Efficacy of High Flow Nasal Cannule in Covid-19 Patients with Acute Respiratory Distress Syndrome: Scoping Review

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ABSTRACT

COVID-19 is caused by SARS-CoV-2, which began in Wuhan, China, in December 2019. On March 11, 2020, WHO (World Health Organization) declared COVID-19 as a pandemic. COVID-19 can be accompanied by life-threatening complications, like heart failure, kidney failure, cerebrovascular disease, acute respiratory disease syndrome (ARDS). ARDS is the most reported complication that happens in patients COVID-19 who need intensive care. A high flow nasal cannula (HFNC) is a beneficial therapy for patients with acute respiratory distress syndrome (ARDS), but its efficacy is not well known in patients with COVID-19. This scoping review aimed to describe the efficacy of HFNC as an oxygen therapy for COVID-19 patients with ARDS. This scoping review study searched articles across four databases (PubMed, WHO COVID-19, ScienceDirect, Portal Garuda) from July 13, 2020. All articles were screened to meet eligibility criteria. We included four articles reporting HFNC's role as therapy for COVID-19 patients with ARDS. The main findings from available data are as follows: (a) HFNC therapy can improve lung function in most COVID-19 patients (b) HNFC therapy can make more than half of the total patients avoid being intubated with an invasive ventilator (c) HFNC therapy can decrease the time of treatment COVID-19 patients (d) HFNC therapy have a risk of aerosolization and the spread of the virus. Based on all articles that we included, HFNC therapy in COVID-19 patients with ARDS appears to be clinically effective and useful to avoid patients being intubated with an invasive ventilator. Larger studies should be conducted to establish the efficacy of HFNC therapy in COVID-19 patients with ARDS.

Keywords: high flow nasal cannula (HFNC), Covid-19, ARDS, coronavirus

1. BACKGROUND

COVID-19 disease is caused by the Corona SARS-CoV-2 virus that started in Wuhan, China, in December 2019. On February 11, 2020, WHO (World Health Organization) gave the disease its official name as coronavirus disease 2019 (COVID-19), and On March 11, 2020, WHO declared COVID-19 a pandemic. At the same time, the International Committee for Taxonomy of Viruses announced that the new virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 belongs to the Coronaviridae family and the beta coronavirus genus. SARS-CoV-2 is an ssRNA virus with genetic material identical to SARS-CoV 79.6%. Coronaviruses are a group of viruses that spread easily. Examples of widely spread coronaviruses are SARS-CoV, MERS-CoV, and SARS-CoV-2 [2].

As of June 4, there are 171 million confirmed cases of COVID-19 worldwide, and 3.6 million

have died. The United States dominates the number of confirmed cases with more than 32 million cases, and 570 thousand more people have died. As of June 4, the number of confirmed cases has reached more than 1.83 million in Indonesia, with more than 51,000 deaths [3].

Diagnosis COVID-19 can be confirmed by anamnesis and assessing the epidemiological risk and contact history of the patient. Reverse-transcriptase polymerase chain reaction (RT-PCR) examination of nasopharyngeal swab specimens is the gold standard for diagnosing COVID-19 [4]. The criteria for establishing a confirmed case diagnosis are (a) person with a positive RT-PCR result, (b) person with a positive SARS-CoV-2 rapid antigen result AND meeting the criteria for a probable or suspected case definition, (c) person without symptoms (asymptomatic) with a SARS-CoV-2 rapid antigen result positive and have a history of close contact with a probable or confirmed case. Confirmed cases of COVID-19 are divided into cases with symptoms (symptomatic) and cases without symptoms (asymptomatic) [5].

In cases with moderate and severe or critical symptoms, the patient is referred and isolated to a COVID-19 referral hospital. For patients with moderate symptoms, bed rest, fluid control, oxygen therapy, complete peripheral blood laboratory monitoring, and similar treatment with mild symptoms can be given, and LMWH/UFH anticoagulation based on DPJP evaluation can be given. Management of cases with severe or critical symptoms is added by serial chest X-ray examination if worsening and monitoring of signs of patient's respiratory function (tachypnea, oxygen saturation, pressure, and oxygen fraction) and appropriate oxygen therapy. Initiate oxygen therapy if SpO2 <93% is found in free air starting from the nasal cannula to NRM 15 L/min, then titrate according to the target SpO2 92-96%. Increase oxygen therapy using an HFNC (High Flow Nasal Cannula) device if clinical improvement does not occur within 1 hour, or clinical deterioration occurs. According to patient comfort, oxygen therapy with an HFNC device initiated with a flow of 30 L/min and 40% FiO2 can maintain a target SpO2 of 92 - 96%. HFNC combined with the awake prone position can improve oxygenation and reduce the need for intubation in mild to moderate ARDS. In the acute phase of ARDS, morphological features of diffuse alveolar damage are seen [6]. The etiology of ARDS can be local or systemic. Local etiology such as pneumonia and pulmonary trauma. Extrapulmonary etiology, e.g., nonpulmonary sepsis and pancreatitis. Risk factors for ARDS include smokers, women, the elderly, and a history of alcohol consumption [4].

High-flow nasal cannula (HFNC) oxygen therapy is a breathing aid capable of supplying warm, moist oxygen at high flow through the nasal cannula. High-flow nasal cannula can provide a flow of up to 60 L/min at a temperature of 31-37 °C with an absolute humidity of 44 mg H2O/L; FiO2 varies between 21-100%. The advantages of HFNC include clearance of pharyngeal dead space, reduced respiratory effort, positive end-expiratory pressure (PEEP) effect, providing a constant fraction of inspired oxygen, improved mucociliary clearance, and patient comfort. HFNC is also known to provide a low PEEP, which can benefit mild to moderate respiratory failure. In addition, by providing a warm, humidified gas, HFNC reduces the metabolic effort required to condition the air. HFNC is better tolerated than other assisted ventilation and reduces the incidence of intubation, thus providing a good clinical prognosis in patients with acute respiratory failure [4].

The use of HFNC as management of

COVID-19 is still under development as part of airway and breathing management in COVID-19 patients. Some journals do not recommend using HFNC or other non-invasive procedures, such as CPAP or NIV. NIV and HFNC have a risk of aerosol formation, so if they are to be applied, preferably in a negative pressure room (or in a room with normal pressure, but the patient is isolated from other patients) with complete PPE standards. Some parties in Western countries do not approve of the use of HFNC, so that the rate of early intubation increases and has the potential to endanger patients such as sedation and length of ICU stay. Besides that, the intubation procedure is also a risky measure for the spread of the virus. During the pandemic, COVID-19 patients with respiratory failure will be given early intubation. Early intubation also increases the need for ventilators and causes ventilators to become scarce. Delaying or preventing mechanical ventilation procedures can reduce the need for a ventilator [7]. One of the ways to delay early intubation is the HFNC procedure. This study aims to see whether HFNC has good efficacy for COVID-19 patients with ARDS.

2. METHOD

The research will use a scoping review to study the efficacy of high-flow nasal cannula as non-invasive therapy in COVID-19 patients by identifying various literature that meets predetermined criteria. In determining the articles to be used in this scoping review, the inclusion criteria are divided into criteria based on the sources, population, and research object. In terms of the type of sources, the criteria to be used are:

a) credible Indonesian and English articles

b) original article with RCT or non-RCT research methods

c) articles published in the range of 2020-2021

Figure 1 The selection process for scoping review articles based on PRISMA-ScR [8]

The original article is the type of article that will be used. The articles used are published in the 2020-2021 range to maintain the novelty value of the research. Articles that have met the inclusion criteria will then be reassessed with the following exclusion criteria:

a) identical articles from search results with various databases

b) articles that cannot be accessed in full text

c) articles that do not clearly explain the research methods carried out

d) articles that do not display the subject in ARDS

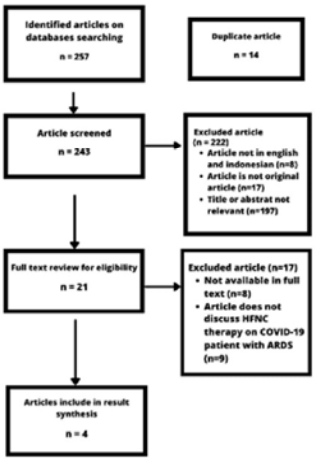
e) articles that do not specifically discuss the role of high flow nasal cannula therapy in COVID-19 patients

Various electronic databases are used as a source of information in the scoping review that will be carried out. The databases used include Science Direct, PubMed, WHO COVID, and the Garuda Portal. Databases such as Science Direct, PubMed, WHO COVID are databases for searching for English articles. Garuda Portal is a database to find articles in the Indonesian language.

The search technique was carried out by Boolean search with the combination of the words "COVID-19" AND "High flow nasal cannula" AND "Acute respiratory distress

syndrome" AND "non-invasive ventilation" AND "Respiratory variable" OR "ROX Index" OR "Mortality". The type of article that will be filtered is in the form of RCT or non-RCT research in clinical studies in the 2020-2021 period. The use of the keyword "COVID-19" can be replaced with "SARS-CoV-2" and the keyword "Acute respiratory distress syndrome" can be replaced with "Respiratory failure" to expand the search results. The article selection process in this study used guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review (PRISMA-ScR).

Figure 2 Article selection process



Microsoft Office Excel application. In this study, several variables will be analyzed, namely:

a. oxygen saturation parameters (SpO2)

b. inspired oxygen fraction (FIO2)

c. Mortality

d. Need for mechanical ventilation

e. Clinical changes of COVID-19 patients

3. RESULTS

The search for journals began on July 14, 2021. A total of 257 articles were included in the initial identification and there were 14 duplicate articles. Then we selected 243 articles based on the title and abstract with a total of 21 articles that matched our criteria. 21 articles were thoroughly read in the journal. The next stage was obtained 4 articles that met the selection criteria and excluded 17 articles that were included in the exclusion criteria. All articles included are articles in English. With a total of 205 conscientious participants, the four articles were then analyzed related to the variables that would be synthesized into research results.

3.1 Respiratory Variable

There are several important respiratory variables in COVID-19 patients with ARDS, namely oxygenation index, oxygen saturation (SpO2), and PaO2/FiO2 ratio. Respiratory varaibles are useful for monitoring and evaluating the therapy the patient is undergoing.

All journals report variable respiratory outcomes which is PaO2/FiO2 ratio. Delbove et al. reported that the HFNC-only group had a higher PaO2/FiO2ratio than the other two groups (HFNC-DNIO and HFNC-intubation) [11]. The HFNC-only group had a PaO2/FiO2 ratio of 191 (162-219) mmHg, while the HFNC-DNIO (do not intubate order) was 127 (117-208) mmHg and the HFNC-intubation group was 121 (103-169) mmHg. Deng, Liehua et al. also reported similar results. They found a higher PaO2/FiO2 ratio in early HFNC than in late HFNC [10]. In early HFNC the PaO2/FiO2 is 230 (218-254) mmHg while in late HFNC it is 172 (165-183) mmHg ($p=<0.001$). In the research of Panadero et al. also reported that the SpO2/FiO2 ratio was significantly better in the non-intubated group than in the intubated group (113.4 ± 6.6 vs 93.7 ± 6.7: $p=0.020$) [12]. Then from research Simioli et al. Reported that nine patients with baseline PaO2/FiO2 109 ± 45 mmHg after 2 hours of initiation of HFNC increased to 254 ± 69.3 mmHg, which then, after 48 hours increased to 396 ± 83.5 mmHg [9]. This proves that HFNC can increase the ratio of PaO2/FiO2, SpO2/FiO2, and SpO2

to improve the respiratory function of COVID-19 patients with ARDS.

3.2 ROX Index

The ROX (Respiratory Rate Oxygenation) index serves as a predictor of failure of HFNC therapy. The ROX index was measured by oxygen saturation versus the fraction of oxygen inhaled versus respiratory rate (SpO2/FiO2/RR). The lower the ROX index, the higher the risk of the patient having to be intubated.

The study of Panadero et al. where the ROX index in the group not requiring intubation was better (5.0 ± 1.6) than the group requiring intubation (4.0 ± 1.0; p = 0.018) with a cut-off of 4.94 measured after 2-6 hours of starting therapy [12]. The same thing was also reported by Simioli et al. obtained after 2 hours of initiation of HFNC ROX index of 9 patients with a mean of 11.17 (7.38 – 14.4) [9]. A ROX index score below 4.94 is associated with an increased risk of intubation. This proves that COVID-19 patients with ARDS undergoing HFNC therapy can prevent the risk of using invasive ventilators.

3.3 Therapy Failure

HFNC therapy can serve as a strategy to prevent intubation. However, some patients with worsening symptoms who can no longer respond to HFNC oxygen therapy should be intubated. In research Delbove et al. reported that of 35 COVID-19 patients with ARDS, 20 (57%) of them had to be continued on mechanical ventilation [11]. The research Deng's supported this and reported that in the early HFNC group, only four people (10.5%) had to be intubated. In comparison, in the late HFNC group, as many as 38 people (52.7%) had respiratory support followed by invasive ventilation [10].

The same thing was also reported in the study of Panadero et al. that 21 patients (52.5%) experienced treatment failure and required intubation on day 30 [12]. In general, the journals included in the study reported failure of HFNC therapy in the range of 52.5 - 57% of all patients. This proves that the use of HFNC in COVID-19 patients with ARDS can prevent intubation in 43 - 47.5% of all patients. The use of HFNC in COVID-19 patients with ARDS can maximize the handling of health facilities to meet the needs of invasive ventilators in critically ill patients to reduce mortality.

3.4 Risk of Transmission to Medical Personnel

The use of HFNC therapy is known to have a risk of aerosolization and the spread of the virus. According to Delbove et al., In his research, it was reported that among 110 health workers who were tested for COVID-19 serology, two people (1.8%) had positive results. One was a nurse in the acute pneumology department, and the other was a conventional ICU nurse without sufficient data for work-related infections [11]. The risk of COVID-19 transmission can be minimized with the right personal protective equipment and patient room strategies. Patients are advised to keep wearing a mask during HFNC therapy. Prevention is in the form of a high-energy particulate accumulator (HEPA) filter and placing the patient in a negative pressure room. This proves that HFNC therapy has a risk of aerosolization and transmission of COVID-19.

3.5 Length of Stay

We also found parameter length of stay in the journals that we included. Length of stay can indicate how effective the treatment for patient. Delbove et al. reported that the HNFC-only group had a shorter treatment time than the HFNC-intubation group. The HNFC-only group had a median ICU stay of 9 (7-13) days and a hospital stay of 17 (10-43) days. In the HFNC-intubation group, the average ICU stay was 18 (14-25) days. The

mean length of hospital stay in the HFNC-intubation group was 27 (19-41) days [11]. While in Deng's study stated that the length of stay in the ICU in the early HFNC group was lower than in the late HFNC group. In early HFNC, the length of stay in the ICU is 12 (10-15) days, while in late HFNC, the length of stay in the ICU is 18 (13-22) days. The length of stay in the hospital was also longer in the late HFNC group. The hospital stays in the early HFNC group was 16 (15-22) days, while in the late HFNC group, it was 30 (27-33) days [10].

Variable recovery time from ARDS reported by Simioli et al. stated that the average patient recovered from ARDS after seven ± 4.1 days [9]. This can maximize health facilities for handling more critical patients. This pandemic situation made the number of patients treated soar in a short time, causing an increase in the ICU bed occupancy rate or BOR (bed occupancy rate). BOR is the percentage of bed usage at a certain time unit. In addition, BOR also functions as an indicator used by policymakers to determine strategies for handling COVID-19.

3.6 Mortality

Three journals reported mortality associated with the use of HFNC therapy. Panadero et al. reported a 22.5% mortality or as many as 9 COVID-19 patients with ARDS who underwent HFNC therapy at the IRCU (Intensive Respiratory Care Unit), all of whom were patients who had failed HFNC therapy. This is quite similar to the Delbove et al. results

Table 1 Characteristic of included article

No	Author	Published Year	Publisher	Study Type	Location	Aim of the study	Participants	Intervention	Comparison	Conclusion
1	Delbove et al.	2021	Therapeutic Advances in Respiratory Disease	Retrospective cohort study	Vannes, Italy	Describe the results of patients suffering from COVID-19 with ARDS who are given HFNC therapy and evaluate the safety of HFNC (patients and health workers)	46	HFNC	Grup HF-NC-only	Grup HFNC-DNIO (do not intubate order)
2	Deng, Liehua et al.	2021	Aging-us	Retrospective cohort study	China	Describe the clinical outcomes of elderly patients suffering from COVID-19 who were treated with HFNC	110	HFNC	Early HFNC Late HFNC	Patients in the early HFNC group were less likely to develop ARDS, a longer time to onset of severe ARDS and a shorter duration of ICU and hospital stay.
3	Panadero et al.	2020	Multidisciplinary Respiratory Medicine	Observarsional Study	Madrid, Spain	Describes the experience of using HFNC in the IRCU during the COVID-19 pandemic, focusing on the benefits of preventing intubation in patients with ARDS	40	HFNC (AIR-VO2) 31-37°c, 50-60 L/min	HFNC success HFNC failure	HFNC can to treat ARDS patients by 47.5% of the total patients without the need for invasive ventilation and with low mortality
4	Simioli et al.	2020	Anaesthesiology Intensive Therapy	Observarsional Study	Naples, Italy	Reporting the experience of the efficacy and safety of HFNC in COVID-19 patients	9	HFNC 34-37 °c, 50-60 L/min	none	Improved ventilation in all patients. The use of 2 hours of HFNC can increase the PaO2/FiO2 variable. All patients recovered from respiratory failure after a median of 7 days.

Table 2 Result of included article

No	Author	Respiratory Variable	ROX Index	Therapy Failure	Risk of Transmission to Medical Personnel	Length of Stay	Mortality
1	Delbove et al.	PaO2/FiO2: HFNC-only : 191 (162-219) mmHg; HFNC-DNIO: 127 (117-208) mmHg; HFNC-intubation: 121 (103-169) mmHg	Not reported	20 person (57%)	2 person (1.8%)	Length of stay in ICU HFNC-only 9 (7-13) days; HFNC-intubation 18 (14-25) days Length of stay in The hospital HFNC-only 17 (10-43) days; HFNC-intubation 27 (19-41) days	20 % (7/35)
2	Deng, Liehua et al.	PaO2/FiO2: early HFNC: (230 (218-254) mmHg Late HFNC: 172 (165-183) mmHg (p=<0.001)	Not reported	38 person (52,7%)	Not reported	Length of stay in ICU early HFNC: 12 (10-15) days; late HFNC: 18 (13-22) days Length of stay in The hospital early HFNC: 16 (15-22) days; late HFNC: 30 (27-33) days	21,8%
3	Panadero et al.	Rasio SpO2/FiO2: Didn't require intubation group: 113.4 ± 6.6 Required intubation group: 93.7 ± 6.7; p=0.020	Didn't require intubation group: 5.0 ± 1.6 Required intubation group: 4.0 ± 1.0; p=0.018	21 person (52.5%)	Not reported	Not reported	22.5%
4	Simioli et al.	baseline PaO2/FiO2: 109 ± 45 mmHg; setelah 2 jam (254 ± 69.3 mmHg); setelah 48 jam (396 ± 83.5 mmHg)	After 2 hours: 11.17 (7.38 – 14.4)	Not reported	Not reported	Average days to recover from ARDS: 7 ± 4.1 days	Not reported

with a mortality of 20% in the HFNC-only and HFNC-intubation groups [11]. Then in a larger-scale study, Deng, Liehua et al. reported that 110 patients who received HFNC therapy had a mortality of 21.8%, with details of patients receiving HFNC therapy in the mild ARDS stage had a mortality of 5.3% in 38 people while in moderate ARDS patients had a mortality of 30.6% in 72 people [10]. HFNC therapy in COVID-19 patients with mild ARDS has a lower mortality percentage than moderate-severe ARDS. This proves that HFNC therapy is quite effective in COVID-19 patients with mild ARDS.

4. CONCLUSION

HFNC therapy is the main oxygen therapy which can also be a strategy to prevent intubation in COVID-19 patients with ARDS. ROX and ARDS indices with PaO2/FiO2 <150 can be predictors of HFNC therapy failure. Prevention of this intubation can affect the need for ventilators and the length of time the patient stays in the hospital. If COVID-19 patients with ARDS can be managed efficiently, it can reduce the need for ventilators and the ICU bed occupancy rate. The potential risk of COVID-19 transmission with HFNC therapy must also be considered by implementing appropriate personal protective policies and placing patients in negative pressure rooms. The limitation of this study is that there are still limited research journals discussing the effectiveness of HFNC in COVID-19 patients with ARDS. Therefore, the authors suggest that further research can add to the journal database to expand the scope of identification of research journals. In conclusion, HFNC therapy is effective for COVID-19 patients with mild ARDS, which serves as a respiratory support and intubation prevention strategy.

AUTHORS' CONTRIBUTIONS

Conceptualization: F.N., M.Y.H.; Methdology: F.N.; Validation: F.N. and M.Y.H.; formal analy-

sis: F.N.; writing- original draft: F.N.; supervision: M.Y.H.

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