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Therapeutic Outcome of High Flow Nasal Cannula (HFNC) for Severe COVID-19 Patients in Isolation Intensive Care Unit

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Abstract

This retrospective descriptive study aimed to understand the outcomes of HFNC therapy in severe COVID-19 patients admitted to isolation ICU during the period of January to June 2021 in Dr. Hasan Sadikin General Hospital Bandung, Indonesia. A total of 134 patients with severe COVID-19 were admitted to the isolation ICU and received HFNC. Among them, 44 patients (32.8%, N:134) were successfully weaned from HFNC and 90 patients (67.2%, N:134) failing HFNC with 10 patients (7.5%, n:134) died on HFNC use, 72 patients (53.9%, n:134) died on ventilator use, 4 patients (2.9%, n:134) moved rooms under HFNC use, and 4 patients (2.9%, n:134) moved to non-ICU isolation with ventilator use as the outcome. Patients' median age was 60 years, most were male (52.3 %, n:134), median BMI was 25.4 kg/m^2, with hypertension and diabetes mellitus as the main comorbidities. There was an improvement in the SpO_2 on the first day after the use of HFNC. The ROX index had a median value of 3.6 on the first day, with the lowest ROX index of 3.2 and the highest of 4.4 during the treatment time. There was an improvement in the P/F Ratio in successful patients with a median initial P/F Ratio of 86.7 to 200.1 at the end of treatment. Overall, HFNC improves the hypoxemic conditions in early admission but does not correlate with general patient outcomes.

Keywords: High flow nasal cannula, intensive care, ROX index, severe COVID-19, therapeutic outcome

Introduction

COVID-19 has a degree of clinical manifestation ranging from asymptomatic, mild, moderate, to severe, with the assessment of the most severe case being pneumonia with acute respiratory distress syndrome (ARDS). COVID-19 degree is defined by clinical symptoms of pneumonia (fever, cough, shortness of breath, rapid breathing) plus one respiratory rate > 30 breaths/minute, severe respiratory distress, or SpO2 <93% on room air. Severe COVID-19 requires monitoring in the ICU because it can develop into ARDS and acute respiratory failure.[1,2,3]

In severe COVID-19, there is more severe lung damage, so supplementation modalities are needed that can provide fractional and higher oxygen flow. High flow nasal cannula (HFNC) is considered to be able to reduce *dead space*, protect the airway mucosa with *humidifier* technology that can maintain a temperature of 31–37 °C, provide oxygen supply with a constant flow and concentration with flow up to 60% and oxygen concentration 100%, HFNC also has a *positive end expiratory pressure* (PEEP) which can increase the residual functional capacity. HFNC, compared with traditional oxygen therapy has better comfort and therapeutic effect. [5,6]

Dr. Hasan Sadikin Hospital Bandung (RSHS), as a referral center for COVID-19 in West Java, is still relatively new to the use of HFNC, so RSHS, as the local setting of this research, is expected to provide a representative picture. The purpose of this study was to obtain an overview of the outcomes of HFNC therapy based on clinical SpO_2 before and after the use of HFNC, ROX index values on the first day, the highest and lowest during treatment, laboratory parameters of PaO_2, PCO_2 and P/F Ratio and demographic data.

Methods

This study is retrospective-descriptive research. The subjects of this study were medical records of COVID-19 patients who were admitted to ICU

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Dr. Hasan Sadikin General Hospital Bandung from January to June 2021. The inclusion criteria of this study were patients aged 18 years above diagnosed with severe COVID-19 and the exclusion criteria were in completed medical record data. The research obtained ethical approval from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, with ethical approval number LB.02.01/X.6.5/16/2022. The data collected including outcome; demographics; value of SpO_2 before HFNC use and on the first day of HFNC use; first-day ROX value, lowest ROX and highest ROX value during treatment; laboratory oxygenation profile (PaO_2, PCO_2, P/F Ratio) after the first day of HFNC use; and at the end before patient discharge from ICU. During the study period, 191 severe COVID-19 patients were admitted to the intensive care unit for COVID-19 isolation at RSUP dr. Hasan Sadikin Bandung. It was found that 57 patients were excluded from this study because they did not receive HFNC therapy. A total of 134 patients are eligible for this study. All these data will be displayed in a distributive table categorized into succeed group (weaning from HFNC) and failed group (went to ventilator use or die). The data is also displayed with statistical explanations accompanied by a discussion on the theoretical basis that has been found previously. Data processing and analysis were done using Statistical Product Service Solution (SPSS) version 25.0 for Windows.

Results

Of the 134 patients with severe COVID-19 who admitted the ICU isolation and received HFNC therapy, 44 patients (32.8%, n:134) succeeded in weaning HFNC, and 90 patients (67.2%, n:134) failed HFNC with an outcome of 10 patients (7.5%, n:134) died on HFNC use, 72 patients (53.9%, n:134) died on ventilator use, 4 patients

Table 1 Demographics of Severe COVID-19 Patients Receiving Therapy HFNC

Variable	Succeed (n=44)	Failed (n=90)
Age (years)		
Median	58.0	60.5
Range (Min.–Max.)	(21.0 –86.0)	(26.0–85.0)
Mode	58.0	65.0
BMI (kg/m^2)		
median	25.4	26.8
Range (Min.–Max.)	(17.6–40.0)	(19,5–34.0)
Gender, n (%)		
Male	21 (47.7%)	49 (54.4%)
Female	23 (52.3%)	41 (45.6%)
Comorbidities n (%)		
Hypertension	22 (50.0%)	38 (42.2%)
Diabetes mellitus	12 (27.2%)	21 (23.3%)
Lung disease	1 (2.2 %)	3 (3.3 %)
Heart disease	7 (15.9 %)	7 (7.7 %)
Kidney failure	4 (9.0 %)	7 (7.7 %)
Immunodeficiency	0 (0%)	3 (3.3 %)
Malignancy	0 (0%)	2 (2,2 %)
Pregnant	1 (2.2 %)	5 (5.5 %)
Hematological disease	3 (6.8%)	0 (0%)
Asthma	2 (4.5%)	3 (3.3 %)

Notes**:** n=frequency, %=percentage

Table 2 Clinical Overview of Severe COVID-19 Patients Receiving HFNC Therapy

Variable	Succeed (n=44)	Failed (n=90)
SpO_2 before HFNC		
Median	86.0	83.0
Range (Min - Max)	(68.0–90.0)	(50.0–90.0)
SpO_2 with HFNC		
Median	97.0	94.5
Range (Min - Max)	(80.0–99.0)	(59.0–100.0)
ROX index day 1		
Median	3.9	3.5
Range (Min.–Max.)	(2.1–8.1)	(1.8–4.1)
Lowest ROX index		
Median	3.6	3.1
Range (Min.–Max.)	(1.8–8.1)	(1.5–4.8)
Highest ROX index		
Median	7.8	4.0
Range (Min.–Max.)	(3.7–22.0)	(2.0–13.0)

Notes: n=frequency, %=percentage

(2.9%, n:134) changed rooms in use HFNC, and 4 patients (2.9%, n:134) moved to a non-isolated ICU with the use of a ventilator. Demographic data found that the median age was 60 years, most were male (52.3%, n:134), and the median body mass index was 25.4 kg/m^2, with the main comorbidities of hypertension and diabetes mellitus.

The clinical outcome was found an improvement in SpO_2 which was assessed on the first day after using HFNC with an increase in SpO_2 values after using HFNC with a median value of 97% in the successful group and 94.5% in the failed HFNC group. The clinical outcome of the ROX index had a median value of 3.6 on the first day. The lowest ROX index was 3.2, and the highest was 4.4 during treatment. The successful group had a higher ROX value than the HFNC failed group.

Improvements in the P/F ratio were found in patients who had successfully weaned HFNC with a median initial P/F ratio of 86.7 mmHg, an increase of 200.1 mmHg at the end of treatment, while in patients who died on a ventilator, hypercapnia was found with an increase in the median PCO_2 54.2.

Discussion

Table 3 Laboratory Overview of Severe COVID-19 Patients Receiving HFNC Therapy

Variable	Succeed (n=44)	Failed (n=90)
PCO_2 early		
Median	29.4	29.8
Range (Min.–Max.)	(13.9–44.1)	(12.7–107.8)
Initial PaO_2		
Median	80.1	68.2
Range (Min.–Max.)	(37.0–209.8)	(40.1–277.1)
Initial P/F Ratio		
Median	86.7	76.6
Range (Min.–Max.)	(37.0–288.0)	(17.8–278.1)
Final PCO_2		
Median	36.0	43.5
Range (Min.–Max.)	(22.3–49.6)	(22.8–148.1)
Final PaO_2		
Median	104.6	73.2
Range (Min.–Max.)	(38.3–189.0)	(35.4–182.1)
Final P/F Ratio		
Median	200.1	77.4
Range (Min.–Max.)	(38.3–189.0)	(28.8–263.2)

Notes: n=frequency, %=percentage

In this study, found a few discrepancies between gender populations. There were 70 male patients with 47.7% (n=44) in the success group, and 64 female patients with 52.3% (n=44) failed group. This finding also showed similar results from other meta-analysis studies involving 3,111,714 patients globally that there was no difference in the proportion between men and women who were infected with COVID-19. However, men had a 3-fold likelihood of needing intensive care in the intensive care unit (ICU). Previous literature has shed light on how gender differs in innate and adaptive immunity. Women have the advantage of having a higher number of CD4+ T cells, more active CD8+ T cell cytotoxic activity, and more production of immunoglobulins by B

cells than men. Females produce more interferon type-1 (IFN). This antiviral cytokine plays a role in the initial response to infection and works potently as a toll-like receptor for detecting viral RNA more than males. In addition, socio-cultural biases and behavioral attitudes contribute to the severity of COVID-19. To illustrate, men are likelier to smoke, rarely wash their hands, and are likelier to leave the house and be in crowds.[7,8]

In the successful group, the median age was 58, and the failed group was 60.5 years old. There were also few discrepancies in age population, but the older population was an important factor influencing the outcome in some literature. In a published quantitative meta-analysis of 2851 patients from 25 HFNC studies, the mean age was 61 years (±13 years). Similar data were also obtained in a quantitative and qualitative meta-analysis of 64,676 patients from 20 studies regarding gender, age, and comorbidities for COVID-19 mortality, which found that aged 50 years had 15.4 times the risk of death compared to patients aged <50 years. Old age correlates with decreased immunity, decreased organ function, more comorbidities, and higher ACE2 gene expression in old age. Some comorbidities, such as diabetes mellitus, are also associated with decreased immunity, inhibiting the body's ability to form antibodies and fight infection. Polypharmacy in old age also influences the body's immunity, where there is downregulation due to drug side effects. ACE inhibitors (ACEIs) and angiotensin II type-I receptor blockers (ARBs) are also associated with the upregulation of ACE-2 receptors in hypertensive and diabetic patients, which can exacerbate SARS-CoV-2 infection.[9]

Body mass index (BMI) in the overall patient population of this study showed that the majority were in the overweight category in both groups, with the successful group with a median value of 25.4 and slightly higher in the failed group with a median value of 26.8. A meta-analysis of 34,390 patients from 12 studies on body mass index and outcome in COVID-19 found that a higher body mass index was associated with a higher risk of mortality and disease severity. This is based on statistical tests based on a dose-response meta-analysis (DRMA) which found a 5% increase in the risk of a worse outcome for every 5 kg/mg2 increase in body mass index. A high body mass index has a higher risk of comorbid diseases, including hypertension, dyslipidemia, type 2 diabetes mellitus, cardiovascular disease, and cerebrovascular disease. A chronic increase in mild systemic inflammation makes it susceptible to infection. Obesity also affects innate and adaptive immunity, as happens in aging as well as in the presence of low physical activity, obese patients also make immunity and the body's defenses against the body weaken. A high body mass index is also associated with poor pulmonary function, including respiratory reserve volume, functional capacity, and low lung compliance, adding to the severity of COVID-19. In addition, intestinal dysbiosis and vitamin D deficiency in obese patients also contribute to a worse COVID-19 outcome.[9,10]

Comorbidity has a significant role in COVID-19 outcomes. In this study, as seen among patients in the failed group, hypertension (42.2%, n=90) was higher than that of the succeeded group. The second most dominant comorbidity among the failed group is diabetes Mellitus (23.3%, n=90). Each comorbidity has its own pathophysiology and mechanistic relationship to SARS-CoV-2 infection and outcome. For example, patients with hypertension and heart failure have a worse outcome risk associated with increased ACE2 expression in mRNA. Diabetes mellitus and chronic kidney disease (CKD) has been associated with inflammation and dysregulation of immune function, which may explain the increased risk of worse outcome and mortality.[9,11]

In this study, we found improvement in SpO2 and ROX index at day one admission after using HFNC. In the success group, the median SpO2 before HFNC was 86%, which improved to 97%. The increase was also seen in the failed group as before HFNC. The SpO2 median was 83% which was improved to 94.5% post-HFNC use. But unfortunately, in the long term, this finding does not correlate with general patient outcome, which was shown by the 60.5% of the patients were in the failed group.

The ROX index was used to monitor the need for mechanical ventilation requirements and a predictor of HFNC success. In this study, patients in the failed HFNC group had a median ROX index of 3.5, which was lower than the HFNC success group, with a median ROX index of 3.7. In the failed HFNC group, the highest ROX index was found on the first day with a median of 4.0, where this value is still at risk of requiring intubation as much as 80% at an index ROX value of <4.8.[12]

The higher number of failed groups in this study could be explained based on some literature studies about the pathophysiology of the COVID-19 pneumonia type. There were two types of pneumonia phenotype in COVID-19: L and H. In the L phenotype, hypoxemia occurs due to dysregulation of perfusion and loss of

the hypoxia pulmonary vasoconstriction (HPV) mechanism. In this type L phenotype, the lung compliance function is still good, the ventilation-perfusion ratio is low, the increase in lung weight is not too increased, the lung tissue with air is still a lot and the need for recruiting alveoli is small. In the L phenotype, average lung volumes were still obtained so the patient could not be short of breath and respond well to non-invasive oxygen therapy. The type H phenotype occurs in approximately 20–30% of patients with symptoms similar to severe ARDS with low lung compliance. There was a significant increase in lung weight, namely an increase in right-to-left shunt perfusion and a higher need for lung recruitment. In this type, H phenotype, lung volume is markedly reduced due to the resulting interstitial and alveolar edema. Type H phenotype requires more significant positive end-expiratory pressure (PEEP) for alveolar recruitment and reduced dead space. The use of HFNC in this type of H phenotype may be less successful because the PEEP provided by HFNC is minimal. Patients may present with one end of the spectrum or in a phase transition between the two spectrums. The transition from the L to the H phenotype is usually determined by disease progression. It is associated with patient-self-inflicted lung injury (P-SILI) caused by increased work of breathing. This pathophysiological course of type L and type H phenotypes may explain why patients with high ROX index scores eventually require a ventilator or experience mortality, as reflected in this study, which could be seen in the failed group.[13,14]

The median value of the initial laboratory output of blood gas analysis (BGA) was obtained with a mean PCO 29.4 mmHg, PaO2 80.1 mmHg, and P/F Ratio of 86.7 in patients with successful HFNC with improvement to PCO_2 36 mmHg, PaO2 104.6 mmHg and P/F Ratio 200.1 at the end of treatment. In the group of patients with HFNC failure, the PCO_2 29.8 mmHg, PaO_2 68.1 mmHg and P/F Ratio 76.6 with an increase in PCO_2 43.5 mmHg, a decrease in PaO2 to 73.2 mmHg and a P/F Ratio of 77.4 were not significantly different from the initial value. From these values, it was shown that at the beginning of the treatment period, all patients were included in severe ARDS according to the Berlin classification.[15]

A similar study in Bangladesh on 240 COVID-19 patients who were admitted to the ICU with HFNC therapy showed significant improvement in oxygenation status. Similar results showed an improvement in the SpO_2 value before HFNC from 83.71% (±6.61) to 93.11% (±2.53) after HFNC administration, a decrease in PaO2 value 56.99 mmHg (±13.89) in patients who died, which is lower than the patients who succeeded PaO_2 70.18 mmHg (±17.13). Also, the P/F Ratio value in the case of dead patients (64.07±17.47) was lower than the survivors (105.18±35.09).[14]

In the successful HFNC group, at the beginning of treatment, there was a hypocapnic condition with an initial PCO_2 of 29.5 than normal with a value of 36 at the end of treatment. In the HFNC failure group, at the end of HFNC administration, there was an increase in PCO_2 to 43.5. This condition of hypercapnia was more prevalent in patients who died on a ventilator with a median PCO_2 of 54.2. Several works of literature explain the possible causes of hypercapnia that occur in COVID-19 patients on mechanical ventilation, among others, related to pulmonary microvascular occlusion and thromboinflammation. Giving a low tidal volume increases the occurrence of dead space. Other investigations suggest a primary injury to the vascular endothelium that activates the clotting cascade in the presence of in situ thrombosis and ischemia of the arteries.[15,16]

This study is a pilot retrospective descriptive study to present the outcome of HFNC use in severe COVID-19 patients, finding that HFNC was improving the hypoxemic conditions in early admission but did not correlate with general patient outcomes. The limitation of this study is that other factors contribute directly to the patient outcome but were not concluded, such as medication given and other evaluations of the patient's systemic condition. This study was conducted during the peak case of the COVID-19 pandemic when all the resources were still limited. This research is meant to be the baseline for further research and evaluate the use of HFNC and managing severe COVID-19 patients in the ICU.

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