone position as per protocol in our institute by ICU consultant. Prone positioning by him or herself or with the help of the trained medical/paramedical staff, consist of placing patient on his or her stomach with the head on one side, for at least three hours during day. We noted related data till patient turned to supine or up to maximum 3 hours, whichever was first. General care for safety of patient and respiratory care were taken.

We observed the effect of prone position on oxygenation in terms of PaO_2/FiO_2 ratio by

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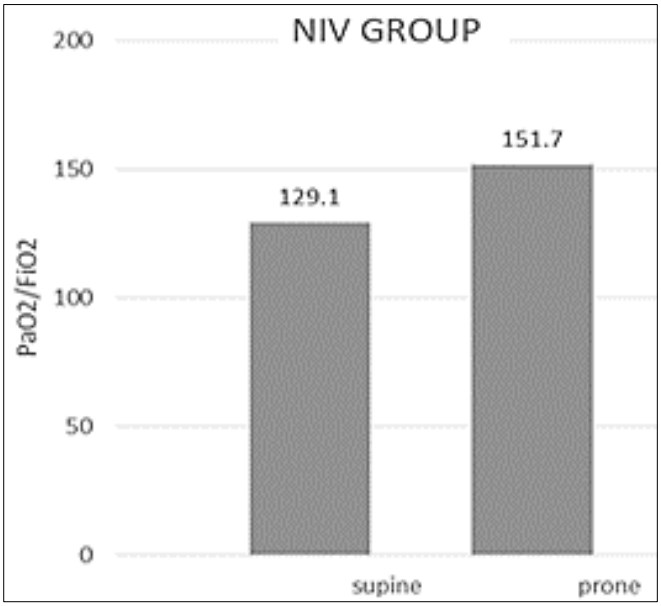
ABGA (arterial blood gas analysis) with ventilator strategies in NIV group and by ABGA with oxygen flow rate in NRBM group at 1 hour after prone position and at time when patients turned to supine or at 3 hrs. whichever was first. As our institutional protocol, Repeat ABGA was only done if we got worsening result after one hour to avoid multiple pricks and patient dissatisfaction. Patients maintained prone position up to their tolerance and this duration was noted. We ensured that Ventilator's parameter FiO_2, PEEP (positive end expiratory pressure) etc did not change during observation.

We also observed hemodynamic parameter (pulse, blood pressure, respiratory rate and oxygen saturation) at 2min up to 10 min and every 15 min interval for initial 1 hr and then hourly interval till patients turned to supine or maximum 3 hrs. whichever was first. We also noted down any adverse event during prone position like desaturation, hypotension, arrhythmia, venous catheter lodgment etc. We also noted down age, sex, weight, history in brief including comorbidities, diagnosis, total hours of prone position, general and systemic examination findings. We did not interfere to consultant critical intensivist/doctors allotted for management of covid-19 patient in the ICU. Any change in PaO_2/FiO_2 ratio of at least 10% of baseline or (≥10 mmHg) during 1st hour of prone position is considered as primary responder and after 1st hour considered as secondary responder.

Results

Table 1: Clinico-social characteristics of study participants [N=110]

Variable	Group		P value
	NIV Group [-N=70]	NRBM Group [-N=40]	
Mean Age [in year]	51.5 ± 8.0	51 ± 9.2	>0.05
Gender			
Male	50 [71.4%]	25 [61%]	>0.05
Female	20 [28.6%]	16 [39%]	>0.05
Mean BMI [wt/ht^2]	26.8 ± 4.4	25.3 ± 3.8	>0.05
Medical H/O			
DM	24 [34.3%]	12 [30.0%]	>0.05
HTN	17 [24.3%]	09 [22.5%]	>0.05
Others	08 [11.4%]	04 [10.0%]	>0.05



Graph 1: ABGA before and after prone among NIV group after one hour [N =70]

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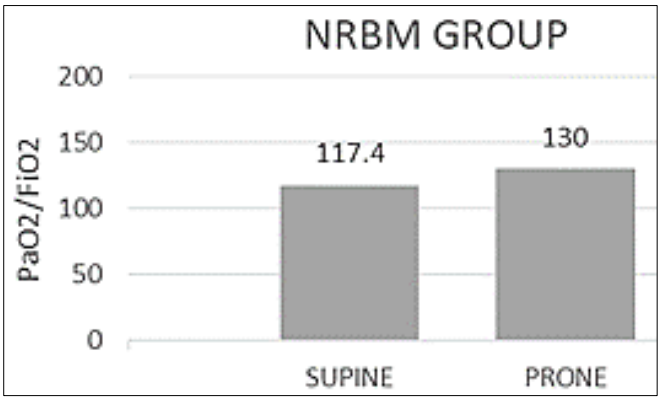

Graph 2: ABGA before and after prone among NRBM group after one hour [N =40]

Mean PaO_2/FiO_2 ratio in NIV and NRBM group after prone position is statistically significant ($p<0.05$).

Table 2: Total duration of prone position

	NIV Group [N=70]	NRBM Group [N=40]	P value
Total Duration of prone position [in min] (mean+/- SD)	124.1 ± 39	131.7 ± 42.1	>0.05

Statistical analysis: The data collected was entered into a database Microsoft excel sheet. The results were expressed as mean ± standard deviation. The statistical analysis was done using SPSS software using the "two tailed student's t test". The difference was considered to be statistically significant when P value < 0.05.

The patients in our study were in age group between 18 to 60 years. There was no significant difference in mean age, BMI and medical history among patients in both groups. Male patients were more than female patients in both groups. [Table 1]

We totally enrolled 111 eligible covid19 patients in our study. We observed 41 patients who were on NRBM and 70 patients who were on BIPAP support. But one patient left the prone position after 15-20 minutes of NRBM group. So we excluded that patient.

Graph 1 shows that in NIV group mean PaO_2/FiO_2 ratio was 129.1 ± 52.3 in supine position and after 1 hour of prone position 151.7 ± 66.6[$p<0.05$] Graph 2 shows that Mean PaO_2/FiO_2 ratio was 117.4 ± 40.6 in supine position and 130.0 ± 42.1 after 1 hour of prone position of group NRBM [$p<0.05$].

In our study, subgroup analysis, in NIV group (n=70 patients), 60 patients (85.7%) are primary responder and 10 patients (14.3%) are secondary responder. Out of this 10 patients, 1 patient (10%) has same PaO_2/FiO_2 ratio after 1hour. 3 patients (30%) had decreased $PaO2/FiO_2$ ratio after one hour. And 6 patients (60%) had improved PaO_2/FiO_2 ratio but that is less than 10 mm Hg. In NRBM group (n=40 patients), 30 patients (75%) were primary responder. And 10 patients (25%) were secondary responder. Out of this 10 secondary responder, 4 patients (40%) had decreased PaO_2/FiO_2 ratio and 6 patients (60%) had improved PaO_2/FiO_2 ratio but that was less than 10 mmHg.

There were no significant changes noted in hemodynamic parameter after prone position. No side effect were noted in any group of our patient during our study.

Discussion

This study was conducted during first covid19 pandemic wave at tertiary health care center with main strength of this study was that for the first time we evaluated effectiveness of prone position in spontaneously breathed covid-19 patients who were on oxygen therapy with or

without pressure support?

SARS CoV-2 virus associated with severe impairment of ventilation/perfusion matching due to defect in hypoxic pulmonary vasoconstriction and presence of thrombi in pulmonary microcirculation leading to high intrapulmonary shunt and dead space, hypoxemic respiratory failure due to direct cytopathic effect over pneumocyte and decrease surfactant level causes atelectasis and significant systemic damage due to dysegulated and excessive immune response(cytokine storm) [2, 9-10] Because of these different pathophysiological mechanism, overwhelming number of patient presented to the hospital with requirement of oxygen only or oxygen with pressure support or invasive ventilation.

NIV-BIPAP, as name suggest it applies PEEP (positive end expiratory pressure) and pressure support which increases functional residual capacity and opens collapsed alveoli resulting into improving ventilation/perfusion matching. In contrast, NRBM provides higher concentration of oxygen without pressure support. NIV and NRBM both were used to improve oxygenation as per patient's requirements. So, we included both type of covid19 patients who required oxygen support with or without pressure support and evaluated effectiveness of prone position over them.

Infiltration is the main characteristics of ARDS. In supine position, this infiltrates accumulates and compromise posterior alveoli affecting ventilation. The anterior alveoli which are fewer than posterior alveoli are only available to maintain ventilation [11]. However, prone position unloaded weight of intra-thoracic and intra-abdominal viscera from the lung and relieves restricted diaphragmatic excursion resulting into the recruitment of atelectatic dorsal lung areas. Apart from it, prone position increases aeration of poorly ventilated dorsal part of lung that are rich in gravity dependent blood flow are placed in nondependent position indicated by finding of Scholten EL *et al.* [12] Moreover, it is new for all of us, what is the effect of prone position over covid19 patients as it has uniquely affects the lungs.so we conducted this observational study.

The favorable response of prone position that we observed among our study participants significant improvement of PaO_2/FiO_2 ratio in both NIV group and NRBM group of patients.

Our primary outcome is observation of oxygenation status of the patient after prone position by PaO_2/FiO_2 ratio measured from ABGA analysis. Our mean PaO_2/FiO_2 ratio in prone position is (151.7 ± 66.6) which is higher than in supine position(129.1 ± 52.3%) after one hour in NIV group [Figure 1], which is statistically significant. Same as in NRBM group, PaO_2/FiO_2 ratio is 130.0 ± 42.1 in prone position [Figure 2], which is higher than supine position (117.4 ± 40.6) which supports result of Ling Ding *et al.*(2020) [13]. They found that PaO_2/FiO_2 ratio was significantly higher in HFNC+PP than in HFNC (130 ± 35mmHg vs 95 ± 22mmHg, P = 0.016). PaO_2/FiO_2 ratio had an upward trend when PP was added to NIV (166 ± 12mmHg vs 140 ± 30mmHg, P = 0.133).

Simioli F *et al.* [14] studied of early Prone Positioning and Non-Invasive Ventilation in a Critical COVID-19 Subset. A Single Centre Experience in Southern Italy. They found Baseline P/F was homogeneously distributed being 96.5 (±35) in group P (prone compliant) and 95 (±92) in group nP. (Non-compliant to prone). PaO_2/FiO_2 ratio during NIV considerably improved in both the groups, being 175.5 (±94) in group P and 175 (±136) in group nP. PaO_2/FiO_2 ratio during PP significantly increased in group P compared with group nP (288±80 vs. 202±122; mean difference, 115.0; p=0.0002), which is similar to our results that improvement in PaO2/FiO2 ratio found more in NIV group (151.7 ± 66.6 vs 129.1 ± 52.3).

In our study, Significant improvement in PaO_2/FiO_2 ratio in NIV group during prone position in covid19 patients due to effect of pressure support as well as proning which improves ventilation perfusion matching, possibly favored redistribution of from dorsal to ventral area. Yagui AC *et al.* [15] also concluded that for improvement of oxygenation in the prone position, it is of fundamental importance that alveoli be opened using PEEP or perhaps

alveolar recruitment maneuvers.
We used an increase PiO2/FiO2 ratio during prone position of at least 10 mmHg as cutoff to define the response to prone position in terms of oxygenation. Using this definition, 60 patients (85.7%) are primary responder in NIV group and 30 patients (75%) were primary responder in NRBM group, which is nearly similar with Blanch *et al.* study they indicated prone position improved oxygenation in the majority (69%) of critically ill patients with ARDS. [16] Elharrar *et al.* have yet ascertained that only 25% were responded to prone position [17] however our observation showed more promising result than him.
We also observed in secondary responder, 3(30%) patients out of 10 (14.3%) and 4 (40%) patients out of 10 (25%) decreased PaO_2/FiO_2 ratio after 1 hour of prone position in NIV and NRBM group respectively, which is improved later on, that may be due to complex pathophysiology of covid-19.
We observed one patient in NRBM group, PaO_2/FiO_2 ratio was significantly increased from 143.3 to 274.4 after 3 hours of prone position, whose PaO_2/FiO_2 ratio after 1hour of prone position was 141.1. Same as in NIV group, PaO_2/FiO_2 ratio was 60 vs 160 after 3 hours of prone position, which was 69 after 1 hour. Such type of slow improvement also observed by Schifino G *et al.* [18]
Primary responder and secondary responder did not differ from another except they admitted to the hospital after 5 to 6 days of onset of symptoms.
We observed Mean duration of prone position was 124.1 minutes with 39 SD and 131.7 minutes with 42.1 SD of group NIV and NRBM respectively[Table:2]. We believe that education regarding beneficial effect with side effect of prone position and encouragement may further improves tolerability of position. Our only one patient drop out this position that is due to subjective reason.
No clinically relevant differences noted in hemodynamic parameters.
We did not observed clinically relevant adverse effects because of proper care of continuation of oxygen tubing, ventilator circuit and IV lines during turning from supine to prone and vigilant monitoring of continuous oxygen plethysmography and other vitals parameter during entire prone position periods by ICU team.

Limitations

Several limitation of our study exist.
Several experimental covid19 therapy were tested during observation of present study (plasma therapy, methylene blue trial, Remdesivir trial etc.) which may affect the study result.
Not all covid19 patients managed with NIV and NRBM, possibly causes misclassification bias and we do not have control group observation. Effectiveness of prone position after changing of position from prone to supine needs to rule out. RCT is required which will demonstrate mortality benefit of prone position. Lastly, it should also be noted that study was conducted in India and there by the environment and resources might be different from other countries.

Conclusion

We observed that awake, spontaneously breathing covid19 patients who were on oxygen therapy in form of noninvasive ventilation or non-rebreathing mask, Using prone position had a favorable effect on oxygenation status as it improves PaO_2/FiO_2 ratio.
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