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ORIGINAL ARTICLE

High-flow nasal cannula oxygen therapy in hypoxemic patients with COVID-19: A retrospective observational study

Oxigenoterapia por cânula nasal de alto fluxo em pacientes hipoxêmicos com COVID-19: um estudo observacional retrospectivo

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ABSTRACT

Objective: To describe high-flow nasal cannula (HFNC) ventilatory assistance in patients with hypoxemic acute respiratory failure due to COVID-19. **Methods:** This is a retrospective study of patients admitted to a single center from May 2020 to December 2021 with hypoxemic acute respiratory failure due to COVID-19 treated with HFNC. Age, gender, APACHE II score, initial HFNC flow, inspired oxygen fraction measurements, ROX index at 2, 6, and 12 hours after its institution, treatment duration, and its outcomes (success or failure rate) were observed, in addition to the length of stay, discharge, and mortality in the intensive care unit (ICU). **Results:** 190 patients were included, with therapy success of 51.05% (97 individuals) (p<0.05). The success group is younger (p<0.0001), APACHE II and expected mortality lower (p<0.002; p<0.005), used HFNC for a longer time (p<0.0001), with lower flow and FiO2 (p<0.002; p<0.0005) and higher ROX index in all measured periods, remained in the ICU for a shorter period (p<0.0001) and all individuals were discharged from the ICU. Significant predictive variables of the primary outcome (success or failure) were the APACHE II score, expected mortality, 12-hour ROX index, days of use in the HFNC, discharge from the ICU, and days of stay in the ICU (p<0.0001). **Conclusion:** HFNC was an effective treatment in non-invasive ventilatory support in patients with hypoxemic acute respiratory failure due to COVID-19.

Keywords: High-flow nasal cannula; COVID-19; SARS-CoV-2; Acute hypoxemic respiratory failure.

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RESUMO

Objetivo: Descrever a assistência ventilatória por Cânula Nasal de Alto Fluxo (CNAF) em pacientes com insuficiência respiratória aguda hipoxêmica (IRpAH) devido à COVID-19. **Métodos:** Trata-se de estudo retrospectivo de pacientes internados em centro único de maio de 2020 a dezembro de 2021 com IRpAH por COVID-19 tratados com CNAF. Foram observados idade, sexo, escore APACHE II, medidas de fluxo e fração inspirada de oxigênio iniciais da CNAF, índice ROX em 2, 6 e 12 horas após sua instituição, tempo de tratamento e seus desfechos (taxa de sucesso ou insucesso), além do tempo de internação, alta e mortalidade na unidade de terapia intensiva (UTI). **Resultados:** Foram incluídos 190 pacientes, com sucesso da terapia de 51,05% (97 indivíduos) (p<0.05). O grupo sucesso é mais jovem (p<0.0001), APACHE II e mortalidade esperada menores (p<0.002; p<0.005), utilizou a CNAF por mais tempo (p<0.0001), com fluxo e FiO2 menores (p<0.002; p<0.0005) e índice ROX maior em todos os períodos mensurados, permaneceu internado em UTI por menor período (p<0.0001) e todos os indivíduos receberam alta da UTI. Observaram-se como variáveis significativas preditoras do desfecho primário (sucesso ou insucesso) o escore APACHE II, mortalidade esperada, índice ROX em 12 h, dias de uso no CNAF, alta da UTI e dias de internação em UTI (p<0.0001). **Conclusão:** CNAF foi um tratamento eficaz no suporte ventilatório não invasivo em pacientes com IRpAH por COVID-19.

Palavras-chave: Cânula nasal de alto fluxo; COVID-19; SARS-CoV-2; Insuficiência respiratória aguda hipoxêmica.

Introduction

At the end of 2019, a group of cases of atypical pneumonia was described in the city of Wuhan (China), with a new strain of the coronavirus named severe acute respiratory syndrome coronavirus (SARS-CoV-2) being identified[1]. The outbreak of the disease (COVID-19) was declared by the World Health Organization in January 2020, as a public health emergency of international concern and recognized as a pandemic on March 11, 2020[2,3]. The currently reported case count underestimates the global epidemiological reality of the disease given the subclinical manifestations and low rate of diagnoses with official registration[4]. A recent study estimated that about 45% of the current population has been infected with the virus at least once, out of an estimated three billion individuals[5]. In Brazil, so far, more than 35.7 million cases have been confirmed, with at least 700,000 deaths[6].

Patients infected with the coronavirus can present an intense inflammatory response evolving to a more severe form of the disease, with acute respiratory distress syndrome and hypoxemic respiratory failure, with disruption of the endothelial barrier, dysfunction in alveolar-capillary gas exchange, and reduced oxygen diffusion capacity[3]. Additionally, in the pathophysiology of the critical form, phenomena such as intravascular thrombosis and loss of hypoxic vasoconstriction may occur resulting from endothelial dysfunction and consequent worsening of the intrapulmonary shunt by diverting blood flow to collapsed areas of the lung[7].

The initial treatment strategy in hypoxemic acute respiratory failure (ARIpAH) is to offer supplemental oxygen therapy through conventional devices, such as low-flow nasal cannulas and face masks, however, these systems may not be sufficient in more severe patients. Within this ventilatory assistance perspective, the high-flow nasal cannula (HFNC) is an alternative device that delivers oxygen with an inspired fraction of oxygen (FiO_2) of up to 100%, at high flows (up to 60 l/min), combined with a heated humidification system, known to reduce the need for invasive care in hypoxemic patients[8]. Systematic reviews and meta-analyses before the COVID-19 pandemic had already shown that HFNC is associated with a lower risk of ICU admission and lower intubation rates in patients with IRpAH of various etiologies[9-11].

HFNC has been effective in the clinical improvement of these patients by reducing the nasopharyngeal dead space[12,13], bringing the device flow rate closer to the patient's peak inspiratory flow, and maintaining a constant FiO_2[14], reducing the work of breathing and improving respiratory mechanics by increasing alveolar recruitment and decreasing airway resistance[15], providing a small positive end-expiratory pressure[16], increasing mucus clearance by improving mucociliary function[18], thus reducing the energy expenditure of the patient[17], in addition to providing better tolerance and comfort[19].

While concerns about implementing aerosol-generating procedures have been raised due to the risk of contamination of healthcare workers, scientific evidence has shown a similar risk of aerosol generation and dispersion to standard oxygen masks[20,21].

Although HFNC treatment is expected to have the potential to improve oxygenation and avoid the institution of invasive mechanical ventilation (IMV) in the setting of COVID-19, delaying orotracheal intubation in patients who do not respond to therapy could worsen their prognosis[22]. Spontaneously breathing patients with ARF may have increased ventilatory drive and breathe with large tidal volumes and potentially harmful transpulmonary pressure swings and may suffer self-inflicted lung injury[23].

In this sense, the respiratory rate oxygenation index (ROX index) can be used to predict early whether HFNC treatment can help to avoid orotracheal intubation. This index is measured through the ratio between the peripheral oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2) by the respiratory rate (RR), at 2, 6, 12, and 24 hours after the establishment of therapy. A ROX index ≥4.88 is consistently associated with a lower risk of intubation, whereas a ROX <2.85, <3.47, and <3.85 at 2, 6, and 12h of initiation of therapy, respectively, are predictors of CNAF failure[24].

At the beginning of the present study, the application of HFNC in the treatment of patients with acute hypoxemic respiratory failure was recommended[25], but with still unknown efficacy in patients with viral infection, especially by COVID-19. Therefore, the primary objective of this study was to describe the experience of using HFNC in COVID-19 in patients with hypoxemia refractory to conventional oxygen therapy admitted to intensive care. The secondary objectives were to correlate the main outcome with the age and sex profile of the patients, APACHE II severity score (Acute Physiology and Chronic Health Evaluation), ROX index, determining the factors associated with therapy failure, in addition to describing the duration of treatment, length of stay, and mortality rate in the Intensive Care Unit (ICU) of the patients who used it.

Methods

Study and patient design

This is a quantitative study with a descriptive design of a single-center retrospective documentary procedure. The non-probabilistic convenience sample consisted of patients hospitalized at the Hospital da Polícia Militar de Minas Gerais (Brazil) from May 2020 to December 2021, with a diagnosis of COVID-19 (positive RT-PCR), with acute hypoxemic respiratory failure, intended for HFNC therapy, according to the following indication criteria: no indication for immediate intubation, with normal mental status, hypoxemia refractory to conventional oxygen therapy (low-flow nasal cannula or face mask), SpO_2 <93%, RR 30 to 35 bpm, without the use of accessory muscles, partial pressure of arterial blood carbon dioxide ($PaCO_2$) <48 mmHg, partial pressure of arterial blood oxygen (PaO_2) < 65 mmHg with oxygen therapy, complaint of dyspnea, heart rate (HR) lower than 120 bpm, systolic blood pressure (SBP) greater than 90 mmHg, without arrhythmias.

Patients with a negative result in the COVID-19 test were excluded, as well as the positive COVID-19 who presented mandatory OTI criteria upon admission to the ICU, such as RR above 35 bpm, moderate to severe respiratory effort, measured level of consciousness Glasgow coma scale (ECG) <8, failure of upper airway protection, cardiorespiratory arrest. Patients who used HFNC therapy, however, who did not meet the inclusion criteria in the present study, were also excluded from the analysis.

Because of the documentary retrospective character of the study, a free and informed consent form was waived and the TCUD (Term of Commitment to Use Data) was adopted and submitted to the ethics committee of the Hospital da Polícia Militar de Minas Gerais under number 01/2022.

Treatment strategy with HFNC

To perform HFNC therapy, the Optiflow Nasal High Flow system (Fisher & Paykel Healthcare) was used, mounted on the TS+ mechanical ventilator (Tecme) with its software, or with compressed air and oxygen flowmeters. The therapy should preferably be performed in a respiratory isolation environment, the team should be equipped with personal protective equipment for the aerosol-generating procedure and all patients were instructed to wear a surgical mask over the cannula. Initially, a flow of 30 to 40 l/min was established and increased by 5 l/min up to a maximum of 60 l/min as tolerated, aiming to maintain RR <25 bpm and evaluating respiratory comfort and relief of dyspnea. When using the Optiflow system on a mechanical ventilator, after titration the maximum tolerated flow, the FiO_2 was titrated to a SpO_2 of 93 to 96% and when using the system with flowmeters, it started with a FiO_2 of 60% (equal flows of compressed air and O_2, following the flow table) to maintain the same SpO_2 levels mentioned. Clinical improvement was evaluated 60 minutes after the start of therapy and hourly throughout the first 24 hours, being defined as follows: SpO_2 >92%, fall in RR, improvement in dyspnea, comfortable adaptation to the device, absence of effort breathing, and use of accessory muscles. If there were signs of clinical deterioration, OTI was indicated. The ROX index was measured at 2, 6, and 12 hours after the institution

of therapy, considering a value ≥4.88 as a criterion for predicting success (lower risk of intubation). The following cutoff points were also considered as predictors of failure: ROX <2.85 in 2h, ROX <3.47 in 6h, and ROX <3.85 in 12h[23]. With the improvement of vital signs and symptoms after 1h, the FiO_2 was initially reduced and the titrated flow was maintained for at least 24h, aiming for a SpO_2 between 93 and 96%. After 24 hours, if patient had improved, weaning from the flow was started, according to tolerance, reducing 5 l/min every 6 hours, observing a RR <25 bpm. HFNC therapy was discontinued if flow <20-30 l/min and SpO_2 <30%, and low-flow oxygen nasal cannula was installed as needed to maintain SpO_2 levels.

Study variables

Data collection took place in the records in medical records and in the HFNC's own control and dispensation list of the mentioned patients (retrospectively analyzed). Such data were tabulated in Microsoft Excel and statistically analyzed in proprietary software (Biostat – version 5.3). Sociodemographic data (age and sex) were collected, the APACHE II clinical severity score was calculated, and data listed in the literature as HFNC descriptors (initial flow and fraction of inspired oxygen, ROX index measured at 2, 6, and 12 hours after the institution of therapy), data related to the length of care (time of use of HFNC and length of stay in the ICU), and the outcomes of therapy by HFNC were analyzed (success or failure rate), in addition to mortality rates and ICU discharge. Treatment success was defined as withdrawal from HFNC support with improved oxygenation without the need for IMV. Therapy failure was considered the need for intubation and the institution of IMV.

Statistical analysis

Discrete and continuous variables were presented as mean and standard deviation. The data that presented Gaussian distribution, were analyzed by the Student's T-test of independent samples and evaluated by multiple linear regression with dependent variable therapy outcome. Nominal variables were analyzed using the chi-square test. A value of $p<0.05$ was considered the statistically significant value.

Results

During the analyzed period, 190 patients with COVID-19 and destined for intensive care were treated with HFNC and included in the study, being further divided according to the outcome of HFNC therapy into positive outcome (success group) and negative outcome (failure group). Thus, 97 individuals (51.05%) had a positive outcome in HFNC therapy, that is, they did not require orotracheal intubation and invasive mechanical ventilation. Data are significantly different from the failure group ($p<0.05$ - chi-square test).

Demographic data of age and gender were collected. Regarding age, the total sample had a minimum age of 28 and a maximum of 96 years, a mean of 62.97±13.83 years, and a median of 62 years. The success and failure groups are different ($p<0.0001$- t-test). The first, has a mean age of 59.35±14.23 years, while in the failure group, the mean was 66.59±12.27 years. That is, younger patients had better outcomes in the HFNC (Table 1). Regarding sex, the studied population consisted of 67 females and 123 males (64%). Gender did not influence the primary outcome ($p>0.05$) (Table 1). Demographic data of the study population and primary outcome are shown in Table 1.

Another characteristic data collected was the APACHE II clinical severity score. This presented an overall average of 10.92±4.88 and the expected mortality was 14.42±10.03 (Table 1). Separating by outcome, the mean APACHE II of the success group was 9.62±4.41, and the failure was 12.26±4.99, while the mean expected mortality of the success group was 12.42±8.58 and the failure was 16.5±10.9. Thus, the results of the success and failure groups were significantly different ($p<0.0002$; $p<0.005$ – t-test), with patients in the success group having lower APACHE II scores and expected mortality.

Table 1. Description of discrete and continuous sample variables.

Features	Mean ± standart deviation	Median	Minimum	Maximum	Quartile 25	Quartile 75
Age (years)	62.97±13.83	62	28	96	52.25	74.75
Apache II	10.92±4.88	10	1	28	7	13
Expected mortality	14.42±10.03	11.3	3.3	56.9	7.77	16.4
Days of use HFNC	4±3.94	4	0	28	1	6
ICU (days)	12.92±11.03	9	2	77	6	15
Gender	**Total**	**%**	**Outcomes**	**Total**	**Percentage**	
Masculine	123	64	Success	97	51.05	
Female	67	36	Failure	93	48.95	
			Discharge ICU	141	74.21	
					Death	

The duration of HFNC treatment and the length of stay in the ICU were also analyzed. The mean treatment time for the studied population was 4±3.93 days (Table 1). Dividing the patients into groups, in the outcome of success, the mean number of days of use was 6.00±3.19, while in the outcome of failure it was 2.0±3.0, showing they were significantly different from each other (p<0.0001 - t-test). Those who were successful in therapy used it longer. Regarding the length of stay in the ICU, the overall mean was 12.92±11.03 days. By groups, those who were successful in the therapy remained hospitalized in the ICU for less time, on average 7.94±4.30 days, against 19.76±13.47 of those who failed in the HFNC (t test - p<0.0001 – t-test) (Table 2).

The secondary outcome was discharge from the ICU and death. Discharge from the ICU occurred in 74.21% of the total sample (p<0.0001 – chi-square test), and in the group that was successful in therapy, 100% were discharged from the ICU, while, in the group that failed in the HFNC, this percentage was 47.31 % (Table 3, Graph 4). The mortality rate of these patients was 25.78% (Table 2).

Regarding the parameters linked to the HFNC, all the variables measured were significantly different between the success and failure groups. The successful group used lower initial flow and FiO_2 and presented a higher ROX index at 2, 6 and 12h after starting therapy (Table 3).

Seeking to understand the behavior and correlation of the collected variables, two multiple regression analyses were performed. With the dependent variable outcome in HFNC therapy, an r2 determination coefficient of 0.76, a correlation coefficient of 0.87 and p<0.0001 were obtained, indicating that these variables have a strong contribution to the primary outcome. Standing out as variables associated with the outcome (success or failure), we have the APACHE II score (p=0.008), mortality (p=0.009), ROX index in 12h (p=0.04), days of use in HFNC (p<0.0001), ICU discharge (p<0.0001) and days of ICU stay (p<0.0001) (Table 4). With the dependent variable ICU discharge or death, a coefficient of determination r2 of 0.63, a correlation coefficient of 0.79 and p<0.0001 are obtained, as well as the variables associated with mortality (p=0.006), age (p=0.003), sex (p=0.012), success in the HFNC treatment strategy (p<0.0001), days of HFNC use (p<0.0001) and days of ICU stay (p<0.0001) (Table 5).

Table 2. Characteristics of patients treated with HFNC.

Features	Total (n= 190)	HFNC therapy outcome		*p*-value
		Success (n=97)	Failure(n=93)	
Days HFNC (days)	4±3.93	6.00±3.19	2.0±3.0	p<0.0001
Days ICU (days)	12.92±11.03	7.94±4.30	19.76±13.47	p<0.0001
Discharge ICU (%)	74.21	100	47.31	p<0.001

Table 3. CNAF parameters.

	Success Group	Failure Group	*p*-value
Initial flow (l/min)	46.8±8.85	50.65±8.22	<0.002 – t-test
FiO_2 (%)	63.63±17.68	73.37±8.34	<0.0005 – t-test
Rox 2	6.52±2.47	5.24±2.18	<0.0004 – t-test
Rox 6	6.88±2.85	5.05±2.68	<0.0001 – t-test
Rox 12	6.74±2.75	4.73±2.99	<0.0001 – t-test

Table 4. Univariate Analysis and outcome in HFNC therapy.

Function	Value	Predictive variables	*p*-value
r2	0.76	APACHE II	=0.008
Correlation coefficient	0.87	Mortality	=0.009
P value	<0.0001	ROX 12	=0.04
		HNFC use	<0.0001
		Length of stay in ICU	<0.0001
		Discharge ICU	<0.0001

Table 5. Multiple regression/dependent variable ICU Discharge/Death.

Function	Value	Predictive variables	*p*-value
r2	0.63	Mortality	=0.006
Correlation coefficient	0.79	Age	=0.003
p-value	<0.0001	Gender	=0.012
		Sucess Group	<0.0001
		Days of HFNC use	<0.0001
		Days in ICU	<0.0001

Discussion

Patients admitted to intensive care related to the COVID-19 infection have hypoxemic acute respiratory failure as their main clinical manifestation and a predominant radiological pattern as diffuse alveolar damage; however, with a wide difference between the population assisted in invasive and non-invasive mechanical ventilation. The difference between centers is due to comorbidities, patient severity, age and different hospital experiences[26].

With regard to age, the cases of COVID-19 that required hospitalization notoriously occurred in patients of more advanced age, with a relationship also established with mortality[27]. There is a possible increase in the infection/fatality ratio by 0.59% every 5 years, from the age of 10 years[28]. In a meta-analysis of 25 studies with 2851 patients with COVID-19 treated with HFNC, the mean age was 61±13 years[29], data that corroborate the mean age of the present study, which was 62.97±13.83 years.

Regarding gender, most of the sample in our study consisted of male patients (64%), data reinforced by the same meta-analysis cited, which included 66.2% of this gender[29]. In other previous cohorts, there was a predominance of males within the profile of critically ill patients, with higher chances of mortality, independently, without relation to age or comorbidities[30,31]. Despite the similarity with other published demographic analyses, in the present study gender did not influence the main outcome.

The use of severity scales is a common practice in intensive care units, one of the most common being the APACHE II clinical severity score and its predictor of mortality, already recognized as an effective predictive tool in COVID-19[32]. In our study, APACHE II and expected mortality were lower in the success group, data corroborated by meta-analyses[29,33]. Such data may suggest that patients with a positive outcome using HFNC therapy could have lower overall disease severity, which should be determined when opting for this treatment strategy[33].

In our study, 51.05% of patients with HFNC-related IRPHA treated with HFNC had successful therapy and did not require invasive mechanical ventilation. The failure rate was defined as the need for intubation and was 48.95%. These rates are in line with a meta-analysis that demonstrated a 47% HFNC failure rate[29].

Although HFNC may avoid the need to institute IMV, a careful ongoing assessment of the effects of this therapy should be performed during its use, in an attempt to identify early signs of failure and avoid delays in intubation. In this sense, the ROX index can be useful in predicting those patients with a higher probability of HFNC failure in COVID-19 patients with IRpAH[29,34]. In our study, we considered a cutoff ≥4.88 for a lower risk of intubation[24], since there were still no publications evaluating HFNC specifically in the population with COVID-19. However, currently, other publications that also evaluated its use in patients with COVID-19 found other values, such as ROX > 5.55 in 6 h associated with a greater possibility of therapy success (OR: 17.821; 95% CI: 3.741-84.903, $p<0.001$)[33], ROX <4.94 in 2 to 6 hours associated with an increased risk of intubation (HR: 4.03, 95% CI: 1.18-13.7, $p=0.026$)[35], ROX <5.99 in 12h best predictor of failure (AUC: 0.7916, 95% CI: 0.6905-0.8927; specificity: 96%, sensitivity: 62%)[36] and ROX >5.35 in 24h predictor of HFNC success[37]. However, prospective HFNC studies in COVID-19 are needed to confirm the findings and standardize ROX index cutoff values at a specific time point for this population.

The days of hospitalization in the ICU were lower in the success group, however, with data not corroborated by a systematic review[10] or 2021 meta-analysis[9]; however, both reviews have a low degree of certainty and use data exclusively from the pre-pandemic period. In view of the many ongoing studies, there is a possibility of changing the panorama of the profile of length of stay and use of HFNC in COVID-19.

In this study, in the linear regression, the APACHE II clinical score and expected mortality, ROX in 12h, days of use of HFNC (those who were successful, used the therapy longer) and days of therapy stand out as predictors of therapy success at ICU admission. The dependent variable was ICU discharge, the predictive variables mortality ($p=0.006$), age ($p=0.003$), sex ($p=0.012$), success in the HFNC treatment strategy ($p<0.0001$), days of use of HFNC ($p<0.0001$) and days of ICU stay ($p<0.0001$).

As shown in our study, compared to the HFNC success group, a recent meta-analysis demonstrated that patients in the HFNC failure group were older and had a lower APACHE II score, and lower baseline ROX after initiation of therapy and shorter duration of HFNC (all $p<0.05$)[29].

The present study has some limitations. First, our results were based on data from patients admitted to a single center and a control group was not used for comparative analysis because it is a study with a retrospective profile.

Second, associated with the HFNC strategy, many patients underwent the awake prone position, with the possibility of repercussions on improved oxygenation and outcomes, but there was no stratification of this data in the present work. A multicenter, international, randomized meta-trial published by Ehrmann et al. (2021)[38] that included 1126 patients with COVID-19-related IRpAH, all treated with HFNC, demonstrated that, compared with standard care, prone positioning applied in 564 patients combined with HFNC decreased the incidence of treatment failure (primary composite outcome of intubation or death).

Conclusion

This study was conducted to describe the experience of HFNC in COVID-19 patients with IRpAH. Our results showed that HFNC was an effective treatment for these patients, and approximately 51.05% of the patients were successful in HFNC therapy, preventing the evolution of invasive ventilatory support. HFNC can effectively improve oxygenation, reduce the likelihood of IMV, and increase the chances of discharge from the ICU environment.

Authors' contributions

Author contributions are structured according to the taxonomy (CRediT) described below:

Study design, study proposal, data analysis, writing and review of the manuscript: CRFA; RMR. Study design, data acquisition and interpretation, data analysis, writing of the manuscript, approval of the final version: LMF. Data acquisition, review of the manuscript, approval of the final version: PJCDS; PSPP; GON.

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