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Analysis of the Experience in the Use of the High-Flow Nasal Cannula as Therapeutics in SARS-CoV-2 Pneumonia

Análisis de la experiencia del uso de cánula nasal de alto flujo como terapéutica en neumonía por SARS-CoV-2

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ABSTRACT

Introduction: During the SARS-CoV-2 pandemic, the high-flow nasal cannula (HFNC) was used as support while waiting for the Intensive Care Unit (ICU) or as an alternative to invasive ventilation.

Objectives: Primary: to determine if the high-flow nasal cannula prevents orotracheal intubation. Secondary: to analyze predictors of success at the start of the high-flow nasal cannula treatment and descriptive analysis of the sample .

Materials and methods: retrospective descriptive observational study. We included patients over 16 years of age positive for SARS-CoV-2, treated in the emergency department and Intensive Care Unit. The patients used the high-flow nasal cannula between October 2020 and March 2021. Data was collected in individual forms, which were then analyzed by an external professional.

Results: The study included 72 patients (16 to 88 years old), 20 women and 52 men. 50 % of the sample avoided orotracheal intubation. Initial IROX, "success" group vs. "failure" group $p = 0.006$. Comparison of IROX at 12hr, "success" group vs. "failure" group $p < 0.001$. Comparison of "Time from admission to start of high-flow nasal cannula treatment", "success" group vs. "failure" group $p = 0.133$ Comparison of "Delta IROX", "success" group vs. "failure" group $p = 0.092$.

Conclusion: Orotracheal intubation was avoided in 50 % of the cases. The initial IROX and the IROX 12 hours after the use of the high-flow nasal cannula were statistically significant, which is a good predictor of success in this population. The date of symptom onset and the use of the HFNC and Delta IROX during the first 12 hours were not statistically significant for the success of the treatment. These data are a useful tool for generating patient selection protocols for this disease.

Key words: High-flow nasal cannula; High-flow oxygen therapy; Respiratory failure; SARS-CoV-2 infection

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RESUMEN

Introducción: Durante la pandemia por SARS-CoV-2, la cánula nasal de alto flujo (CNAF) se usó como soporte en espera de Unidad de terapia intensiva (UTI) o como alternativa a la ventilación invasiva.

Objetivos: Primario: Determinar si la cánula nasal de alto flujo evita la intubación orotraqueal. Secundarios: Analizar predictores de éxito al inicio de la cánula nasal de alto flujo y análisis descriptivo de la muestra.

Materiales y métodos: Estudio observacional descriptivo retrospectivo. Se incluyeron pacientes mayores de 16 años positivos para SARS-CoV-2, atendidos en guardia y unidad de terapia intensiva, que utilizaron cánula nasal de alto flujo entre octubre de 2020 y marzo 2021. Se recolectaron datos en planillas individuales, analizadas por un profesional externo.

Resultados: Se incluyeron en el trabajo 72 pacientes (de 16 a 88 años), 20 mujeres y 52 hombres. El 50 % de la muestra evitó la intubación orotraqueal. El IROX inicio grupo "éxito" vs. grupo "fracaso", $p = 0,006$. Comparación Irox 12 h grupo "éxito" vs. grupo "fracaso" $p < 0,001$. Comparación "tiempo desde ingreso a inicio de cánula nasal de alto flujo" grupo "éxito" vs. grupo "fracaso", $p = 0,133$. Comparación "Delta IROX" grupo "éxito" vs grupo "fracaso" $p = 0,092$.

Conclusión: Se evitó la intubación orotraqueal en el 50 % de los casos. El IROX de inicio y el IROX a las 12 h del uso de cánula nasal de alto flujo fue estadísticamente significativo, lo que es un buen predictor del éxito en esta población. La fecha de inicio de síntomas y el uso de cánula nasal de alto flujo y el delta del IROX durante las primeras 12 h no fue estadísticamente significativo para el éxito de la terapia. Estos datos son una herramienta útil con el objeto de generar protocolos de selección de pacientes para esta patología.

Palabras claves: Cánula nasal de alto flujo; Oxigenoterapia de alto-flujo; Insuficiencia respiratoria; Infección por SARS-CoV-2

INTRODUCTION

The use of the high-flow nasal cannula (HFNC) increased during the COVID-19 pandemic due to the high demand from patients with acute respiratory failure (ARF).

The use of high-flow oxygen therapy was a point of controversy among major critical care medical societies worldwide during the COVID-19 pandemic, especially due to concerns regarding the safety of the healthcare personnel and the delay in starting therapy.[1]

Therefore, the therapeutic measures traditionally implemented to counteract COVID-19-related hypoxemia have included conventional oxygen therapy and invasive mechanical ventilation.

The use of oxygen (O_2) through a conventional oxygen therapy mask has long been the first-line therapy for patients with acute respiratory failure (ARF).

However, this strategy is far from ideal because conventional oxygen therapy does not reduce respiratory effort or improve alveolar ventilation.

On the other hand, the gas delivered by conventional devices is dry and cold, which can irritate the airways, disrupt mucociliary clearance, and cause discomfort to the patient.[2]

The use of the HFNC allows for improved oxygenation through various mechanisms, such as a reduction in the dilution of the oxygen administered with ambient air,[3,4] a decrease in dead space,[4,5] an increase in circulating volume,[5,6] and the generation of positive airway pressure (CPAP),[6-8] resulting in a reduction of respiratory effort and respiratory rate.[6-10]

The use of the HFNC allows for the delivery of a gas flow of up to 60 L/min through silicone nasal cannulas, with the supplied gas conditioned to ideal temperature and humidity levels (37°C and 100 % relative humidity).

Several studies have demonstrated that using flow rates between 35 and 60 L/min results in mean expiratory pressures at the pharyngeal level of 2-3 cmH2O with the mouth open and 5-7 cmH2O with the mouth closed.[11-12] Furthermore, it has been shown that the use of the HFNC increases lung impedance at the end of expiration,[5, 6] a parameter correlated with lung volume. Alveolar recruitment is optimized,[13] due to increased airway pressures.

Considering the positive outcomes observed with the early application of the HFNC in patients with moderate to severe COVID-19 pneumonia,[14,15] and using the IROX index[16,17] as a predictor of success, this retrospective observational study aims to establish an objective relationship between treatment success and failure with the analyzed variables, offering a robust tool for managing the disease.

Faced with the high mortality observed during the first wave of the pandemic, there arose a need for more efficient approaches to treat hypoxemia in COVID-19 patients.[18,19]

The primary objective of this study is to determine whether the HFNC avoids orotracheal intubation. As secondary objectives, the study aims to analyze whether the initial IROX, the IROX at 12 hours, the Delta IROX during the first 12 hours, and the start of HFNC treatment from the onset of symptoms serve as predictors of treatment success.

MATERIALS AND METHODS

Designs

This is a retrospective and descriptive study of patients attended at the Hospital Central, a regional hospital in the region of Cuyo, Argentina, who were admitted to the Emergency Department and Covid Intensive Care Unit.

The ARF is the inability of the respiratory system to fulfill its basic function, which is the gaseous exchange of oxygen and carbon dioxide between ambient air and circulating blood; with the presence of arterial hypoxemia (PaO_2 below 60 mmHg), at rest, at sea level, and breathing ambient air, with or without hypercapnia ($PaCO_2$ above 45 mmHg). We will refer to hypoxemia only in cases where the PaO_2 is between 60 and 80 mmHg. With pulse oximetry, oxygen saturation values of 90 % to 95 % can be considered equivalent to a PaO_2 of 60 to 80 mmHg (hypoxemia), and if they are 90 %, they are equivalent to a PaO_2 of 60 mmHg (respiratory failure).[21]

The HFNC is a non-invasive respiratory support designed to deliver flows between 30-60 L/min. It works by mixing air and oxygen, humidified and heated through a nasal cannula specifically designed for these therapeutics.[2]

The IROX is a variable used to evaluate the success or failure of a high-flow nasal cannula for respiratory failure; it is the ROX index (IROX) that combines oxygenation (SpO_2/FiO_2) and respiratory work (RR). Its validity in COVID-19 pneumonia has a high sensitivity for predicting therapy failure and is associated with high mortality (45.4 %).[16, 17]

The diagnosis of Covid-19 was made by nasopharyngeal swabbing by the on-call laboratory staff and referred to the molecular biology service of the Hospital Central, where the sample was analyzed by PCR (polymerase chain reaction through viral RNA) with the Schep SARS-CoV-2 Multi-FAST Kit.

Sample

In the period between October 2020 and March 2021, with confirmed Covid 19 and suspicious symptoms. The sample included patients older than 15 years, and collaborators who tolerate the device and follow the operator's indications within their psychophysical limitations. The Cabrini Respiratory Strain Scale (CAB-RSS) (Annex 1) was used as a guide for orotracheal intubation criteria with a CAB-RSS score of 3 to 5; patients without orotracheal intubation criteria, with poor clinical prognosis for intubation and confirmed diagnosis of COVID-19 by rapid test or nasopharyngeal swab. Patients with criteria of imminent need for OTI (orotracheal intubation) and CAB-RSS scale of less than 2 or greater than 6 were excluded.

Variables

In patients who met the inclusion criteria, the following variables were analyzed during the first 24 hours: age, sex, comorbidities, initial IROX, and IROX at 1, 2, 4, 6, 12 hours after starting treatment with HFNC, success or failure of treatment in relation to the days elapsed between the date of symptom onset and the start of treatment with the high-flow nasal cannula.

The data were collected in individual patient spreadsheets and shared by means of a drive between on-call kinesiologists in each area from Monday to Sunday, and then analyzed using the Access program.

On admission, the patient was clinically evaluated with the CAB-RSS scale; if he/she showed signs of hypoxemia and a score of up to 2 on this scale, conventional oxygen therapy was continued with eventual prone decubitus positioning. If the CAB-RSS score was between 3 and 5, the HFNC was placed and the patient was put in prone decubitus position. After the placement of the HFNC and eventual change of decubitus, clinical signs were evaluated thoroughly during the first 12 hours with IROX. If the IROX was equal to or lower than 2.85 in the first place, it suggested OTI; if the IROX was equal to or higher than 3.85, treatment was continued and evaluations were performed in the following hours. If IROX was lower than 4.88 at 6 hours after initiation, it was considered as treatment failure; and if it was higher, treatment was continued (Figure 1).

Monitoring HFNC placement in patients was performed through the ROX index (IROX), which is defined as the ratio between pulse oximetry/ fraction of inspired oxygen (SpO_2 /FiO_2) and respiratory rate (RR). Roca et al[20] identified patients at high risk of HFNC failure when this index was < 4.88 at 12 hours. The cutoff values were different, as were the cutoff times for predicting failure. A recent meta-analysis was able to evidence in the subgroup using an IROX > 5 greater discriminatory accuracy in predicting failures compared to a cutoff value ≤ 5. [17]

HFNC treatment was started with high flows of 50-60 L/min, adjusting the FiO_2 to maintain the SpO_2 between 92 %-96 %. The temperature was automatically regulated

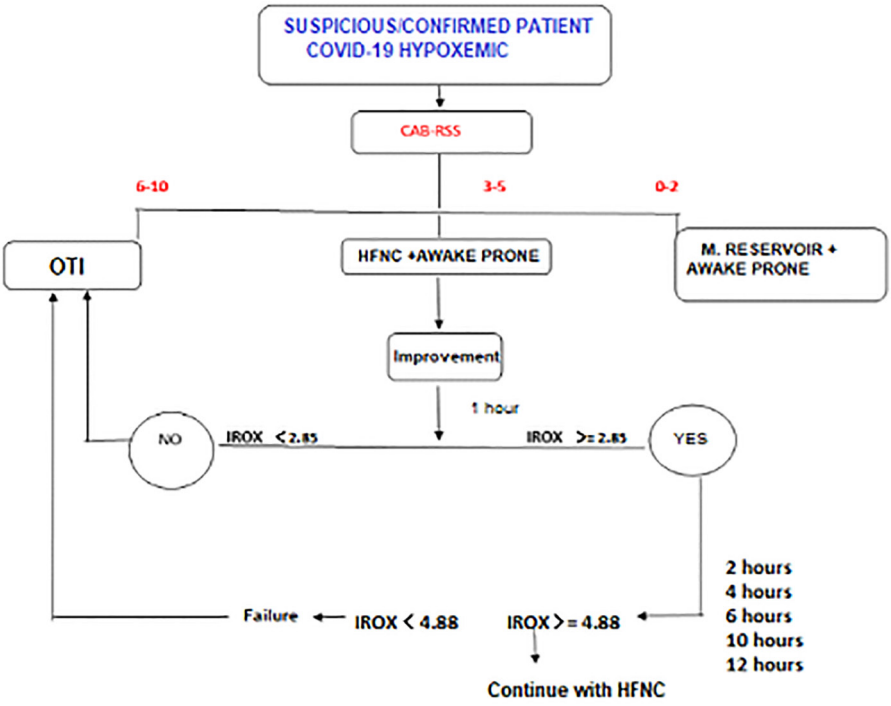

Figure 1. Algorithm showing how the HFNC is used.

by the equipment. Patients were put in prone decubitus position from the beginning, and were alternated with lateral decubitus positions depending on their tolerance. Patients were monitored by noninvasive measurement of heart rate and blood pressure, oxygen saturation and respiratory rate. The FiO_2 was gradually reduced while maintaining the target SpO_2. The flow was also decreased gradually depending on patient tolerance and respiratory rate reduction.

The failure of the HFNC is defined as the escalation to invasive mechanical ventilation (IMV) or death. Standard indications for orotracheal intubation (OTI) included the following: respiratory rate (RR) of more than 35 breaths/min, obvious activity of accessory respiratory muscles or paradoxical abdominal breathing, progressively increase of $PaCO_2$, hemodynamic instability, and inability to protect the airways or inability to obtain saturation above 93 % with a FiO_2 of more than 80 %.

For the implementation of the HFNC, a patient interface was used, which consisted of a flexible nasal cannula instead of face masks, allowing the patient to be independent in functions such as eating, drinking, talking and sleeping easily without interrupting therapy, and is available in several sizes adapted according to the patient's anatomy (AquaNaseE); high flow and precise O_2 system allowing to deliver a flow between 0 to 60 L/min and FIO_2 from 21 % to 100 % (Neumovent tecme TS, Leistung Luft 3, R203P14, R219P86), humidifier-heater system with or without temperature control (Fisher&paykel, AquaVENT AMHH2600A), non-condensing tubing (Armstrong Medical AquaVent).

Statistical analysis

For the statistical analysis we had the IBM SPSS software platform, which was used by a professional external to the study. The results are presented for categorical variables such as count and their proportion within the category. Numerical variables, whether they are continuous or discrete, are observed as appropriate to their distribution, such as mean and standard deviation or median and interquartile range.

To compare the association between categorical variables, we used the Student's t-test or Mann-Whitney U test for numerical variables depending on their distribution. For non-parametric variables, we used the Kolmogorov-Smirnov test. The chi-squared test was used for comparing qualitative variables. A value of $p < 0.05$ in two-tailed tests was considered to be statistically significant.

RESULTS

A total of 154 patients were reviewed, and a sample of 72 patients who had been consecutively selected and had completed the data collection form was included. 82 patients were excluded due to missing data (Figure 2). 50 % of the patients avoided orotracheal intubation. The population's characteristics are presented in Table 1.

It was observed in the group of patients that those who experienced failure were older adults with two or more comorbidities, with a significant p-value of $p < 0.001$ (Table 2).

The initial IROX is significantly different between both groups, with a mean of 7.10 (95 % CI

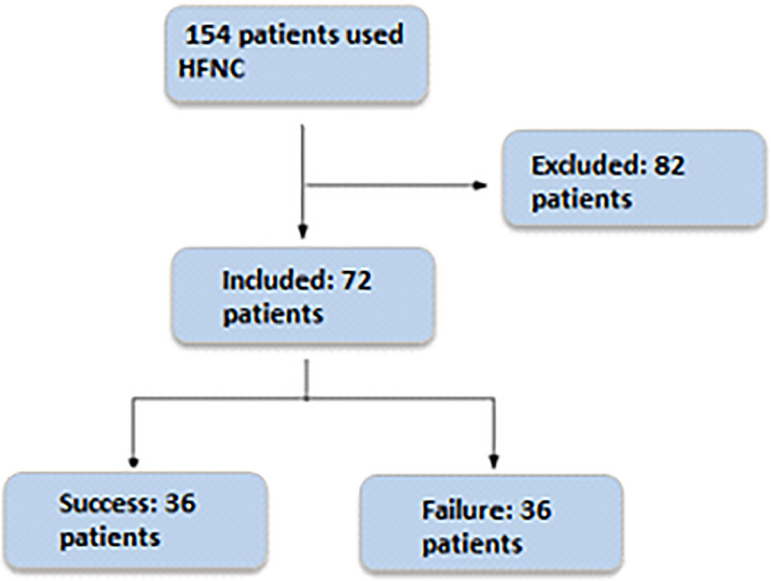

Figure 2. Patient flow diagram.

6.41-7.79), a median of 6.78, and a standard deviation of 2.94. The comparison of the initial IROX between the success group and the failure group yielded a mean ± of 6.24 ± 2.32, with a *p*-value of 0.006 (Figure 3).

The IROX score at 12hr is significantly different between both groups, with a mean of 7.26 (95 % CI 6.25-8.27), a median of 7.18, and a standard deviation of 4.29 with a $p < 0.001$ (Figure 4).

The time elapsed between symptom onset (SO) and the start of the HFNC doesn't have a statistically significant relationship with a *p*-value of 0.133, mean of 8.76 (95 % CI 7.47-10.05), a median of 8 and a standard deviation of 5.254. (Graph 3).

The Delta IROX (initial IROX/IROX at 12hr) wasn't statistically significant with a p-value of 0.092, mean value of 0.16 (95 % CI 0.76-1.07), a median of 1.19 and a standard deviation of 3.9 (Figure 5).

DISCUSSION

After several months of the pandemic, a high mortality rate was observed in patients who were under invasive ventilation; early intubation in COVID-19 is not correlated with a favorable prognosis, as noted by Plotnikow et al[18] and Farkas et al.[19] The use of the HFNC reduces the need for early intubation in adult patients with acute respiratory failure. This helps to prevent the associated risks of invasive mechanical ventilation, such as delirium, cognitive decline, ICU-acquired weakness, and secondary infections.

High-flow oxygen therapy through the HFNC is an innovative technique that combines O_2 and compressed air, allowing the delivery of high concentrations of O_2 at flow rates exceeding the peak inspiratory flow in patients with high ventilatory demands.

This oxygenation strategy is particularly comfortable for the patient due to the nasal cannula that provides humidified and warm gas, similar to physiological conditions. It also allows functional independence for activities like oral feeding, communicating, sitting up, and changing decubitus position without complications, as noted by Mellado-Artigas et al.[21]

The IROX has been suggested as a tool to predict the outcome of the HFNC in patients with ARF. In the initial phase (within the first hour of HFNC treatment), we have demonstrated that the IROX is capable of distinguishing between the success and failure of HFNC treatment in COVID-19 patients, but not with the threshold value suggested by Roca et al,[9] since we have shown better prediction accuracy with a higher threshold value.

The time elapsed between the SO and the start of the HFNC treatment was not found to be sig-

TABLA 1. Características de la cohorte

Característica	Total (72)	Success (36)	Failure (36)	%
Age (years)	58 (16-88)	51 (16-81)	64 (20-88)	
Man	51	26	25	70.83
Woman	21	10	11	29.16
Comorbidities				
Arterial hypertension	32	9	23	44.44
Obesity	24	9	15	33.33
Diabetes	21	7	14	29.16
Smoking	12	4	8	16.66
Hypothyroidism	7	2	5	9.7
COPD	3	1	2	4.16
Leukemia	3	0	3	4.16
Nephropathy	2	0	2	2.77
Glaucoma	2	0	2	2.77
Arthrosis	2	0	2	2.77
Pulmonary thromboembolism	2	2	0	2.77
Dyslipidemia	2	2	0	2.77
Renal failure	2	2	0	2.77
Use of illicit substances	2	1	1	2.77
Alcoholism	2	1	1	2.77
Stroke	2	1	1	2.77
Cardiomyopathy	2	2	0	2.77
Arrhythmia	2	1	1	2.77
Lung cancer	1	0	1	1.38
Home oxygen therapy	1	1	0	1.38
Epilepsy	1	1	0	1.38
Breast cancer	1	1	0	1.38
Colon cancer	1	1	0	1.38
Prostate cancer	1	0	1	1.38
Kidney cancer	1	1	0	1.38
Rheumatoid arthritis	1	0	1	1.38
Hypoacusis	1	0	1	1.38
Pulmonary fibrosis	1	0	1	1.38
Hepatic cirrhosis	1	0	1	1.38
Chronic venous insufficiency	1	0	1	1.38
Depression	1	0	1	1.38
Dementia	1	1	0	1.38
Pancreatitis	1	1	0	1.38
Parkinson disease	1	0	1	1.38
Hip replacement	1	1	0	1.38
No comorbidities	9	7	2	12.5

TABLE 2. Comorbidities per age group

		Without comorbidities	1 comorbidity	2 comorbidities	More than 2 comorbidities
15 to 30 years	Success	3	0	0	0
	Failure	1	0	0	0
31 to 45 years	Success	2	3	1	0
	Failure	1	0	0	0
45 to 60 years	Success	2	5	6	3
	Failure	2	1	2	8
More than 60 years	Success	0	6	2	3
	Failure	0	3	9	9
	p value	$p < 0{,}001$			

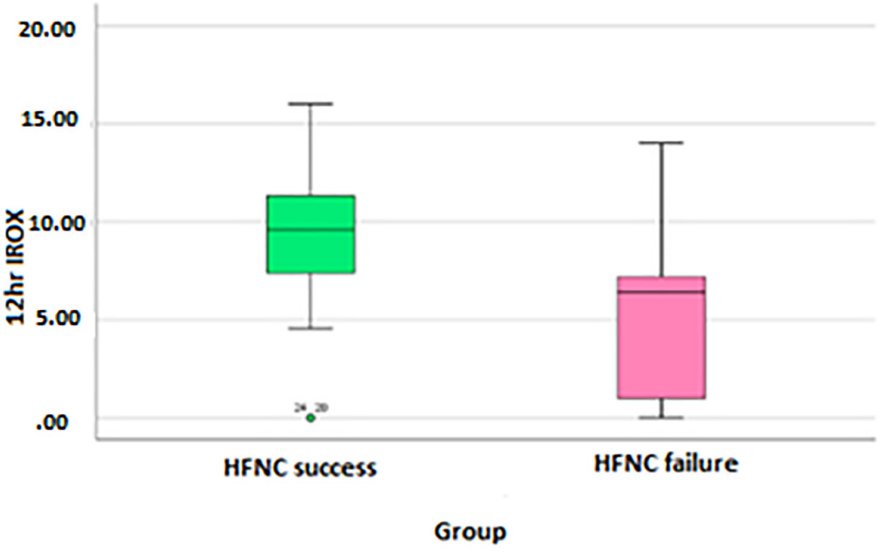

Figure 3. Initial IROX of the success group versus the failure group.

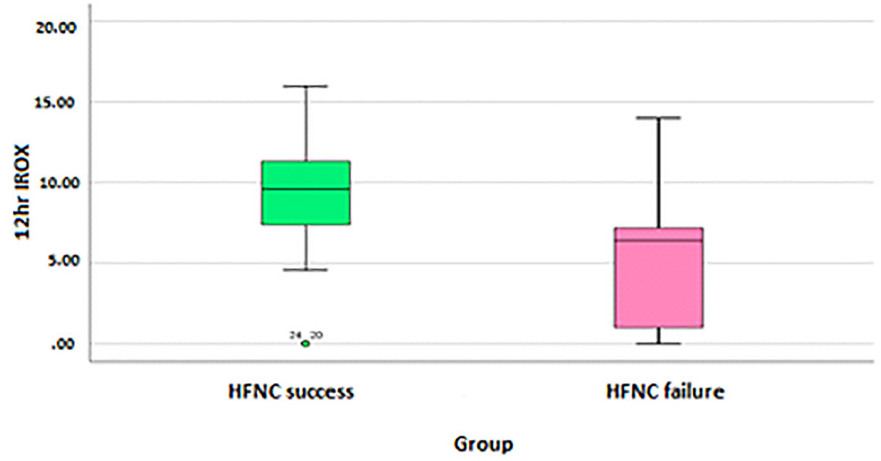

Figure 4. IROX at 12hr of the success group versus the failure group.

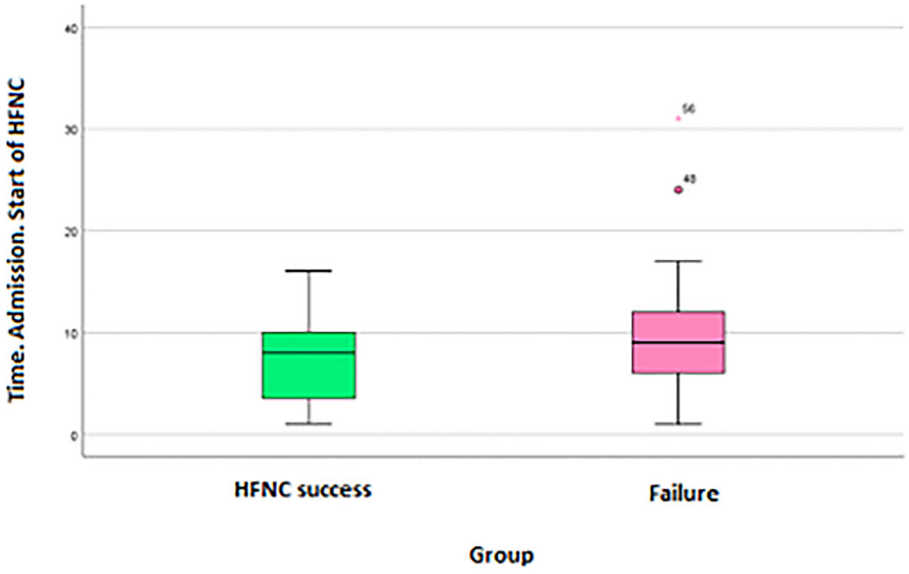

Figure 5. Relationship of symptom onset and start of HFNC between the success group and failure group.

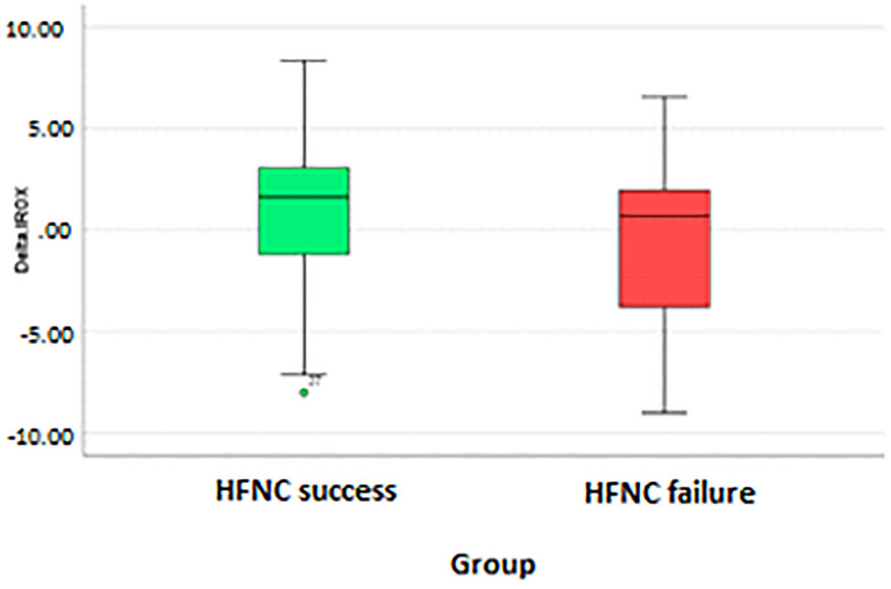

Figure 6. Initial Delta IROX versus 12hr IROX between the success group and failure group.

nificant. This data may reflect a direct relationship with a lower severity index at the beginning of treatment. The average IROX in patients who started HFNC treatment late (after 10 days). The success or failure of treatment could be related to the initial level of hypoxemia and respiratory mechanics involvement, regardless of the number of days since symptom onset.

Older adults, defined as those aged 60 years or older with two or more comorbidities, accounted for half of the total failures. This information is useful for hospital management, so that HFNC can be used with critical care units or units nearby for older patients, and in regular wards or peripheral hospitals in the case of the other group of patients.

Limitations

In the first place, this is a retrospective analysis, but it was based on prospectively collected data. Due to the retrospective nature, the standardization of intubation was not decided a priori. Furthermore, it's a single-center study, which means we cannot compare different population characteristics in the same region. Additionally, these results cannot be extrapolated to other non-SARS-CoV-2-related conditions that also cause acute respiratory failure due to a lack of evidence.

Conclusion

Our work demonstrates that the HFNC is a valuable tool for avoiding orotracheal intubation in patients with ARF caused by SARS-CoV-2 pneumonia.

The initial IROX and the IROX at 12 hours are predictors of the therapy's success.

It would be interesting to investigate the value of this method in other etiologies of ARF.

Conflict of interest

Authors have no conflicts of interest to declare.

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ANNEX

Cabrini respiratory strain scale (CAB-RSS)

Parameters	Puntos
Respiratory rate	
< 20	0
20-30	1
31-40	2
>40	4
Use of accessory mucles/refraction	0
None	1
Little	2
Significant	
Respiratory amplitude	0
Normal	1
Increased	2
Higly elevated	
General satus	0
Relaxed	1
Restiess	2
Very anxious	

CAB-RSS: 0-2: low 3-5 moderate; 6-10 high