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ORIGINAL RESEARCH

The effects of high-flow nasal cannula oxygen therapy in dyspnea patients with and without hypercapnia in the emergency department: a retrospective, propensity score-matched cohort study

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Abstract

We aimed to study the difference in treatment outcomes and prognoses in patients with or without hypercapnia who visited the emergency department for dyspnea and received high-flow nasal cannula (HFNC) therapy. This was a retrospective observational study. Patients who received HFNC therapy were divided into hypercapnic and non-hypercapnic. The intubation rates were compared for the primary outcome. For the secondary outcomes, intensive care unit (ICU) admission, length of hospital stay, length of ICU stay, and mortality were compared. Moreover, changes in arterial blood gas results were reported in terms of group, time, and group-by-time interaction. A total of 517 patients were enrolled, of whom 126 were included in the hypercapnic group. After propensity score matching, 94 patients were selected. The intubation rate was not significantly different between the two groups ($p = 0.23$). No differences were found in ICU admission, length of hospital stay, length of ICU stay, and mortality. The changes in arterial blood gas results pre- and post-HFNC therapy showed a difference in the group-by-time interaction for partial pressure of carbon dioxide ($p = 0.038$). We found that there was no difference in treatment outcomes and prognoses in patients with or without hypercapnia who visited the emergency department for dyspnea and received HFNC therapy.

Keywords

Oxygen therapy; High-flow nasal cannula; Hypercapnia; Intubation; Mortality

1. Introduction

Acute dyspnea with hypoxemia is a major problem in emergency departments (EDs); oxygen therapy is an essential supportive treatment to correct these issues [1].

Conservative oxygen therapy (COT) consists of a nasal cannula, a simple oxygen mask, and a non-rebreathing oxygen mask. Noninvasive ventilation (NIV) or endotracheal intubation with mechanical ventilation is required if COT does not provide sufficient supplemental oxygen. According to the official European Respiratory Society/American Thoracic Society clinical practice guidelines, NIV is effective in patients with hypercapnic respiratory failure [2]. However, NIV is not easy to apply to patients who visit the ED, and presents several contraindications [3]. Similarly, endotracheal intubation is invasive, requires patient sedation, and can have adverse effects [4].

The high-flow nasal cannula (HFNC) has been increasingly used in patients with dyspnea, helping them feel comfortable and reduce breathing frequency, possibly by providing low levels of positive airway pressure [5]. Moreover, active humidification improves mucociliary function, facilitates secretion clearance, and decreases atelectasis formation [6–8].

In a previous study, HFNC therapy in acute hypoxemic respiratory failure reduced mortality and the need for mechanical ventilation (NIV or invasive ventilation) [5]. In a multicenter randomized clinical trial, when HFNC therapy was compared with COT and NIV, the intubation rate of each group was not statistically significant; however, the HFNC group had longer ventilator-free days at day 28 and lower 90-day mortality than the other two therapies [9]. According to the results of these studies, the HFNC helps improve oxygen saturation while increasing physical comfort in patients and reducing mechanical ventilation and mortality.

However, HFNC therapy has not been considered for the treatment of hypoxia with hypercapnia. A previous study showed that the short-term HFNC therapy is safe in patients with stable normocapnic and hypercapnic chronic obstructive pulmonary disease (COPD); however, this study recruited 77 patients and applied an abnormally low flow of 15 L/min over 60 min [10]. Another study showed that HFNC therapy reduced carbon dioxide (CO_2) in patients with acute respiratory

failure with hypercapnia when an appropriate level of fraction of inspired oxygen (FiO_2) was provided; however, the study had a small sample size (33 patients) and was not controlled [11].

This study aimed to study the difference in treatment outcomes and prognoses in patients with or without hypercapnia who visited the emergency department for dyspnea and received HFNC therapy. Moreover, we evaluated whether other variables could affect the outcomes of interest.

2. Materials and Methods

2.1 Study population and data collection

We conducted a retrospective observational study of patients older than 18 years with dyspnea who received HFNC therapy in the ED between January 2015 and August 2019. HFNC therapy was used in the following circumstances: oxygen saturation $\leq$93%; complaints of severe dyspnea; and the emergency physician's decision. The treatment began with a FiO_2 of 0.4–0.5 and a flow of 30–40 L/min and was subsequently monitored by the emergency physician according to the patient's status [5, 12]. We further selected patients using the following exclusion criteria: age $<$18 years; discharge from the emergency room after symptoms improvement; transfer to other hospitals for unknown results; discharge against medical advice; and absence of an arterial blood gas test before HFNC therapy. Patients were divided into two groups based on whether they were hypercapnic. The non-hypercapnic and hypercapnic groups had partial pressure of carbon dioxide (PCO_2) $<$45 and $\geq$45 mmHg, respectively, before HFNC therapy.

The HFNC device (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand) consisted of an air-oxygen blender that could generate an air-oxygen flow of up to 60 L/min and a FiO_2 between 0.21 and 1.00 and heated humidification (MR850 pass-over humidifier, Fisher & Paykel Healthcare). The air-oxygen mixture at 37 °C was delivered via a single-limb heated inspiratory circuit through a nasal cannula [13].

2.2 Outcomes

The primary outcome was the intubation rate, and the secondary outcomes were intensive care unit (ICU) admission, length of hospital stay, length of ICU stay, and mortality. We also compared the arterial blood gas results between the two groups to evaluate the effect of HFNC therapy.

2.3 Statistical analyses

According to normality testing, categorical variables were described as frequencies with percentages, while continuous variables were described as means with standard deviations (SDs) or medians with interquartile ranges. Comparisons between the non-hypercapnic and the hypercapnic group were performed using the chi-squared test or Fisher's exact test for categorical variables and the independent *t*-test or Mann-Whitney U test for continuous variables.

To reduce selection bias and potential confounding factors in an observational study, we calculated the propensity score and performed matching between the non-hypercapnic and the hypercapnic group. Matching was performed using logistic regression with the nearest-neighbor matching algorithm (caliper width, 0.05 of the SD of the logit score). We assessed the balance of covariates by evaluating standardized differences between the non-hypercapnic and the hypercapnic group. We considered covariates with a standardized difference of less than 20% to be well balanced. We used McNemar's test for categorical variables and Wilcoxon signed-rank or paired *t*-test for continuous variables to compare the two groups in the propensity score-matched cohort. We utilized generalized estimating equations using linear regression to compare the arterial blood gas changes pre- and post-HFNC application between the two groups.

All analyses were performed using R version 3.5.2 and the Statistical Package for the Social Sciences version 26 (IBM Corporation, Armonk, NY, USA), and differences with a *p*-value less than 0.05 were considered to be statistically significant.

3. Results

During the study period, 2236 patients required oxygenation above the face mask capacity, and among them, 517 received HFNC therapy (Fig. 1). The non-hypercapnic group and the hypercapnic group included 262 and 126 patients, respectively.

The patients' baseline characteristics are shown in Table 1. The two groups were different in terms of medical history before matching. Patients in the hypercapnic group had a higher prevalence of underlying chronic lung diseases and malignancies and had significantly higher systolic and diastolic blood pressure than the non-hypercapnic group. In terms of etiology, the largest proportion of patients with pneumonia was found in the non-hypercapnic group, whereas the largest ratio of patients with cardiogenic edema was found in the hypercapnic group; moreover, the frequency of acute exacerbation of COPD was higher in the hypercapnic group than in the non-hypercapnic group, while that of extrapulmonary acute lung injury was higher in the non-hypercapnic group than in the hypercapnic group.

After propensity score matching, we selected 94 pairs of patients with similar baseline characteristics, except for the arterial blood gas results. There were no significant differences between the two groups, including medical histories, initial vital signs, and etiologies.

The outcome variables are shown in Table 2. There were no significant differences between the two groups.

The changes in arterial blood gas results pre- and post-HFNC therapy were compared (Fig. 2). An arterial blood gas test was performed at 68.53 $\pm$ 53.42 min. The PO_2 increased in both groups. The hypercapnic group showed a decrease in PCO_2 between pre- and post-HFNC applications ($p = 0.038$).

4. Discussion

This study showed no difference in treatment outcomes and prognoses in patients with or without hypercapnia who visited the ED for dyspnea and received HFNC therapy. As we aimed to examine the outcome of HFNC therapy on hypercapnia,

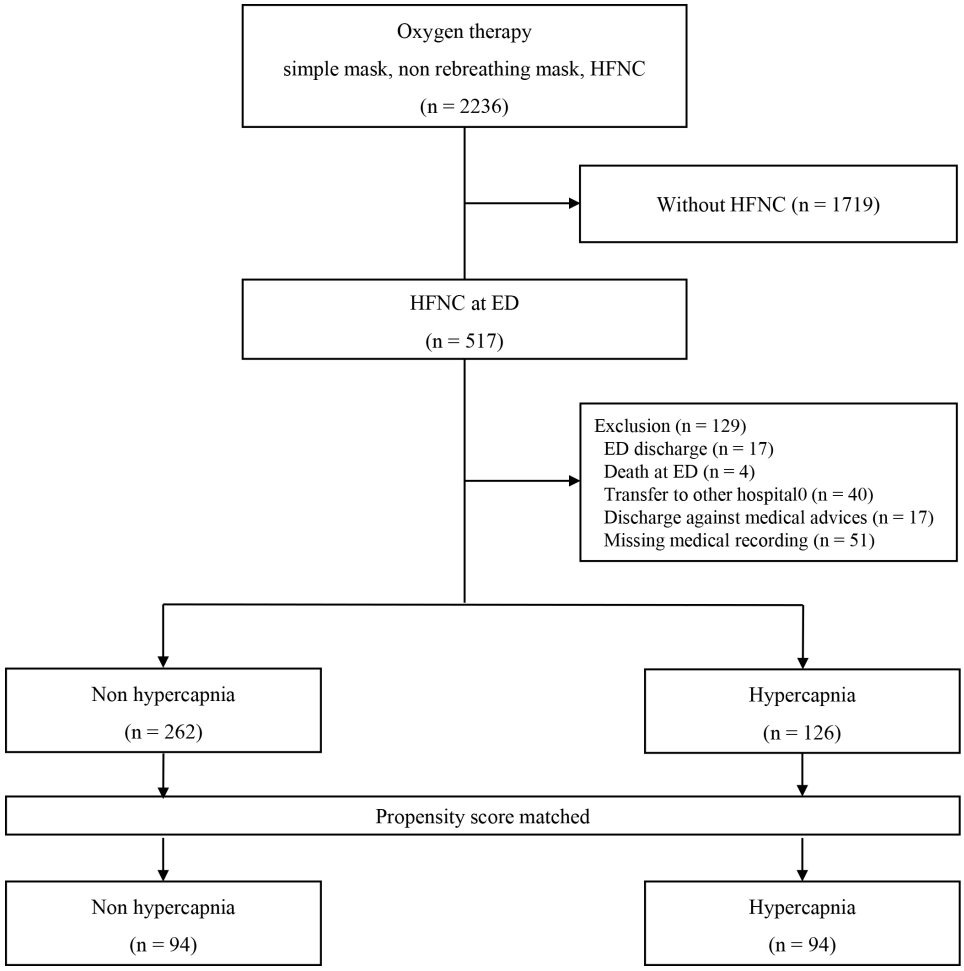

FIGURE 1. Distribution of the study populations. HFNC, high-flow nasal cannula; ED, emergency department.

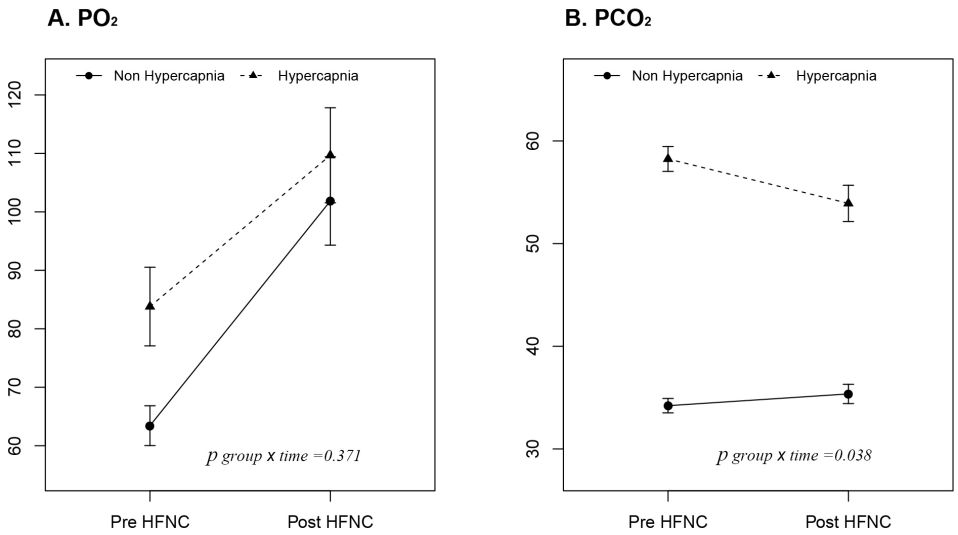

FIGURE 2. Changes in arterial blood gas analysis parameters between non-hypercapnic and hypercapnic groups in pre and post HFNC. (Fig. 2A: PO_2 and Fig. 2B: PCO_2) HFNC, high flow nasal cannula; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide.

several variables were controlled for through propensity score matching. There were no significant differences between the two groups in terms of intubation, ICU admission, length of hospital stay, and mortality. In both groups, HFNC therapy improved oxygenation, while in the hypercapnic group, PCO_2 levels were reduced.

The HFNC is a newly introduced device that has been widely used and studied in patients with dyspnea in the ED [12, 14–17]. Compared with COT, HFNC therapy can decrease the need for escalation of oxygen therapy and improve dyspnea

TABLE 1. Baseline characteristics in study patients who received HFNC therapy before and after propensity matching.

	Before matching			After matching		
	Non-hypercapnia (n = 262)	Hypercapnia (n = 126)	SMD	Non-hypercapnia (n = 94)	Hypercapnia (n = 94)	SMD
Age, year	75.22 ± 14.21	76.04 ± 11.83	0.063	75.27 ± 12.95	76.86 ± 11.27	0.131
Gender, men	143 (54.6)	56 (44.4)	0.204	44 (46.8)	43 (45.7)	0.021
Underlying diseases						
Hypertension	150 (57.3)	63 (50.0)	0.146	58 (61.7)	53 (56.4)	0.108
Diabetes mellitus	97 (37.0)	43 (34.1)	0.061	39 (41.5)	31 (33.0)	0.177
Chronic lung disease	29 (11.1)	29 (23.0)	0.322	10 (10.6)	16 (17.0)	0.186
Ischemic heart disease/heart failure	72 (27.5)	38 (30.2)	0.059	29 (30.9)	32 (34.0)	0.068
Cerebral vascular disease	24 (9.2)	10 (7.9)	0.044	7 (7.4)	9 (9.6)	0.076
Chronic kidney disease/dialysis	36 (13.7)	17 (13.5)	0.007	14 (14.9)	13 (13.8)	0.03
Malignancy	41 (15.6)	7 (5.6)	0.332	9 (9.6)	6 (6.4)	0.118
Glasgow coma scale	13.60 ± 2.56	13.63 ± 2.42	0.01	13.71 ± 2.46	13.69 ± 2.39	0.082
Initial vital signs						
SBP	133.27 ± 38.30	150.11 ± 43.25	0.412	143.45 ± 43.43	147.71 ± 42.42	0.019
DBP	77.39 ± 21.20	84.05 ± 21.90	0.309	81.97 ± 24.69	83.06 ± 21.73	0.019
RR	23.98 ± 4.75	24.98 ± 5.64	0.192	24.50 ± 5.20	24.59 ± 5.31	0.027
HR	104.06 ± 24.73	105.05 ± 22.88	0.042	106.6 ± 27.64	104.99 ± 23.22	0.042
SpO_2	87.80 ± 8.51	87.13 ± 11.72	0.065	87.41 ± 8.19	87.59 ± 11.03	0.108
Initial ABG						
pH	7.39 ± 0.11	7.26 ± 0.12		7.38 ± 0.11	7.26 ± 0.11	
PCO_2	33.31 ± 9.31	60.38 ± 14.4		35.23 ± 11.95	58.59 ± 12.07	
PO_2	64.05 ± 31.99	87.30 ± 66.85		63.20 ± 32.72	83.67 ± 64.17	
HCO_3	20.28 ± 5.35	27.34 ± 7.03		21.19 ± 5.79	27.08 ± 7.03	
BE	−4.60 ± 6.91	−0.02 ± 8.15		−3.58 ± 8.07	−0.28 ± 8.10	
SaO_2	86.58 ± 10.39	83.94 ± 14.86		85.67 ± 11.31	83.55 ± 15.07	
Etiology			0.657			0.177
Pneumonia	108 (41.2)	33 (26.2)		34 (36.2)	32 (34.0)	
AE COPD	6 (2.3)	17 (13.5)		5 (5.3)	5 (5.3)	
ILD aggravation	15 (5.7)	8 (6.3)		6 (6.4)	4 (4.3)	
Cardiogenic edema	79 (30.2)	56 (44.4)		42 (44.7)	42 (44.7)	
Extrapulmonary ALI	52 (19.8)	10 (7.9)		6 (6.4)	10 (10.6)	
Others	2 (0.8)	2 (1.6)		1 (1.1)	1 (1.1)	

SMD, standardized mean difference; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; HR, heart rate; ABG, arterial blood gas; PCO_2, partial pressure carbon dioxide; PO_2, partial pressure of oxygen; HCO_3, bicarbonate; BE, base excess; SaO_2, oxygen saturation; AE COPD, acute exacerbation of chronic obstructive pulmonary disease; ALI, acute lung injury; ILD, interstitial lung disease.

and comfort levels.

According to guidelines, the use of NIV for the treatment of patients with hypercapnic respiratory failure is strongly recommended [2]. When NIV treatment is insufficient, endotracheal intubation is performed. In studies applying HFNC therapy and NIV to patients with acute moderate hypercapnic respiratory failure, there was no difference in 30-day mortality and intubation rates [18, 19]. Fewer nursing interventions and skin breakdown episodes were reported in the HFNC group. Moreover, HFNC therapy is helpful for medical staff working in the ED by optimizing the use of medical resources. However, physicians may be reluctant to use the HFNC in patients with dyspnea and hypercapnia due to the high risk of intubation for CO_2 excretion in hypercapnia; thus, we compared the intubation rates of patients with and without hypercapnia among those treated with HFNC.

TABLE 2. Clinical outcomes in the non-hypercapnia and hypercapnia groups.

	Non-hypercapnia	Hypercapnia	*p*-value
	n = 94	n = 94	
Intubation (n, %)	11 (11.7)	18 (19.15)	0.23
ICU admission (n, %)	29 (30.85)	41 (43.62)	0.07
Length of hospital stay (days)	10 (6, 19.75)	10 (6.25, 19)	0.64
Length of ICU stay (days)	6 (2, 12)	4 (3, 11)	0.92
Mortality (n, %)	21 (22.34)	18 (19.15)	0.7

ICU, intensive care unit.

In previous studies, the application of HFNC was shown to require precautions in patients with dyspnea with hypercapnia. According to Nishimura's study, an analysis of several studies showed that HFNC therapy reduces the respiratory rate, but not PCO_2 to a significant degree [7]. Another study showed that HFNC therapy reduced respiratory effort but did not change arterial blood gas results in patients with COPD [20]. Nevertheless, in this study, we found significant changes in PCO_2 pre- and post-HFNC therapy in the hypercapnic group, suggesting that HFNC may be an effective oxygen therapy that decreases PCO_2 in dyspnea with hypercapnia patients.

COPD may be hypothesized to be the most frequent cause of dyspnea with hypercapnia; however, here, we showed that the frequency of cardiogenic edema was the highest, followed by pneumonia. Moreover, these patients could also be hypercapnic depending on the state of dyspnea. As oxygen therapy is prioritized in dyspnea with hypercapnia patients in the ED before the cause is identified, determining the most suitable method of treatment for these patients is crucial. Thus, if HFNC therapy is proven to be beneficial to patients with dyspnea with hypercapnia due to a variety of causes, it would be useful to determine the therapeutic plans for the patients.

Despite numerous applications and reported effects, cases requiring intubation due to oxygenation failure via the HFNC occur in 38% of patients, with a 30% mortality rate reported in a previous study [4]. The HFNC therapy from the previous study showed that intubation performed 48 h after HFNC application due to treatment failure has been shown to influence ICU mortality, extubation success, ventilator weaning, and ventilator-free days; thus, when applying the HFNC in patients with dyspnea with hypercapnia, care should be taken to prevent delayed intubation.

Indications for HFNC therapy are not as well defined as those for NIV and intubation; therefore, HFNC therapy may be extended or limited. In our study, HFNC therapy, even in patients with dyspnea who visited the ED, did not increase intubation rate, length of stay, and mortality rate in the hypercapnic group. These findings are expected to be useful in deciding whether to apply HFNC therapy in patients admitted to the ED due to dyspnea with hypercapnia.

This study has some limitations. First, this study was designed retrospectively at a single center; therefore, its findings cannot be generalized. Second, the HFNC application was dependent on the decision of the emergency physician; therefore, it remains unknown how FiO_2 was regulated owing to the lack of written records. Future prospective studies should investigate the influence of FiO_2 application, treatment, and prognosis of patients with hypercapnia. Third, we did not have non-HFNC hypercapnic patients as controls; therefore, our results cannot be used to compare the effects of HFNC and other treatments (non-HFNC) in patients with hypercapnia. Fourth, a trend of short application time of the arterial blood gas test was shown in the hypercapnic group. The arterial blood gas test time should be fixed for consistency in future studies. Finally, although COPD is predicted in most patients with dyspnea with hypercapnia, the subjects in this study who showed acute exacerbation of COPD were not a significant proportion; therefore, care should be taken when applying the findings of this study to patients with acute COPD exacerbation.

5. Conclusion

HFNC therapy as an oxygenation method in the ED is steadily increasing. Although hypercapnia might be associated with poor prognosis in patients with respiratory failure, this study showed no difference in treatment outcomes and prognoses in patients with or without hypercapnia who visited the ED for dyspnea and received HFNC therapy. Therefore, emergency physicians can apply HFNC therapy to patients with respiratory distress, regardless of the presence or absence of hypercapnia.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YSC—responsible for the conception and the writing of the study and had full access to all of the data; HC—takes responsibility for the integrity of the data and the accuracy of the data analysis; SP—contributed substantially to the study design, data analysis and interpretation. All authors contributed and have approved the final article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Research ethics board approval was obtained for Soonchunhyang university hospital seoul research (No. 2020-04-026), and informed consent was waived because of the retrospective design of the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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