Original Research Article

Effectiveness and safety of non invasive pressure ventilation in severe COVID-19 disease: A retrospective analysis

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ARTICLE INFO

Article history:
Received 23-01-2021
Accepted 19-02-2021
Available online 25-08-2021

Keywords:
COVID19 disease
ARDS
NIV
Aerosolization

ABSTRACT

Introduction: Noninvasive ventilation (NIV) has a controversial role in treating acute hypoxemic respiratory failure in Severe COVID-19 disease. Noninvasive ventilation has been known to avoid intubation and prevent complications associated with mechanical ventilation, but the risk of aerosolization and consequent contraction of disease deterred clinicians from using it.

Materials and Methods: The medical records of 18 patients having severe COVID -19 disease with Acute respiratory distress syndrome (ARDS), who received NIV therapy in a tertiary care hospital were scrutinized from a period of 15th June 2020 to 28th June 2020. The parameters like respiratory rate (RR)and PaO2/FiO2(PF ratio) and SOFA score were collected from the day of admission to 5th day of ICU stay. Other parameters like outcomes of NIV therapy, complications and time taken from weaning from NIV were recorded. Forty-five health care workers, involved in the treatment were educated about use of PPE and NIV and were tested for COVID -19 by RT-PCR post-ICU rotation.

Statistical analysis: The statistical analysis was done by statistical package for social science version(SPSS) 22.0. The parameters were compared by using repeated measure analysis of variance.

Results: The mean age group of the patient in the study was 47.44 years. The respiratory rate and PaO2/FiO2 at the time of ICU admission were 29.28±3.74 per minute and 121.06±29.05 respectively. There was significant improvement in PF ratio throughout the observation (p=0.021) and the respiratory rate decreased after NIV therapy from the day of admission to the subsequent days (p=0.001). The major proportion (i.e. 88.8%) of patients with ARDS but SOFA score <5, had a favorable outcome with NIV therapy. 45 HCWs tested negative for SARS-CoV-2.

Conclusion: Non-invasive ventilation can be safely used as an effective therapy for moderate to severe ARDS due to COVID-19 disease.

1. Introduction

COVID-19 Disease, caused by novel Coronavirus SARS-CoV-2 virus was declared a pandemic by World Health Organization (WHO) on 11th March 2010. The disease has a wide spectrum of clinical manifestations ranging from asymptomatic infections to severe ARDS, septic shock, and multi-organ failure. In severe COVID-19 disease with ARDS, treating hypoxemia with oxygen therapy is the main treatment modality for the management of COVID-19 disease. High flow nasal cannula (HFNC), Noninvasive ventilation (NIV), and mechanical ventilation are some of the methods of oxygen therapy in severe cases of COVID-19 disease. Earlier in the pandemic stress was laid on early intubation to treat refractory hypoxemia and minimize aerosolization procedures. In Europe, due to overwhelming resources and shortage of ventilators,
patients were put on NIV therapy but the risk of aerosol dispersion associated with NIV therapy and consequent contraction of COVID-19 disease was a constant fear amongst health care workers. Complications of invasive mechanical ventilation in Severe COVID-19 diseases like high rate of mortality, difficult weaning, barotrauma, and Ventilator-associated pneumonia(VAP) have led to renewed interest in the utility of NIV. In patients with ARDS, HFNC, NIV, and severe cases invasive ventilation is the last resort for the management. The use of NIV has its advantages and disadvantages over endotracheal intubation and invasive mechanical ventilation. But the theoretical risk of dispersion of aerosol and self-induced lung injury prevents clinicians from using NIV.

Therefore, we planned to conduct a retrospective study to evaluate the effectiveness, complications, and more importantly safety of NIV and its effect on clinical parameters in case of severe COVID-19 disease.

2. Materials and Methods

2.1. Study design

We conducted a retrospective observational study from 15th June 2020 to 28th June 2020 in a COVID intensive care unit in a tertiary care hospital in New Delhi, India. After obtaining permission from the institutional ethical committee, the medical records of 28 patients with COVID-19 disease admitted in the ICU during that time interval were retrieved. Out of the 28 patients, 18 patients had ARDS and were treated with NIV. Ten patients did not have ARDS but were given oxygen therapy by non-rebreathing masks. As it was a retrospective study, written consent from the patients or their relatives was not taken.

2.2. Patient selection

Berlin criteria were used to diagnose and determine the severity of ARDS in the ICU patients; The patients were classified as mild ARDS when PaO2 / FiO2 ratio was between 300-200, moderate ARDS when PaO2 /FiO2 ratio was between100-200mmHg, and severe ARDS when PaO2/FiO2 ratio was less than 100 mm Hg.

2.3. Inclusion criteria

1. Patients treated with non-invasive positive pressure ventilation with severe COVID-19 disease.
2. Conscious, oriented patients.
3. No history of risk of aspiration/facial trauma or burns.
4. Hemodynamically stable patients.

Eighteen patients with a diagnosis of ARDS due to COVID 19 Disease who received non-invasive ventilation (NIV) were selected as the study population.

2.4. Exclusion criteria

1. Patients intubated before admission in ICU.
2. Patients treated with oxygen therapy by using non-rebreathing face mask/venturi/face mask and suffering from COVID-19 disease.
3. Unconscious disoriented patients.
4. History of aspiration/facial burns or trauma.
5. Hemodynamically unstable patients.

2.5. Interventions

The patients were counseled regarding the proper use and compliance of NIV. As per the ICU protocol, the patients were started NIV with a mechanical ventilator. NIV was provided by a full-faced non vented NIV mask (Classic Star, Drager) as the interface with the head-up position of 30 degrees. The adult male patients were applied with a large-sized full faced NIV mask whereas the female patients received a medium sized NIV mask. The initial NIV setting was kept at EPAP/IPAP of 6/12Cm H2O. The IPAP of the NIV was adjusted as per the patient’s comfort, relief of dyspnea, respiratory rate <28/min, good patient –ventilation synchrony and to generate a tidal volume up at least 6 to 8 ml/kg of ideal body weight(IBW).

The EPAP of NIV was titrated to achieve minimum carbon dioxide re-breathing and maximize oxygenation. The fraction of oxygen was titrated to maintain SPO2 >90%. The NIV mask was applied for the major part of the day, approximately 18 hours per day except while taking food and resting. Patients were monitored for air leaks, changes in initial symptoms, and any other complications associated with NIV.

The arterial blood gas (ABG) was measured twice a day as per the ICU protocol with a machine. The success of NIV was defined as the avoidance of the need for intubation and discontinuation of NIV for more than 24 hours.

2.6. Monitoring

Any complication associated with NIV, failure leading to intubation, and outcome of the patient was noted. The demographic profile of the patients, as well as the comorbidities, were listed. The clinical parameters at the time of admission in the ICU like Respiratory rate (RR) and oxygen saturation SPO2 and arterial blood gas (ABG) data like PaO2 were obtained and PaO2/FiO2 and SOFA score were calculated from the medical records.

The parameters like respiratory rate (RR) and PAO2/FiO2 were extracted from the medical records daily till the fifth day of ICU stays. The time interval between the application of NIV to weaning from NIV, the outcome of NIV therapy, and complications from NIV therapy were also documented.
2.7. Safety measures

All healthcare workers were briefed and educated about donning, doffing, anti-infective measures, and care of COVID 19 patients on NIV before their posting in the intensive care unit.

All the healthcare workers and paramedical staff were provided with a tight-fitting, fit-tested N 95 mask as well as an appropriate size PPE kit. In the intensive care unit, there were 15 air exchange cycles per hour with good ventilation. After the 14 days’ cycle of the ICU duty, every healthcare workers (HCWs) were provided with 14-day mandatory quarantine with self-monitoring of signs and symptoms of COVID-19 disease. Two samples of nasopharyngeal and oral pharyngeal RT-PCR of all the healthcare workers with a gap of 48 hours were tested for SARCov-2 after the completion of the fifth day of ICU duty.

2.8. Statistical method

Descriptive analysis of the data was done. Categorical data were presented as frequencies whereas numerical data were expressed as numbers /percentages or mean ± standard deviation (SD). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 22.0 The parameters like respiratory rate and PaO2/FiO2 ratio (PF Ratio) were analyzed using repeated measured analysis of variance, with Benferroni adjustments for multiple comparisons). P < 0.05 was considered to be statistically significant.

3. Results

Data from eighteen patients who received NIV were collected from a period of 15th to 28th June 2020 in COVID-19 ICU. Out of 18 patients, 13 were male and the rest were females. The age of the patients was from 24 to 65 years with a mean age of 47.44 yrs. Most of the patients were from age of between 20 years to 40 years (72.20%). Hypertension, Diabetes mellitus, and CAD are the three diseases associated with the study population with a percentage of 38.9%, 27.78%, and 11.11% respectively.

After analysis of arterial blood gas and requirement of oxygen, it was found that 13 out of 18 patients (i.e. 72.20%) had moderate ARDS whereas the rest of the patients had severe ARDS with PaO2/FiO2 less than 100. (Table 1)

| Variables                             | n=18                      |
|---------------------------------------|----------------------------|
| Male gender, No. (%)                  | 5/18 (27.8%)               |
| Female gender, No (%)                 | 13/18 (72.2%)              |
| Age (in years)                        | 47.44                      |
| ARDS Classification (PaO2/FiO2)       |                            |
| Mild ARDS, No (%)                     | 0%                         |
| Moderate ARDS, No (%)                 | 13/18 (72.20%)             |
| Severe ARDS, No (%)                   | 5/18 (27.80%)              |
| SOFA Score                            | 5.11 ± 1.93                |
| PaO2 (day 1 in mmHg)                  | 87.26 ± 16.308             |
| PaO2/Fio2 (Day1)                      | 121.06 ± 29.05             |
| Respiratory Rate (Day 1 in )          | 29.28 ± 3.74               |
| SPO2 (Day 1 in %)                     | 93.28 ± 3.33               |
| PaCO2 (in mmHg)                       | 38.6                       |

Our results showed that the mean age of the patient was 47.44 years ± 10.32. The mean SOFA Score of the patients at the time of admission to ICU was 5.11 ± 1.93. The mean PaO2/Fio2 ratio (PF Ratio) and mean respiratory rate at the day of ICU admission were 121.06 ± 29.05 and 29.28 ± 3.74 per minute respectively. The mean SPO2 on the day of presentation was 93.28 ± 3.33%. The mean baseline PaCO2 level was 38.6 mmHg. (Table 1)

- We found that the mean PF Ratio from Day-1 to 5 were 121.06 ± 29.05, 125.12 ± 32.57, 151.42 ± 47.07, 158.54 ± 44.54 and 177.17 ± 45.34 respectively. There was a significant day-wise improvement in the PaO2/Fio2 ratio from the day of admission in ICU (p=0.021) (Graph 2)

Graph 1: Graphical representation of percentages of patients with different comorbidities.

Graph 2: Graphical representation of PaO2/Fio2 from Day 1 (baseline) to Day 5 of ICU stay

- The mean respiratory rate (RR) from 1st Day of ICU admission to the 5th day was 29.28±3.74 per
minute, 24.67±5 per minute, 21.94±5.54 per minute, 20.69±5.79 per minute, and 19.92±5.89 per minute respectively. There is a statistically significant decline in the mean Respiratory rate from the day of admission in ICU to subsequent days of observation (p=0.001). (Graph 3)

| Days | Respiratory rate (R R) |
|------|------------------------|
| 1    | 30                      |
| 2    | 20                      |
| 3    | 20                      |
| 4    | 20                      |
| 5    | 20                      |

Graph 3: Graphical representation of Respiratory rate from Day 1 (baseline) to Day 5 of ICU stay

- The mean day from a change from NIV to NRBM was ranged from 4 to 18 days with the average days taken from initiation of NIV to application of Non-rebreathing mask was 8.19±4.60 Days.
- There was no correlation found between severity of ARDS and days of weaning from NIV to other oxygen devices.

4. Outcome & Complications
Out of 18 patients, two patients were eventually intubated due to sepsis and hemodynamic instability and they eventually expired. Sixteen patients were successfully weaned from NIV and discharged. Those two patients who expired had sepsis and SOFA scores of 9 and 11 at the time of admission.

Two patients out of 16 patients who were weaned from NIV were shifted to Non- COVID ICU after a negative COVID-19 RT-PCR report. One patient developed post-COVID pulmonary fibrosis and has become oxygen dependent. The other patient developed secondary bacterial pneumonia and was intubated on day 26 and eventually expired due to sepsis and multi-organ failure on day 36. (Graph 4 & Table 2)

Personal protective equipment (PPE) was used by all the health care workers (HCWs) inside the ICU as per the standardized hospital protocol. A nasopharyngeal swab was taken from 45 HCWs working in that study period. RT-PCR for SAR-CoV-2 was performed twice after the completion of one cycle of ICU duty with a gap of 48 hrs. None of the reports of HCWs came positive for SAR-CoV-2 and none of them reported signs or symptoms of COVID-19 disease during or 14 days of post ICU rotation.

5. Discussion
As per the World Health Organization (WHO), COVID 19 has been categorized into mild, moderate, and severe disease. Approximately 14% of COVID 19 patients develop severe disease, which includes patients suffering from pneumonia, acute respiratory distress syndrome (ARDS), and sepsis. Such patients are critically ill and approximately 5% of patients require admission to Intensive care units.

Treating hypoxemia with oxygen therapy, with or without mechanical ventilation is a mainstay of treatment in severe COVID 19 disease. An alternative to intubation in COVID 19 ARDS patients is non-invasive ventilation but studies regarding its use in the treatment of ARDS with severe COVID19 disease are lacking. The results of this study show that NIV can be safely used in treating hypoxemia due to acute respiratory failure and preventing invasive ventilation in patients with severe COVID 19 disease. Initially in the pandemic, stress was laid on early intubation to avoid crash intubation in rapidly deteriorating refractory hypoxemia and the risk of aerosol generation deterred clinicians from using NIV. However worldwide reported mortality from invasive ventilation is very high, ranging from 50-97%. There are sporadic case reports on the use of NIV in COVID19 patients in literature but to the best of our knowledge, this is
a first retrospective analysis of the effectiveness and safety of NIV in severe COVID-19.\textsuperscript{10}

The role of NIV is well documented in acute exacerbation of COPD, cardiogenic pulmonary edema, and community-acquired pneumonia, but its role in severe COVID-19 is yet to be investigated.\textsuperscript{11-14} Alraddadi et al in a study of 302 patients concluded that NIV was not useful in acute hypoxicem failure due to Middle East Respiratory Syndrome, in Saudi Arabia.\textsuperscript{15} Cheung et al found NIV to be useful in 70% of patients in acute hypoxicem failure associated with Severe Acute Respiratory Distress, in Hong Kong.\textsuperscript{16} In our study, 16 out of 18 patients (88.8%) with acute hypoxicem respiratory failure and ARDS associated with severe COVID-19 disease were successfully treated with NIV, and intubation was avoided.

The common predictors of NIV failure described in various studies are low PaO2/FiO2 ratio at baseline and after 1 hour of NIV administration and poor Simplified Acute Physiology Score (SAPS). Antonelli et al described the failure of NIV if PaO2/FiO2 was less than 175 and Thille et al described NIV failure if it was less than 150.\textsuperscript{17,18} Both studies concluded that low oxygenation with poor SAPS score was associated with NIV failure. However, in our study, we observed that there was no association between low PaO2/FiO2 ratio and NIV failure. Mean PaO2/FiO2 on day 1 was 122, 125 on day 2, and gradually improved to 175 on day 5. There were 8 patients with severe ARDS (PaO2/FiO2 less 100), who were given NIV therapy and had a successful outcome. Two patients with NIV failure had a PaO2/FiO2 ratio of 111 and 150 and a SOFA score of 9 and 11. The rest of the 16 patients had a SOFA score ranging from 4 to 6. Hence the authors observed that in severe COVID-19 disease with ARDS, a subset of patients having a low PaO2/FiO2 ratio but good SOFA score are more likely to have a successful outcome with NIV therapy. Based on our experience the authors noticed that although we kept a high threshold for intubation and went ahead with NIV in severe ARDS cases, we had to monitor for signs of respiratory distress and clinical deterioration very closely.

The pathophysiology of ARDS in COVID-19 is yet to be understood. ARDS causes diffuse alveolar damage in the lungs and ultimately lung fibrosis.\textsuperscript{19} Despite extensive inflammatory changes in the lungs that are radiologically evident, ventilation seems to be less severely impaired than gas exchange resulting in severe hypoxemia without hypercapnia. Indeed, patients often have no difficulty moving large volumes of air in and out of lungs, thus the lack of hypercapnia has led to the observation that dyspnea may be absent or disproportionately mild as compared to the severity of disease.\textsuperscript{20} In our study mean PCO2 level was 38.6 mm of Hg and the mean respiratory rate was 29/min at baseline. There was a significant improvement on day 2 and subsequent days.

There is considerable confusion about the risk of aerosolization and transmission of viruses due to NIV. NIV has not been clearly shown to increase the risk of infection with SARS or other viral diseases; however, studies and case reports are describing an association.\textsuperscript{21,22} The WHO guidelines have included the use of NIV as an aerosol-generating procedure but the evidence in support of these guidelines is rather weak.\textsuperscript{7} They base their guidance on the widely referenced systematic review by Tran et al. which identifies tracheal intubation as the only procedure which is consistently associated with SARS transmission.\textsuperscript{21}

In a widely referenced and simulated study, Hui et al. demonstrated that air originating in a patient’s airways may be spread within a radius of ~1 m during NIV use.\textsuperscript{23} Subsequent studies showed that incorrect fitting of masks considerably increased the spread of exhaled air, in general, there is not widespread dispersion of exhaled air.\textsuperscript{24} Furthermore, there is little evidence of droplet or aerosol particles even within the 1 m range.\textsuperscript{25} Of 138 patients who were hospitalized with confirmed COVID-19 in Wuhan, China, in January 2020, 40 (29%) patients were health-care workers who were presumed to have contracted the virus in the hospital.2 Of these health-care professionals, 31 (78%) worked on general wards, 7 (18%) in the emergency department, and 2 (5%) in the intensive care unit (ICU).\textsuperscript{26} The risk of transmission was highest among health-care workers who had been exposed to patients with COVID-19 with low clinical suspicion and, therefore, were unlikely to have worn PPE. The clinically relevant question is what are the chances of healthcare workers being infected while taking care of sick patients on NIV when infection control measures are taken and personal protective equipment are worn?.

Cheung et al. in 2003 in Hong Kong during the SARS epidemic reported on 105 HCWs exposed to 20 patients undergoing NIV that none of the HCWs were infected.\textsuperscript{16} However, they did not mention what anti-infection precautions did they take or did they wear any protective gear. Moreover, 3 HCWs did not undertake the RT-PCR test. Hence although they concluded that NIV was a safe treatment modality in SARS-associated ARDS, the role of anti-infection precautions and PPE remained unexplained.

Loeb et al. and Yu et al. also reported an association between NIV and SARS transmission but found a stronger association related to oxygen masks.\textsuperscript{27,28} It is hypothesized that NIV may provide a protective benefit by limiting the dispersal of droplets as patients cough.\textsuperscript{29}

As per ATS and NHS guidelines, the following precautions are recommended for reducing aerosolization and safety of HCWs while using NIV.\textsuperscript{30-32}

1. Negative pressure room (>10 cycles/hour air exchanges.
2. Neutral pressure room or a simple side room (if negative pressure room not available).
3. Cohorting if outside ICU, with a clear plan for intubation.
4. CPAP interface, in order of preference:
   (a) Full face mask, non-vented with a viral filter on the expiratory limb.
   (b) Helmet CPAP if a full face mask not available.
   (c) Standard mask (least preferred option).
   (d) Must have the ability to entrain oxygen.
5. Avoid vented mask.
6. Use HME/ viral filter fitted to all exhaust systems.
7. Ensure staff PPE and avoid disconnections.
8. Use of dual limb systems.

In our study 45 healthcare workers who were involved in the care of patients with NIV, always wore personal protection kits, with fit-tested N-95 masks, goggles face shield, and shoe covers at all times in the ICU. In our setup, we used non-vented masks without helmets and HMEF filters attached to an expiratory limb, dual limb systems, and air conditioning with 15 cycle changes /min. Negative pressure and HEPA filters could not be applied due to financial constraints and limited resources. None of the health care workers had any symptoms suggestive of COVID 19 during the 15-day ICU rotation. 2 Nasopharyngeal swab samples were taken on day-5, 48 hours apart after the end of the rotation in the intensive care unit. Reverse Transcriptase – Polymerase Chain Reaction test was conducted on all the swabs and was found to be negative for all health care workers. Thus no health care worker contracted COVID 19 infection while caring for patients with NIV.

Complications of NIV included secondary bacterial pneumonia in 2 patients. One patient recovered but the other one had to be intubated and expired on day 36 due to sepsis and multi-organ failure. One post-partum patient developed lung fibrosis and has become oxygen dependent. Intolerance and compliance to NIV was also an issue and 2 patients complained of claustrophobia but could be managed by counseling and encouragement. The authors would like to mention that almost all patients were extremely apprehensive and initially uncomfortable with NIV and required encouragement and counseling by the health care workers. Communication with the patient wearing a PPE kit was challenging but most patients were comfortable within a few hours of initiation of NIV. One patient developed a pressure sore on the nasal bridge on day 7 but was managed conservatively.

Our study has a few limitations. The sample size is small and it is a single-center retrospective study. More prospective randomized controlled trials are required to evaluate the efficacy and safety of NIV in COVID 19 patients. Radiological classification and scoring of ARDS were not done due to constraints in resources and manpower.

With our experience, we would like to recommend that NIV can be used safely to treat acute hypoxemic failure associated with Severe COVID 19 infection, provided HCWs are educated about infection control measures. Patient selection and counseling are important for a favorable outcome. More studies are required to validate the effectiveness and safety of NIV in ARDS with severe COVID 19 infection.

6. Conflict of Interest
The authors declare that there are no conflicts of interest in this paper.

7. Source of Funding
None.

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Cite this article: Gupta A, Dalal N, Das AK. Effectiveness and safety of non-invasive pressure ventilation in severe COVID-19 disease: A retrospective analysis. *Panacea J Med Sci* 2021;11(2):209-215.