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ORIGINAL ARTICLE

Non-Invasive Ventilation an Alternative to Invasive Ventilation in Covid-19 Patients

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Abstract

Objectives: To study the role of non-invasive ventilation (NIV) in the treatment of COVID-19 patients with mild to moderate acute respiratory distress syndrome (ARDS).

Material and methods: Patients with positive RT-PCR for SARS-CoV-2 who required intensive care unit (ICU) admissiondue to COVID-19 related pneumonia with mild to moderate ARDS were included in the study. ARDS was treated with NIV, or mechanical ventilation (MV) if NIV failed. NIV was considered for patients admitted to the ICU with mild to moderate ARDS. Primary outcomes were NIV success and failure, defined by intubation and mechanical ventilation, and mortality. Secondary outcomes were determined by the duration of NIV and the number of days stayed in ICU.

Results: NIV was successful in 37 patients (50%), whereas 37 patients required endotracheal intubation and invasive mechanical ventilation (50%). In the study, 15 (40.5%) of the 37 failed NIV patients who required intubation were successfully extubated and discharged from the ICU, whereas 22 (59.5%) died. Disease progression to severe ARDS, infection, and agitation were the leading causes of NIV failure, accounting for 60% of the cases related to severe ARDS. The number of comorbidities and complications caused by the illness itself had a high association with the death rate.

Conclusion: This study revealed that noninvasive ventilation can be used as an alternative to mechanical ventilation as respiratory support for mild to moderate ARDS in COVID-19 patients. However,future multi-centric studies with a larger sample are required for more reliable evaluation.

Keywords: Noninvasive Ventilation, Respiratory Distress Syndrome, COVID-19, Aerosols, Pneumonia, Intensive Care Units.

Introduction

The COVID-19 pandemic is a respiratory illness caused by the novel coronavirus SARS-Cov-2. Among all the COVID-19 patients, 13.8% were severe, whereas only 4.7% were critical, and the most likely cause of death was reported as severe respiratory failure.[1] Respiratory support can be given either by invasive mechanical ventilation or non-invasive ventilation as the ultimate treatment for COVID-19 related acute hypoxemic respiratory failure.

In the early days of the outbreak, most clinicians were maintaining a low threshold for endotracheal intubation, for the management of COVID-19 ARDS respiratory failure. Many studies have reported high mortality with invasive mechanical ventilation as compared to NIV.[2,3] Additionally, most organizations and studies support NIV as a mode of ventilation in COVID-19 patientswith acute respiratory failure.[4,5] Despite the benefits of NIV, many recommendations against its use were based on concerns about aerosol generation and infection transmission. In contrast, somestudies showed a low risk of airborne transmission to healthcare providers and a favorable outcome in COVID-19 patients treated with NIV.[6]

A single technique of respiratory support cannot be applied for all COVID-19 patients. For this reason, it is extremely important to accurately determine the role of NIV in treating mild to moderate ARDS.

Material and methods

This study is a retrospective review of clinical data on characteristics, ventilator treatment, and outcomes of patients with COVID-19 ARDS admitted to the intensive care unit at Armed Forces Hospital, Muscat.

The primary outcomes were NIV success and failure. Success was defined by recovery on NIV, whereas failure was defined by intubation and mechanical ventilation or mortality. Secondary outcomes were determined by the duration of NIV and the number of days in the ICU.

The study included all adult patients with positive RT-PCR for SARS-CoV-2 who required ICU admission due to COVID-19-related pneumonia with mild to moderate ARDS, as defined by PaO2: FiO2 ratio and lung infiltrates.

Acute respiratory failure due to COVID-19 ARDS was treated with NIV, or if NIV failed, mechanical ventilation.

NIV was considered for those patients admitted to the ICU with mild to moderate ARDS, with a PaO2: FiO2 ratio of > 100 and < 200 mm Hg despite O2 supplementation by a simple Hudson mask, escalated to a non-rebreathing high concentration mask (HCM) with reservoir bag.

The target for NIV was to achieve FiO2 <50%, respiratory rate of <30/min, tidal volume >5ml/kg witha pressure support of <10cm H2O and positive end-expiratory pressure (PEEP)< 8 cm H2O.

Once the target was achieved, NIV was de-escalated to an HCM mask or a Venturi mask. Frequent arterial blood gas (ABG) analysis was done to adjust the NIV settings.

Consequent need of intubation due to NIV failure was decided in case of persistent hypoxia or low PaO2/FiO2 ratio (<100), high respiratory rate despite maximum optimal NIV settings with inspiratory positive airway pressure (IPAP) up to 20cm H2O, maximum PEEP of 12-15 cm H2O and FiO2 of maximum 1 to obtain SpO2 higher than 90%. Subsequently, an intubation decision was made in case of persistent or worsening of respiratory failure, persistent low SpO2 <88% and respiratory rate (RR)>35/min, and progressive loss of consciousness or coma and hemodynamic instability. Other criteria for NIV failure, other than the worsening severity of ARDS were sepsis and most importantly, patient agitation.

IBM SPSS software Version 25 was used for statistical analysis. Categorical variables were presented with frequency and percentages, as well as with continuous mean or SD, median, or interquartile range.

Results

A hundred consecutive patients with sudden worsening of respiratory failure were admitted to the Intensive Care Unit at Armed Forces Hospital, Muscat between April 2020 and December 2020.

All patients (71 males and 29 females) had a confirmed RT-PCR for SARS-CoV-2 infection and required ICU admission for respiratory failure due to COVID-19 pneumonia with ARDS. The severity of ARDS was determined by the PaO2/FiO2 ratio and the chest X-ray showing lung infiltrates.

Out of the 100, the NIV trial was given to 80 patients, and 20 were immediately intubated due to severe ARDS, and these were excluded from the study. In addition, six patients who were declared “do not resuscitate (DNR)" status after multidisciplinary evaluation due to the presence of severe disease with multiple comorbidities and for whom NIV was connected only as palliative therapy were excluded from the study.

The demographic data (Table 1), showed a statistically significant association between the recovery rate found in the younger age group (49.58 ± 14.98) and the death rate was more in older age group (66.58 ± 8.66) with a significant *p*-value of < 0.001. Of the 74 patients, 54 were males and 20 were females who contracted the disease and required ICU admission. There was no significant gender-related difference in mortality.

Out of the 74 NIV trials, the patients were divided into two groups: NIV success and NIV failure. It was observed that, NIV was successful in 37 patients (50%), whilst endotracheal intubation and invasive mechanical ventilation were required for 37 patients (50%) (Table 2). Among NIV failures requiring intubation, 15 (40.5%) patients were successfully extubated and discharged fromthe ICU, while 22 (59.5%) patients died due to an increase in the severity of the disease or due to complications related to ventilation and COVID-19 disease itself. The study also evaluated the reasons for NIV failure, which showed that the main reason for failure wasthe progress of disease to severe ARDS in 24 patients who required endotracheal intubation and MV due to an increase in the severity of the disease. Secondly, sepsis and agitation were the two main and common reasons for NIV failure, noted in 9 and 4 patients, respectively (Table 2). Inthe group of patients who failed NIV and were intubated, compared to those who continued NIV successfully, there was no significant increase in mortality rate.

The NIV success group required NIV for approximately a median of three days (*p* value of 0.631), whereas the number of days in the ICU was 7. Patients admitted to the ICU, regardless of ventilation type, were nursed in a prone position for an average of 3.8 days. While the prone position only improved oxygenation, it did not show any advantage in the mortality rate (Table2).

The study observations (Table 3) showed a correlation of co-morbidities with the disease course and mortality rate. The most commonly associated co-morbidities were hypertension and diabetes mellitus. The comorbidities were segregated into 4 categories, and it was noted that out of those who received NIV successfully and recovered, 49% of patients were without any comorbidity, whereas 24.5% were with one to two comorbidities, and 26.5% were with three or more comorbidities.

Secondly, it was observed (Table 4) that mortality was also associated with the complications that developed during the illness. Most of the patients died due to acute kidney injury (*p*-Value <0.001)and the second most common reason was sepsis/septic shock (*p*-Value 0.005). Patients who developed complications were categorized into 4 groups, which showed that 72% of patients who recovered were without any complications, whereas the morality rate significantly increased withthe number of complications, 29.2% of patients who died had more than 3 complications.

Table 1: Demographic data

Variables	Patient status		p-Value
	Recovered (n=50)n (%)	**Dead (n=24) n (%)**	
Age*	49.58±14.98	66.58±8.66	<0.001
Gender			
Male	35 (70.0)	19 (79.2)	0.577
Female	15 (30.0)	5 (20.8)	

*Mean±SD

Table 2: Non-invasive ventilation success and failure with patient status

Variables	Patient status Recovered (n=50) n (%)	 Dead (n=24)n (%)	p-Value
Successful NIV (n=37)			
Reason for NIV Failure (n=37)			0.325
AgitationSepsis	3 (20.0)	1 (4.5)	
Severe ARDS	3 (20.0)	6 (27.3)	
	9 (60.0)	15 (68.2)	
Days of NIV – Median*	3 (2,5)	3 (1,5)	0.631
Days of MV – Median*	0 (0,4)	8 (3,14)	<0.001
Days in ICU – Median*	7 (4, 11)	15 (10,26)	<0.001
Proning days – Median*	3 (2,6)	3 (1,5)	0.575
Total hospital stay days-Median*	13 (10,23)	16 (11,34)	0.105

* Median (Q1, Q3), n = number of patients, n (%) = percentage of patients, NIV- Non-invasive Ventilation, ARDS- Acute Respiratory Distress Syndrome, MV-Mechanical Ventilation, ICU – Intensive Care Unit.

Table 3: Patient status and comorbidities

Variables	Patient status Recovered (n=50) n (%)	 Dead (n=24) n (%)	p-Value
Co-morbidities			
Hypertension	19 (39.6)	15 (62.5)	0.083
Diabetes mellitus	16 (33.3)	12 (50.0)	0.205
Ischemic heart disease	1 (2.1)	4 (16.7)	0.042
Dyslipidemia	9 (18.8)	4 (16.7)	1.000
Bronchial Asthma	3 (6.3)	-	0.546
Chronic obstructive pulmonarydisease	1 (2.0)	-	1.000
Smoker	1 (2.0)	1 (4.2)	1.000
Obesity	3 (6.1)	-	0.546
Obstructive sleep apnea	1 (2.0)	-	1.000
Atrial fibrillation	1 (2.0)	-	1.000
Chronic kidney disease	4 (8.2)	5 (20.8)	0.144
Heart Failure	3 (6.1)	1 (4.2)	1.000
Comorbid category			
No comorbidities	24 (49.0)	6 (25.0)	0.099
1-2 comorbidities	12 (24.5)	11 (45.8)	
≥3 comorbidities	13 (26.5)	7 (29.2)	

n = number of patients, n (%) = percentage of patients

Table 4: Patient status and complications

Variables	Patient status Recovered (n=50)n (%)	 Dead (n=24)n (%)	p-Value
Complications			
Acute kidney injury	3 (6.0)	14 (58.3)	<0.001
Sepsis/Septic shock	7 (14.0)	12 (50.0)	0.002
Difficult weaning	4 (8.0)	2 (8.3)	1.000
Pneumothorax	2 (4.0)	1 (4.2)	1.000
Tracheostomy	4 (8.0)	2 (8.3)	1.000
Pulmonary embolism	1 (2.0)	3 (12.5)	0.097
Lung Fibrosis	-	-	-
Critical illness myopathy	-	1 (4.2)	0.324
Heart Failure	2 (4.0)	1 (4.2)	1.000
Cardiac arrest	-	4 (16.7)	0.009
Multi-organ failure	-	2 (8.3)	0.102
Arrhythmias	2 (4.0)	3 (12.5)	0.321
Complication's category			
No complication	36 (72.0)	3 (12.5)	<0.001
1 complication	8 (16.0)	7 (29.2)	
2 complications	2 (4.0)	7 (29.2)	
≥3 complications	4 (8.0)	7 (29.2)	

n = number of patients, n (%) = percentage of patients

Discussion

Noninvasive ventilation (NIV) techniques can avoid endotracheal intubation and its furtherconsequences such as mechanical stress, the strain causing lung injury, and sedation requirement.

In the early days of the pandemic, the decision to manage the respiratory failure in COVID-19, either with NIV or to proceed with early endotracheal intubation, was much debated and controversial.[7] Maddani *et al.* conducted a multicenter survey on ventilator management of COVID-19 related ARDS (CARDS). In this study, 32% of the responders said that they would be using NIV (high-flow nasal oxygen, HFNO-19%, Noninvasive ventilation-13%).[8]

WHO interim guidelines on acute respiratory failure in COVID-19 currently recommends NIV, only in a selected group of patients with mild to moderate hypoxemic respiratory failure.

Cheung *et al,* reported that NIV was effective in the treatment of acute respiratory failure associated with COVID-19 related ARDS.[9] The HOPE COVID-19 registry reported that NIV haseffectively supported and prevented the need for intubation of more than half of the patients included in the cohort study and NIV is considered a useful mode of therapy in patients with acuterespiratory failure (ARF) due to COVID-19.[10]

Some of the other studies conducted on critically ill patients undergoing invasive mechanical ventilation reported a mortality rate between 52.4% and 86.5%.[2,11] Menzella *et al*. showed a mortality rate of 43% in NIV failure and then being intubated, whereas 36% in those who continued NIV.[12]

An early NIV procedure within one hour of ICU admission may be useful to categorize ARDS patients clinically and can avoid unnecessary endotracheal intubation in more than half of the patient population, as shown in a previous multi-center study.[13]

In this study, 80 patients were treated with NIV and admitted to the ICU, which was the only placewhere NIV was performed in the hospital. The study hospital was organized with a model of escalationof care: the patients were admitted at the Accident and Emergency department and triaged on the severity of respiratory failure into two areas: the first where only conventional oxygen was administered, called the COVID ward, and the second where NIV, as well as mechanical ventilation, were provided, represented by the ICU.

Conventionally, any confirmed case of COVID-19 infection with worsening of respiratory failure represented by a PaO2: FiO2 ratio of less than 200 and a respiratory rate of more or equal to 30 breaths per minute was admitted to the ICU for NIV or, if needed, intubation and mechanical ventilation. Those patients with a PaO2/FiO2 ratio of between 200 and 300 mm Hg were admitted to the COVID ward and treated with standard oxygen therapy.

In the group of NIV failure, for non-responder patients, NIV was stopped without a delay for endotracheal intubation. NIV failure was correlated with older age, with the presence of more thanthree comorbidities, and with an increase in the severity of the ARDS compared to the NIV successfulpatients. Six patients had DNR status with a do-not-intubate policy due to multiple comorbidities and severe ARDS with a very low PaO2: FiO2 ratio who received NIV as the last rescue therapy toreduce the work of breathing.

In this study, out of the 74 NIV trial cases, the patients were divided into two groups: NIV success and NIV failure. It was observed that NIV was successful in 37 patients (50%), whereas endotracheal intubation and invasive mechanical ventilation were required for 37 patients (50%). Of the NIV failure and intubated patients, 15 (40.5%) were successfully extubated and discharged from the ICU, while 22 (59.5%) patients died due to an increase in the severity of the disease course, or due to complications related to ventilation.

The study noted a correlation between comorbidities and mortality rates. Out of those who received NIV successfully and recovered, 49% were without comorbidity, whereas 24.5% had one to two comorbidities, and 26.5% had more than three comorbidities. Another significant factor was increased complications related to the COVID-19 disease itself, which led to increased mortality.

With the use of NIV as respiratory support in

COVID-19 patients, the most important concerns raised by clinicians would be an increased risk of aerosol generation and transmission of infection to health care workers. Hence, the guidelines suggest the use of NIV in an isolated negative pressure room or ward for all the confirmed cases. All the medical staff should wear full personalprotective equipment (PPE), including eye protection, N95 or respirators, gloves, and long-sleevedgowns.

Cheung *et al.* reported that NIV was effective in the treatment of acute respiratory failure associated with COVID-19 related ARDS and none of the healthcare providers tested positive forSARS-CoV-2 at the end of the study.[9] Another study by Cascella *et al*, reported a low risk of airborne transmission to healthcare providers and a favorable outcome in COVID-19 patients treated with NIV.[6]

Ashwin *et al.* reported that doctors predominantly preferred managing noninvasive oxygen therapies in negative-pressure rooms.[14] However, a recent Italian study has confirmed that NIV application outside the ICU is safe for health care providers, is convenient, and associated with similar favorable outcomes as the ICU.[15]

In this study, all patients were treated with NIV in an ICU setup. Furthermore, the study did not note a higher mortality rate in patients with failed NIV and those who required intubation as compared to those patients with successful NIV trials. In this study, the researchers preferentially used mask NIV, due to past favorableexperience with this technique. Hence, for mild to moderate disease patients, NIV has been the first choice in the ICU unit of the study setting hospital. The study did not note any healthcare workers who contracted the virus while taking care of the patients on NIV.

This study has some limitations. Firstly, it was a single-center observational study with a relatively small number of patients included in the data. Secondly, it was conducted during the first wave of the pandemic with overwhelming ICU admissions and little knowledge about the pathophysiology of the virus, which might have led to different patient selection criteria regarding the NIV failure and possible endotracheal intubation.

Conclusion

NIV has significant advantages over traditional mechanical ventilation. Mild to moderate COVID-19 ARDS patients with specific demographics, such as a young age or fewer comorbidities, may benefit from early and meticulously supervised NIV support rather than more invasive intubation. However, these patients with hypoxemia and ARDS require a greater understanding of the different modalities of respiratory support and an evaluation of the effectiveness of NIV. The preliminary data from our ICU focused mainly on non-invasively ventilated patients with mild to moderate COVID-19 ARDS, which showed that NIV was effective in half of the patients. This also dramatically reduced the pressure on the ICU nursing staff, avoiding endotracheal intubationsin a large number of patients. However, future multi-center, larger studies are needed for more reliable evaluations.

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