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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2019/2020

Maria da Graça Maciel Carvalho

Comparison Between High-Flow Nasal Cannula and Noninvasive Ventilation for Acute Hypoxemic Respiratory Failure: A Retrospective Study

MAIO, 2020

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Mestrado Integrado em Medicina

Área: Ciências médicas e da saúde – Medicina Clínica

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Dr. Rui Pedro Rodrigues Gonçalves Veiga

E sob a Coorientação de:

Dr. Nuno Cruz Reis

Trabalho organizado de acordo com as normas da revista:

Journal of Critical Care

MAIO, 2020

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TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Comparison Between High-Flow Nasal Cannula and Noninvasive Ventilation for Acute Hypoxemic Respiratory Failure: A Retrospective Study

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Comparison Between High-Flow Nasal Cannula and Noninvasive Ventilation for Acute Hypoxemic Respiratory Failure: A Retrospective Study

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Comparison Between High-Flow Nasal Cannula and Noninvasive Ventilation for Acute Hypoxemic Respiratory Failure: A Retrospective Study

ABSTRACT

PURPOSE: To evaluate the impact of high-flow nasal cannula (HFNC) on patients with acute hypoxemic respiratory failure (AHRF) when compared to noninvasive mechanical ventilation (NIV).

METHODS: We conducted a retrospective single-center study of patients with AHRF admitted in the Intensive Care Unit (ICU) who performed HFNC or NIV. The primary outcomes included mortality during ICU stay and 90-day mortality. The need for invasive mechanical ventilation (IMV) and ICU length of stay were defined as secondary outcomes.

RESULTS: A total of 101 patients were included in the study (NIV 82; HFNC 19). Mortality during ICU stay (NIV 19.5% versus HFNC 0%; p=0.037) and need for IMV (NIV 45.1% versus HFNC 15.8%; p=0.018) were significantly lower in the HFNC group. No differences were observed in 90-day mortality or ICU length of stay. In the subgroup analysis, HFNC was associated with a decreased risk of longer ICU stay in the following subgroups: $100<P_aO_2/F_iO_2$ ratio$\leq$200; $200<P_aO_2/F_iO_2$ ratio$\leq$300; Pneumonia, Acute respiratory distress syndrome or Other as cause of AHRF. However, in patients with Decompensated heart failure, HFNC was associated with an increased risk of longer ICU stay.

CONCLUSION: Among AHRF patients, HFNC was associated with significantly lower mortality during ICU stay and need for IMV.

KEYWORDS: High-flow nasal cannula, acute hypoxemic respiratory failure, noninvasive ventilation.

INTRODUCTION

Acute respiratory failure (ARF) is a threatening condition often observed in the context of intensive and intermediate care units, which can result from several clinical etiologies such as pneumonia, cardiogenic pulmonary edema, exacerbation of chronic obstructive pulmonary disease (COPD) or acute respiratory distress syndrome (ARDS) [1, 2]. In these circumstances, mortality rates may reach values in the range of 35 to 50% [3, 4]. Despite the attempt to correct hypoxemia using conventional oxygen therapy (through a nasal cannula, face mask or venturi mask), this strategy is frequently insufficient in patients with ARF, and the escalation to noninvasive mechanical ventilation (NIV) or, ultimately, invasive mechanical ventilation (IMV), is necessary.

Recently, the high-flow nasal cannula (HFNC), a device widely applied in neonatal and pediatric settings, has increasingly been used in the management of patients with ARF in intensive care units (ICU). HFNC incorporates an air heating and humidification system that favors physiological mucociliary clearance and the fluidity of respiratory secretions, allowing the patient to tolerate higher flows up to a maximum of 60L/min and reaching fractions of inspired oxygen (F_iO_2) of 100% [5-7]. Besides, the use of maximum flows allows the generation of an expiratory positive airway pressure (EPAP) up to 5cmH_2O [8], culminating in a wash-out effect in the upper airways that increases the elimination of CO_2 [9], improves oxygenation and, consequently, decreases respiratory work, which can be particularly relevant in certain diseases, attending to the pathophysiology behind.

Despite the lack of consensus in the current scientific panorama, data from observational studies and randomized clinical trials suggest that high-flow nasal cannula may be more favorable than noninvasive ventilation in a specific set of patients. In fact, evidence shows a decrease in mortality in patients treated with HFNC due to acute hypoxemic respiratory failure (AHRF) [10] or due to ARF in the context of pneumonia [11], when compared to NIV treated patients. Also, a decrease in the intubation rate has been demonstrated in a subgroup of patients with AHRF and P_aO_2/F_iO_2 (P/F) ratio$\leq$200 submitted to HFNC [10]. Finally, patients treated with HFNC presented higher comfort scores and lower dyspnea scores than those treated with NIV [1, 10, 12, 13].

We undertook a retrospective single-center study including patients admitted in the ICU with acute hypoxemic respiratory failure in order to evaluate whether high-flow nasal cannula could have a positive impact on patient's mortality, need for IMV or ICU length of stay, when compared to NIV.

METHODS

Study Design and Population

The present study consists of a single-center, retrospective cohort analysis of 2 respiratory support interventions, HFNC and NIV. This analysis regarded patients with AHRF admitted in the Intensive Care Unit of Centro Hospitalar Universitário de São João, Porto, Portugal, between January of 2018 and June of 2019. The study was approved by the hospital's ethics committee.

Patients were included in the study if they fulfilled the following criteria: (1) age$\geq$18 years old; (2) an estimated P/F ratio$\leq$300; and (3) having performed HFNC or NIV as respiratory support intervention. Exclusion criteria were defined as (1) $P_aCO_2\geq$45 mmHg (2) post-operative or post-extubation patients, (3) patients with do-not-intubate or do-not-resuscitate

order or (4) incomplete data. There were no established protocols for the discriminated use between HFNC or NIV. Therefore, the choice was made by the attending physician.

Data Collection and Outcomes

Data were collected by the research team from the available electronic clinical records. For each patient, the extracted data included: birth date; gender; admission and discharge dates from the ICU; severity assessment scores [Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II] on ICU admission; pre-intervention respiratory rate (bpm), blood pH, P_aO_2 (mmHg) and F_iO_2 (%); type of respiratory support intervention used (HFNC or NIV); need for IMV; cause of AHRF (by the attending physician's assessment); mortality during ICU stay and mortality at 90 days post-discharge.

The primary outcomes were defined as mortality during ICU stay and 90-day mortality. The need for IMV and ICU length of stay (in days) were established as secondary outcomes.

Statistical Analysis

Clinical data and outcomes were compared between HFNC and NIV groups. Data are expressed as number (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables, according to the data distribution. Univariate analyses were carried out using the Fisher's exact test for categorical variables and the t-test for continuous variables. Univariate logistic regression analyses were carried out to determine the Odds Ratios (OR) for 90-day mortality and need for IMV. Since there was a reduced number of patients in the HFNC group, multivariate logistic regression analyses were not performed. Considering there was no mortality during ICU stay reported in the HFNC group, logistic models were not conducted in this matter. Univariable Poisson regression was carried out to determine the Risk Ratio (RR) for ICU length of stay. The interaction between the type of respiratory support and subgroups was evaluated by adding interacted items of them to the above regression models. All analyses were performed using the IBM SPSS Statistics® software (version 26). The statistical significance level was fixed at 0.05.

RESULTS

Patients' Characteristics

From January of 2018 to June of 2019, a total of 101 patients admitted in the ICU of Centro Hospitalar e Universitário de São João met the established criteria to be enrolled in the present study. Of these, 19 patients performed HFNC and 82 patients performed NIV.

Demographics and baseline characteristics of the study groups are presented in **Table 1**. Patients in the HFNC group were significantly younger (52.8 versus 65.0; p=0.021), with lower SAPS II values (32.26 versus 45.50; p=0.002) and higher blood pH levels (7.46 versus 7.41; p=0.004). The 2 groups were similar in terms of gender, P/F ratio, cause of AHRF, SOFA and APACHE II scores on ICU admission and pre-intervention respiratory rate. In both groups, the most frequent cause of AHRF was pneumonia (63.2% in the HFNC group and 37.8% in the NIV group), although there were no patients reported in the HFNC group with acute pulmonary edema or exacerbation of COPD. In both groups, most patients presented a pre-intervention $100<$P/F ratio≤ 200 (47.4% in the HFNC group and 54.9% in the NIV group).

Table 1. Demographics and baseline characteristics of patients treated with high-flow nasal cannula (HFNC) or noninvasive mechanical ventilation (NIV).

	HFNC (n=19)	*NIV (n=82)*	*p-value*
Gender			0.086
Female	10 (52.6%)	26 (31.7%)	
Male	9 (47.4%)	56 (68.3%)	
Age	52.84 (20.17)	65.05 (14.64)	0.021*
SOFA score	4.95 (1.39)	5.77 (2.35)	0.052
SAPS II	32.26 (14.61)	45.50 (17.04)	0.002*
APACHE II score	17.63 (6.49)	21.23 (8.40)	0.083
Cause of AHRF			0.272
Pneumonia	12 (63.2%)	31 (37.8%)	
Decompensated heart failure	1 (5.3%)	10 (12.2%)	
ARDS	2 (10.5%)	14 (17.1%)	
Acute pulmonary edema	0 (0.0%)	10 (12.2%)	
Exacerbation of COPD	0 (0.0%)	5 (6.1%)	
Other†	4 (21.1%)	12 (14.6%)	
P/F ratio‡			0.748
P/F ratio≤100	3 (15.8%)	14 (17.1%)	
100<P/F ratio≤200	9 (47.4%)	45 (54.9%)	
200<P/F ratio≤ **3**00	7 (36.8%)	23 (28.0%)	
Respiratory rate	32.16 (6,80)	31.44 (5.20)	0.610
Blood pH	7.46 (0.05)	7.41 (0.10)	0.004*

Values are expressed as number (percentage) or mean (standard deviation).
Abbreviations: HFNC, High-flow Nasal Cannula, NIV, Noninvasive Mechanical Ventilation, SOFA, Sequential Organ Failure Assessment, SAPS II, Simplified Acute Physiology Score II, APACHE II, Acute Physiology and Chronic Health Evaluation II, AHRF, Acute Hypoxemic Respiratory Failure, ARDS, Acute Respiratory Distress Syndrome, COPD, Chronic Obstructive Pulmonary Disease, P/F, P_aO_2/F_iO_2.
* Statistically significant.
† Other causes of respiratory failure included extrapulmonary septic shock, interstitial lung disease, pulmonary hemorrhage, hemoptysis, aspiration pneumonitis, pulmonary metastasis from germinal tumor, tracheobronchitis and myocarditis.
‡ F_iO_2 was estimated as: (oxygen flow in liters per minute) x 0.4 + 0.20.

Outcomes

The defined outcomes for the two groups are represented in **Table 2**. In the univariate analysis of all patients, patients in the HFNC group had a significantly lower need for IMV (15.8% versus 45.1%; *p*=0.018) and mortality during ICU stay (0% versus 19.5%; *p*=0.037), with no case reported among patients who performed HFNC in the last outcome. As regards to 90-day mortality and ICU length of stay, no significant differences were observed between the groups.

Table 2. Primary and secondary outcomes, according to study groups.

	HFNC (n=19)		*NIV (n=82)*		
	Yes	**No**	**Yes**	**No**	***p-value***
Mortality during ICU stay	0 (0%)	19 (100%)	16 (19.5%)	66 (80.5%)	0.037*
90-day mortality†	2 (10.5%)	17 (89.5%)	7 (10.6%)	59 (89.4%)	>0.990
Need for IMV	3 (15.8%)	16 (84.2%)	37 (45.1%)	45 (54.9%)	0.018*
ICU length of stay	6.0 (4.0 – 9.0)		6.0 (3.0 – 16.0)		0.698

Values are expressed as number (percentage) or median (interquartile range).
Abbreviations: HFNC, High-flow Nasal Cannula, NIV, Noninvasive Mechanical Ventilation, ICU, Intensive Care Unit, IMV, Invasive Mechanical Ventilation.
* Statistically significant.
† Excluded 16 ICU deaths in the NIV group.

The subgroup analyses ORs for 90-day mortality and need for IMV are shown in **Tables 3** and **4**, respectively. The subgroup analysis RRs for ICU length of stay are presented in **Table 5**. As regard to 90-day mortality, no significant statistical association was observed.

HFNC was associated with a decreased risk of need for IMV (OR 0.23; 95% CI 0.06 – 0.84). This was also verified in the subgroup analysis in patients with pneumonia as cause of AHRF (OR 0.11; 95% CI 0.01 – 0.96; p=0.046).

HFNC was also associated with a decreased risk of longer ICU length of stay in the following subgroups of patients: 100<P/F ratio≤200 (RR 0.61; 95% CI 0.46 – 0.81; p<0.001); 200<P/F ratio≤300 (RR 0.39; 95% CI 0.27 – 0.55; p<0.001); Pneumonia (RR 0.52; 95% CI 0.40 – 0.69; p<0.001), ARDS (RR 0.40; 95% CI 0.25 – 0.65; p<0.001) or Other (RR 0.65; 95% CI 0.43 – 0.98; p=0.040) as cause of AHRF. However, in patients with Decompensated heart failure as cause of AHRF, HFNC was associated with an increased risk of longer ICU length of stay (RR 2.70; 95% CI 1.34 – 5.44; p=0.005).

Table 3. Subgroup analysis Odds Ratios for 90-day mortality with High-flow Nasal Cannula (HFNC) versus Noninvasive Mechanical Ventilation (NIV).

	Odds Ratio	***95% CI***	***p-value***
Overall	0.99	0.19 – 5.22	
P/F ratio[†]			
P/F ratio≤100	2.78	0.16 – 50.0	0.484
100<P/F ratio≤200	(a)	(a)	(a)
200<P/F ratio≤ 300	1.41	0.11 – 20.0	0.791
Cause of AHRF			
Pneumonia	0.52	0.05 – 5.26	0.581
Decompensated heart failure	(a)	(a)	(a)
ARDS	(a)	(a)	(a)
Acute pulmonary edema	(a)	(a)	(a)
Exacerbation of COPD	(a)	(a)	(a)
Other[‡]	(a)	(a)	(a)

Univariate logistic regression analysis with calculated Odds Ratio for HFNC versus NIV (reference).
Abbreviations: 95% CI, 95% Confidence Interval, P/F, P_aO_2/F_iO_2, AHRF, Acute Hypoxemic Respiratory Failure, ARDS, Acute Respiratory Distress Syndrome, COPD, Chronic Obstructive Pulmonary Disease.
(a) Not possible to calculate due to absence of cases.
***** Statistically significant.
[†] F_iO_2 was estimated as: (oxygen flow in liters per minute) x 0.4 + 0.20.
[‡] Other causes of respiratory failure included extrapulmonary septic shock, interstitial lung disease, pulmonary hemorrhage, hemoptysis, aspiration pneumonitis, pulmonary metastasis from germinal tumor, tracheobronchitis and myocarditis.

Table 4. Subgroup analysis Odds Ratios for need for Invasive Mechanical Ventilation (IMV) with High-flow Nasal Cannula (HFNC) versus Noninvasive Mechanical Ventilation (NIV).

	Odds Ratio	*95% CI*	*p-value*
Overall	0.23	0.06 – 0.84	
P/F ratio[†]			
P/F ratio≤100	(a)	(a)	(a)
100<P/F ratio≤200	0.16	0.02 – 1.35	0.092
200<P/F ratio≤ 300	0.37	0.06 – 2.27	0.283
Cause of AHRF			
Pneumonia	0.11	0.01 – 0.96	0.046*
Decompensated heart failure	(a)	(a)	(a)
ARDS	(a)	(a)	(a)
Acute pulmonary edema	(a)	(a)	(a)
Exacerbation of COPD	(a)	(a)	(a)
Other[‡]	0.24	0.02 – 3.03	0.268

Univariate logistic regression analysis with calculated Odds Ratio for HFNC versus NIV (reference).
Abbreviations: 95% CI, 95% Confidence Interval, P/F, P_aO_2/F_iO_2, AHRF, Acute Hypoxemic Respiratory Failure, ARDS, Acute Respiratory Distress Syndrome, COPD, Chronic Obstructive Pulmonary Disease.
(a) Not possible to calculate due to absence of cases.
* Statistically significant.
[†] F_iO_2 was estimated as: (oxygen flow in liters per minute) x 0.4 + 0.20.
[‡] Other causes of respiratory failure included extrapulmonary septic shock, interstitial lung disease, pulmonary hemorrhage, hemoptysis, aspiration pneumonitis, pulmonary metastasis from germinal tumor, tracheobronchitis and myocarditis.

Table 5. Subgroup analysis Risk Ratios for Intensive Care Unit (ICU) length of stay with High-flow Nasal Cannula (HFNC) versus Noninvasive Mechanical Ventilation (NIV).

	Risk Ratio	*95% CI*	*p-value*
P/F ratio[†]			
P/F ratio≤100	0.80	0.52 – 1.21	0.284
100<P/F ratio≤200	0.61	0.46 – 0.81	<0.001*
200<P/F ratio≤ 300	0.39	0.27 – 0.55	<0.001*
Cause of AHRF			
Pneumonia	0.52	0.40 – 0.69	<0.001*
Decompensated heart failure	2.70	1.34 – 5.44	0.005*
ARDS	0.40	0.25 – 0.65	<0.001*
Acute pulmonary edema	(a)	(a)	(a)
Exacerbation of COPD	(a)	(a)	(a)
Other[‡]	0.65	0.43 – 0.98	0.040*

Univariable Poisson regression with calculated Risk Ratio for HFNC versus NIV (reference).
Abbreviations: 95% CI, 95% Confidence Interval, P/F, P_aO_2/F_iO_2, AHRF, Acute Hypoxemic Respiratory Failure, ARDS, Acute Respiratory Distress Syndrome, COPD, Chronic Obstructive Pulmonary Disease.
(a) Not possible to calculate due to absence of cases.
* Statistically significant.
[†] F_iO_2 was estimated as: (oxygen flow in liters per minute) x 0.4 + 0.20.
[‡] Other causes of respiratory failure included extrapulmonary septic shock, interstitial lung disease, pulmonary hemorrhage, hemoptysis, aspiration pneumonitis, pulmonary metastasis from germinal tumor, tracheobronchitis and myocarditis.

DISCUSSION

In this retrospective single-center study, we found that high-flow nasal cannula, as compared to noninvasive ventilation, was associated with reduced mortality during ICU stay. No differences were observed on 90-day mortality. In addition, HFNC treated patients also presented a lower intubation rate, particularly when pneumonia was the cause of AHRF, and shorter ICU length of stay in subgroups with P/F ratio>100 and Pneumonia, ARDS or Other as cause of AHRF. However, patients with Decompensated heart failure presented a longer ICU stay when treated with HFNC.

The use of HFNC, although widely compared with conventional oxygen therapy in the most recent literature, has also been compared with NIV and studied as a possible substitute or complement for this in certain clinical settings. This comparison has been made mainly in post-extubation and post-operative patients, or even in patients whose indication for NIV is controversial. In fact, despite its proven efficacy in hypercapnic respiratory failure due to a COPD exacerbation and in ARF due to cardiogenic pulmonary edema, its use in contexts of acute hypoxemic respiratory failure remains questionable, so that the 2017 European Respiratory Society/American Thoracic Society NIV clinical practice guidelines didn't recommend the use of NIV for *de novo* ARF [14].

Among acute hypoxemic respiratory failure etiologies, the most recent literature suggests HFNC non-inferiority when compared to NIV [5], with a randomized clinical trial showing reduced mortality in the ICU and at 90 days in patients treated with HFNC as opposed to NIV. This study also demonstrated a reduced intubation rate in patients with P/F ratio≤200 in the HFNC group [10]. This, together with the fact that higher comfort scores have been reported with the use of HFNC, as well as the ease in feeding, communicating and receiving oral medication that this device offers, make HFNC a potential alternative to NIV.

The decreased mortality observed in our study, as well as the shorter ICU stay, may have been a consequence of the decreased intubation rate reported in the HFNC group, particularly in patients with pneumonia as cause of AHRF. In addition, several studies also mentioned that NIV could favour a higher mortality rate once it facilitates the development of large tidal volumes [15] and heterogeneous aeration of the lungs [16], which leads to a higher risk of overdistention and volutrauma and, consequently, development or worsening of lung injury. With the HFNC, the work of breathing and minute ventilation are probably reduced due to its washout effect on the upper airways and reduction of the dead space, without increasing the tidal volume [17], which results in a lower risk of lung injury [11]. However, an important limitation must be taken into account: the reduced number of patients in the HFNC group (n=19) during the study period. This fact prevented adjustments for potential confounders to be made during the statistical analysis and so, we cannot assert with certainty that the results observed are exclusively due to the differential effect of the treatment methods or if it only happened because populations were different from the start. As previously mentioned, patients in the HFNC group were significantly younger and presented lower severity assessment scores, particularly on the SAPS II. If patients had less severe clinical conditions and were younger, there was a greater probability of survival, which may justify the observed decrease in mortality during ICU stay. Furthermore, the less severe clinical condition could enhance a lower need for IMV and, these factors combined, result in a shorter stay in the Intensive Care Unit.

Other limitations of this investigation are related to the study design. Since this is a retrospective study, there was no control over the allocation of the intervention, neither defined protocols for the use of HFNC or NIV. Once there were no protocols, there were no established values for the initial flow in the HFNC group, which remained at the discretion of the attending physician and could influence the development of the clinical condition and, consequently, the outcomes studied. Besides, the cause of acute hypoxemic respiratory failure was determined based on the primary diagnosis established by the attending physician and some patients could

present concomitant causes contributing to the clinical status, which could also have an impact on the performance of the respiratory support intervention. In addition, the fact that this is a single-center study raises questions about the general applicability of the results.

In the future, additional studies with larger populations should be conducted in order to infer the real effect of HFNC in comparison with NIV. Besides, the possibility of combined treatment with HFNC-NIV, as well as the established flow during HFNC treatment are two topics that were not addressed in this study and that would be relevant to explore in further investigations.

CONCLUSION

In patients with acute hypoxemic respiratory failure, HFNC was associated with lower mortality during ICU stay when compared to noninvasive mechanical ventilation, even though no differences in the 90-day mortality were observed. Additionally, HFNC led to decreased need for invasive mechanical ventilation, particularly in patients with pneumonia. Although our findings suggest that HFNC may be a strong alternative to NIV, the results should be confirmed by further investigations, including a prospective randomized trial.

FUNDING

This research did not receive grant funding from any agency in the public, commercial or not-for-profit sectors.

DECLARATIONS OF INTEREST

None.

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APPENDIX

JOURNAL OF CRITICAL CARE – GUIDE FOR AUTHORS

GUIDE FOR AUTHORS

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AGRADECIMENTOS

Em primeiro lugar, gostaria de agradecer ao Dr. Rui Veiga, não só pela orientação neste trabalho, mas por ser capaz de, pelo exemplo, me motivar a ser uma melhor profissional e, sobretudo, uma melhor pessoa.

Agradeço também à minha família, pelo apoio constante durante todo este percurso.

Por último, mas não menos importante, agradeço aos meus amigos e companheiros dos últimos 6 anos. Com eles (e por eles) tudo valeu a pena. Em especial, agradeço à Catarina, à Helena, à Lídia, à Maria, à Marta e à Sara. Agradeço, não porque partilham a mesma cidade como casa, mas por serem, elas próprias, a minha Casa.