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Brief report

Benefits of early use of high-flow-nasal-cannula (HFNC) in patients with COVID-19 associated pneumonia☆

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ABSTRACT

Introduction: Severe COVID-19 is associated with hypoxemic bilateral pneumonia that leads to mechanical ventilation in a considerable proportion of patients. To the best of our knowledge, there are no recommendations about the best time to initiate high flow nasal cannula (HFNC).
Patients and methods: Retrospective study of all patients admitted for COVID-19 pneumonia who required HNFO between March 2020 and February 2021. Patients were grouped in early HNFC or late HNFC, according to the modified Kirby index.
Results: 53 patients were included. Forty-four of them were included in the early HFNC and 9 in late HNFC. There were no statistically significant clinical-epidemiological differences. Early use of HFNC was associated with a decrease in the need for intubation (29.5 vs. 66.6%, p = 0.044), hospital stay (18.8 d vs. 36 d, p = 0.022) and mortality (22.7 vs. 55.5%, p = 0.061).
Conclusions: Early HFNC use is associated with a decrease in the need for intubation, mortality and overall hospital stay.

Beneficio del empleo precoz de la oxigenoterapia nasal de alto flujo (ONAF) en pacientes con neumonía por SARS-CoV-2

Palabras clave:
ONAF
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RESUMEN

Introducción: La COVID-19 grave se asocia con una neumonía bilateral hipoxemiante, que desemboca en la necesidad de ventilación mecánica en un considerable número de pacientes. Hasta la fecha no existen recomendaciones acerca del momento óptimo para el inicio de la ONAF.
Pacientes y métodos: Estudio retrospectivo de todos los pacientes ingresados por neumonía por COVID-19 y que precisaron ONAF entre marzo de 2020 y febrero de 2021. Se agruparon los pacientes en función del momento de inicio de la ONAF de acuerdo con la PaFi modificada.
Resultados: Se incluyeron 53 pacientes, en 44 se inició la ONAF precozmente y en nueve de ellos se inició tardíamente. No existieron diferencias clínico-epidemiológicas significativas. La utilización precoz de la ONAF se asoció con una disminución de la necesidad de intubación (29,5 vs. 66,6%, p = 0,044), de la estancia hospitalaria (18,8 d vs. 36 d, p = 0,022) y de la mortalidad (22,7 vs. 55,5%, p = 0,061).
Conclusiones: El empleo precoz de la ONAF se asocia con una disminución de la necesidad de intubación, de la mortalidad y de la estancia hospitalaria global.

Introduction

High-flow nasal cannula (HFNC) oxygen therapy has demonstrated benefits in a number of situations where gas exchange is compromised. There are many benefits provided by HFNC therapy, the most important being the achievement of a more stable FiO_2 at a higher flow rate, the reduction of air resistance by obtaining

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Table 1
Patient laboratory values on admission and at HFNC initiation.

Variable	Admission	HFNC	p
CRP (mg/L)	102.6	103.6	0.907
Ferritin (ng/mL)	697.11	838.2	0.020
LDH (IU/L)	345.6	407.5	0.032
DD (mg/L)	1.09	1.47	0.295
SHI (n)	32	46	0.035

Values are presented as mean, except SHI, which reflects the number of patients.
DD: D-dimer; LDH: lactate dehydrogenase test; HFNC: high-flow nasal cannula oxygen therapy; CRP: C-reactive protein; HIS: hyperinflammatory syndrome.

warm and properly humidified air, the reduction of dead space and the improvement of alveolar ventilation.[1]

On the other hand, SARS-CoV-2 infection causes bilateral hypoxemic pneumonia in some patients, which progresses rapidly, requiring increased oxygen therapy and, in up to 15-20% of patients, admission to the Intensive Care Unit (ICU) for orotracheal intubation (OTI) and connection to mechanical ventilation (MV).

Despite the known benefits of HNFC therapy in patients with respiratory failure, the initial expert recommendation was early intubation of patients with hypoxemic COVID-19 pneumonia because of the risk of aerosolization and infection,[2] as well as doubts about the efficacy of HNFC therapy in these patients, recommending the use of continuous positive airway pressure (CPAP)[3] if oxygenation other than Ventimask® or nasal cannula was required.

Oxygen therapy of patients with bilateral hypoxemic COVID-19 pneumonia has seen improvements in our hospital as our understanding of the pathophysiology of COVID-19 has improved, with HFNC therapy starting earlier and earlier. From an initial use in patients with SpO_2 <90% with FiO_2 50% (Ventimask >10 bpm) to early use in patients with a PaO2/FiO2 < 300 with FiO_2 40% (Ventimask 6-8 bpm). This has led us to comparatively evaluate the outcome of early versus non-early application of HFNC therapy.

Patients and methods

Retrospective study including all patients requiring HFNC therapy as part of treatment during admission, seen in our hospital from March 2020 to February 2021. HLA Inmaculada Hospital is a private specialty hospital with 83 conventional hospital beds and six ICU beds.

For the definition of early HFNC therapy and non-early HFNC therapy, PaO2/FiO2 was used, substituting PaO_2 by SpO_2.[4] In this way, early HFNC therapy was defined as that which began in patients without severe respiratory distress (SpO_2/FiO_2 > 100), and non-early HFNC therapy if started in patients with severe respiratory distress ($SpO_2/FiO_2 \leq 100$).

A patient was considered to have a hyperinflammatory syndrome if they he/she met two or more of the following criteria: CRP > 100 mg/L, ferritin > 500 ng/mL, LDH > 300 IU/L and D-dimer > 1 mg/L.

Results

53 patients were included, 32 (60%) of whom were male. The mean age of the patients was 68.5 years (48-90 years), of whom 44 had some comorbidity, with HTN (19/53), obesity (14/53) and DM (6/53) being the most common.

Table 1 shows the laboratory values at the time of admission and at the time of HFNC therapy initiation.

Of the total number of patients, 20 (37.7%) required admission to the ICU for OTI and MV and 15 patients (28.3%) died.

Of the 53 patients, nine (17%) had severe respiratory distress at the time of starting HFNC therapy, so it was considered that nine patients had non-early HFNC therapy, and 44 patients (83%) had early HFNC therapy.

Table 2
Characteristics of patients with early HFNC vs. Non-early HFNC.

	Early HFNC (n = 44)	Non-early HFNC (n = 9)	p
Age	67.6	73	0.212
Sex, male n (%)	29 (66%)	3 (33%)	0.075
Sx up to admission (days)	6.98	8.22	0.273
Sx up to HFNC (days)	9.4	11	0.227
CRP (mg/L)	97.5	127.6	0.183
Ferritin (ng/mL)	703	667	0.886
LDH (IU/L)	335	393	0.140
DD (mg/L)	1.12	0.9	0.719
HIS, n (%)	36 (81.8%)	9 (100%)	0.200
SpO_2/FiO_2	**216**	**93.8**	**0.0001**
Immunosuppressants, n (%)	11 (25%)	1 (11.1%)	0.338
ICU n (%)	**13 (29.5%)**	**6 (66.6%)**	**0.044**
Death n (%)	10 (22.7%)	5 (55.5%)	0.061
HFNC days	**7.20**	**2.56**	**0.0001**
Admission days	**15.8**	**37.1**	**0.001**

Data presented as mean, except sex (male), HIS, IS, ICU and *death* that show the number of patients who presented this characteristic.
DD: D-dimer; immunosuppressants: use of immunosuppressants (tocilizumab, baricitinib and/or anakinra); LDH: lactate dehydrogenase test; HFNC: high-flow nasal cannula oxygen therapy; CRP: C-reactive protein; Sx: symptoms; HIS: hyperinflammatory syndrome; ICU: Intensive care unit.

Table 2 details the epidemiological and laboratory characteristics of patients with early HFNC therapy and patients with non-early HFNC therapy.

Discussion

In this study, the use of early HFNC therapy, that is, when there is a progressive increase in oxygen requirements, but before the patient develops severe respiratory distress, was associated with a statistically significant decrease in the need for ICU admission (p = 0.044) and a reduction in mortality that was very close to reaching statistical significance (p = 0.061). It was also associated with a significant reduction in days of hospitalisation, a difference that also reached statistical significance (p = 0.011).

In accordance with the WHO recommendations on the use of HFNC,[2] the use of this ventilatory modality was reserved for patients with extremely high requirements, with deeply disappointing results. Therefore, following the publication of data on the safety of the HFNC in terms of the risk of infection transmission,[5] we decided to start early HFNC therapy, despite the lack of clinical trials in patients with COVID-19.

Recently, some studies and reviews have been published which, like ours, demonstrate a reduction in the need for admission to the ICU for OTI and MV, mortality and overall hospital stay[6,7]; however, and unlike our study, they do not differentiate between the early and non-early use of HFNC therapy. Although the use of HFNC therapy, even in patients with severe respiratory distress, may be associated with some benefit, the application of HFNC therapy in the initial phases is the most effective strategy, which is consistent with what has been reflected by other authors,[8] who already consider HFNC therapy as the non-invasive ventilatory modality of choice in patients with COVID-19.

Our study has some limitations, such as its retrospective nature, although given the development of the pandemic it was not possible to establish a clinical trial, so a retrospective design was the only option. However, given the limited number of professionals involved in the management of patients with COVID in our hospital, and the inclusion of all patients who underwent HFNC therapy, we believe that the biases inherent to this type of study do not exist. On the other hand, we decided not to assess the existence of

dyspnoea as a criterion for the use of HFNC, given that in COVID-19 there is often a dissociation between the patient's hypoxia and dyspnoea, known as happy hypoxia in patients with COVID-19,[9] and we therefore decided not to assess this aspect. Finally, although the decrease in mortality did not reach statistical significance, there was a very-close-to-significance trend (p = 0.061), with a considerable reduction in mortality (22.7 vs. 55.5%), which makes it clinically relevant. Finally, we believe that there are no confounding factors regarding the treatment which would affect the results; all patients received glucocorticoids according to the hospital's treatment protocol, methylprednisolone 1.5-2 mg/kg/d IV due to the development of respiratory failure; with respect to the use of immunosuppressants (tocilizumab, baricitinib, anakinra), there were no significant differences between the two groups (p = 0.338), although there were percentage differences (25 vs. 11%, early HFNC vs. late HFNC). We cannot rule out the possibility that, given the sample size, there may be some undetected bias, although given the magnitude of the p, we do not believe this to be the case.

It is important to note that patients with early HFNC therapy spent more time on HFNC therapy than those with late HFNC therapy (7.2 days ± 3.2 vs. 2.56 days ± 1.74, p = 0.0001), explained by the lower need for ICU admission and higher patient survival.

The results of this study suggest that the early use of HFNC therapy is associated with a decrease in the need for intubation, mortality and overall hospital stay, and its use should be implemented as soon as patients reach SpO_2/FiO_2 < 300 with FiO_2 >40% (Ventimask at 6-8 bpm).

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Conflict of interests

The authors declare that they have no conflict of interest.

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