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Clinical efficacy of high-flow nasal cannula compared to noninvasive ventilation in patients with post-extubation respiratory failure

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Background/Aims: Post-extubation respiratory failure (PERF) is associated with poor clinical outcomes. High-flow nasal cannula (HFNC) oxygen therapy has been used in patients with respiratory failure, but the clinical benefit in patients with PERF remains unclear. The aim of this study was to evaluate the clinical efficacy of HFNC compared to noninvasive ventilation (NIV) in patients with PERF.

Methods: A historic retrospective cohort analysis was performed in 28 beds in the medical Intensive Care Unit (ICU) at a single medical center in South Korea. In total, 73 patients with PERF were enrolled: 39 patients who underwent NIV from April 2007 to March 2009 and 34 patients who received HFNC from April 2009 to May 2011.

Results: The rate of avoidance of reintubation was not different between the HFNC group (79.4%) and NIV group (66.7%, $p = 0.22$). All patients with HFNC tolerated the device, whereas five of those with NIV did not tolerate treatment ($p = 0.057$). The mean duration of ICU stay was significantly shorter in the HFNC group than in the NIV group (13.4 days vs. 20.6 days, $p = 0.015$). There was no difference in ICU or in-hospital mortality rate.

Conclusions: HFNC is likely to be as effective as, and better tolerated than, NIV for treatment of PERF.

Keywords: Post-extubation respiratory failure; Noninvasive ventilation; High-flow nasal cannula

INTRODUCTION

Post-extubation respiratory failure (PERF) occurs in ~10% to 20% of patients with planned extubation and results in reintubation [1-3]. Reintubation due to PERF is associated with poor outcomes, including an increased incidence of ventilator-associated pneumonia, increased mortality rates, and longer Intensive Care Unit (ICU) and hospital stays [4-6]. An international consensus conference considered noninvasive ventilation (NIV) to be a promising modality in terms of avoiding reintubation associated with PERF and improving clinical outcomes [7]. However, two randomized clinical trials did not demonstrate a benefit of NIV in terms of avoiding reintubation in patients with PERF [8,9].

A high-flow nasal cannula (HFNC), a relatively new oxygenation device, provides adequate heated humidity in addition to a high flow of oxygen. Due to the high flow rate of gas, HFNC can produce a continuous positive airway pressure effect in the airway, and thus may

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exert a favorable physiologic effect [10]. Due to the combination of these effects, HFNC may serve to improve oxygenation, maintain bronchial hygiene, and alleviate respiratory distress [11]. Several studies have reported the usefulness of HFNC in patients with acute respiratory failure, showing beneficial effects on clinical signs and oxygenation [12-15]. Although one work investigated the clinical outcomes in pediatric, and especially neonatal, populations [16], studies focusing on the clinical outcomes of HFNC—such as reintubation, mortality, or ICU stay—in adults with PERF. are lacking. The aim of our study was to evaluate the clinical outcomes of HFNC in patients with PERF compared to those of NIV.

METHODS

Patients

This historic retrospective study was conducted in a university-affiliated hospital with a 28-bed medical ICU in Seoul, South Korea. Medical record charts were reviewed retrospectively. Two groups were established based on the period of treatment: the first group (NIV group) included patients who received treatment from April 2007 to March 2009, while the second group (HFNC group) included patients who underwent treatment from April 2009 to May 2011. The Institutional Review Board of Asan Medical Center approved this study. The requirement for informed consent was waived due to the retrospective nature of the analysis.

Inclusion and exclusion criteria

Medical patients ≥ 18 years old who had been extubated were enrolled. Respiratory failure that developed within 48 hours was regarded as PERF, and NIV or HFNC was performed. Respiratory failure was defined as clinical signs of increased effort on breathing (such as active contraction of the accessory respiratory muscles) that developed within 48 hours of extubation, plus one of the following: (1) respiratory acidosis (defined as an arterial pH < 7.35 with a partial pressure of arterial carbon dioxide of > 45 mmHg); (2) respiratory rate greater than 25 breaths per minute; (3) hypoxemia defined as (partial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] < 300 mmHg or pulse oxygen saturation [SpO_2] of < 90%). Patients were excluded if they had 'do-not-resuscitate' status or a previous experience of home bilevel positive airway pressure (BiPAP).

NIV protocol: before undergoing NIV, patients were positioned with their beds at a 45° angle. The patient put on an orofacial mask to function as an interface. In the pressure support mode with > 4 cmH_2O positive end-expiratory pressure, an initial target estimated tidal volume of 6 mL per predicted kilogram of body weight and a respiratory rate of less than 24 breaths per minute were set. The FiO_2 was titrated to maintain the SpO_2 at > 90%.

HFNC (Optiflow; Fisher & Paykel Healthcare, Auckland, New Zealand) protocol: oxygen was supplied via HFNC, using an initial inspiratory flow rate of 30 L/min and was titrated until the respiratory effort of patients was minimized. FiO_2 was adjusted to achieve a SpO_2 of > 90%.

Data collection

Avoidance of reintubation, duration of ICU and hospital stay, ICU and hospital mortality rates, and incidence of ICU-acquired pneumonia associated with PERF were evaluated and compared between the two groups. Device intolerance was defined as patients' refusal of continuous use of devices. The avoidance of reintubation was defined as no reintubation due to respiratory failure after applying HFNC or NIV during the ICU stay.

ICU-acquired pneumonia was defined using either clinical criteria (new or progressive radiologic pulmonary infiltrate together with at least two of the following: temperature > 38°C or < 36°C, leukocytosis > 12,000/mm^3 or leukopenia < 4,000/mm^3 , or purulent respiratory secretions) or a simplified Clinical Pulmonary Infectious Score greater than or equal to six points [17].

Statistical analysis

Categorical and non-categorical variables are expressed as number (percentage) and mean ± standard deviation, respectively. The Fisher exact or chi-square test was used to compare categorical variables. The Mann-Whitney *U* test was used for comparisons of non-categorical variables. A value of $p \leq 0.05$ was considered to indicate statistical significance. The SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Baseline characteristics of the enrolled patients

A total of 73 patients were enrolled in this study: in the first-period group, 39 patients underwent NIV for the treatment of PERF, while in the second-period group, 34 subjects were treated by HFNC. Of all patients, 43 patients (58.9%) were males. Their age was 62.6 ± 16.3 years. The baseline characteristics of the enrolled patients are shown in Table 1. There was no significant difference in gender, age, or Acute Physiology and Chronic Health Evaluation II or Sequential Organ Failure Assessment score between the two groups. The proportion of neoplasm as an underlying disease was higher in the NIV group than the HFNC group. Acute heart failure was a more common cause of acute respiratory failure in the NIV group than in the HFNC group. Duration of invasive mechanical ventilation until extubation did not differ between the two groups. There was a trend toward shorter duration from extubation to the onset of respiratory failure in the HFNC group.

Physiologic parameters and laboratory data of patients with PERF

The physiologic parameters and laboratory findings of patients at the onset of PERF are summarized in Table 2. Regarding vital signs, only body temperature differed significantly between the two groups. In the arterial blood gas analysis results, lower pH, higher partial pressure of carbon dioxide, and lower arterial blood saturation were found in the NIV group compared to the HFNC group. There was a trend toward lower levels of sodium and potassium in the HFNC group. Other laboratory data did not differ between the two groups.

Comparison of clinical outcomes between the NIV and HFNC groups

The clinical outcomes of the NIV and HFNC groups are described in Table 3. Overall, 53 patients (72.6%) did not

Table 1. Baseline characteristics of the enrolled patients

Characteristic	NIV group (n = 39)	HFNC group (n = 34)	*p* value
Male sex	25 (64.1)	18 (52.9)	0.334
Age, yr	62.9 ± 16.1	62.1 ± 16.8	0.969
Acute Physiology and Chronic Health Evaluation II score	19.2 ± 3.9	19.7 ± 4.1	0.480
Sequential Organ Failure Assessment score	6.3 ± 3.5	5.5 ± 2.5	0.461
Underlying disease			
Diabetes mellitus	4 (10.3)	5 (14.7)	0.725
Neoplasm	11 (28.2)	18 (52.9)	0.031
Chronic lung disease	14 (35.9)	11 (32.4)	0.750
Chronic heart disease	9 (23.1)	5 (14.7)	0.365
Chronic renal disease	8 (20.5)	2 (5.9)	0.093
Liver cirrhosis	4 (10.3)	3 (8.8)	1
Causes of mechanical ventilation before extubation			
Pneumonia	22 (56.4)	18 (52.9)	0.766
Sepsis	8 (20.5)	10 (29.4)	0.379
AE of chronic obstructive pulmonary disease	7 (17.9)	4 (11.8)	0.461
AE of idiopathic pulmonary fibrosis	1 (2.6)	4 (11.8)	0.177
Acute respiratory distress syndrome	2 (5.1)	5 (14.7)	0.240
Acute heart failure	9 (23.1)	2 (5.9)	0.041
Duration of invasive MV before extubation, hr	182.9 ± 148.8	132.7 ± 85.6	0.243
Time elapsed from extubation to respiratory failure, hr	10.7 ± 11.6	8.6 ± 11.8	0.097

Values are presented as number (%) or mean ± SD.
NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; AE, acute exacerbation; MV, invasive mechanical ventilation.

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Table 2. Physiologic parameters and laboratory findings of the patients at the onset of post-extubation respiratory failure

Variable	NIV group (n = 39)	HFNC group (n = 34)	*p* value
Physiologic parameter			
Systolic blood pressure, mmHg	131.8 ± 21.2	136.3 ± 16.9	0.678
Diastolic blood pressure, mmHg	64.2 ± 14.8	71.4 ± 10.8	0.224
Heart rate, beats/min	101.9 ± 21.7	102.6 ± 18.4	0.799
Respiratory rate, beats/min	22.8 ± 5.2	20.9 ± 6.0	0.115
Body temperature, °C	36.8 ± 0.6	36.6 ± 0.6	0.035
Arterial blood gas analysis			
pH	7.40 ± 0.1	7.48 ± 0.07	0.003
PaO_2, mmHg	76.4 ± 24.2	82.9 ± 30.3	0.419
$PaCO_2$, mmHg	48.2 ± 17.8	38.2 ± 6.6	0.030
PaO_2/FiO_2 ratio	190.6 ± 82.8	188.9 ± 73.8	0.757
Pulse oxygen saturation, %	93.3 ± 4.3	95.2 ± 3.4	0.032
White cell count, × 10^3 cells/μL	12 ± 6.5	13.6 ± 7.1	0.291
Hemoglobin, g/dL	9.9 ± 1.9	10.5 ± 1.9	0.162
Platelet, × 10^3 cells/μL	176.3 ± 133.6	185.8 ± 110.1	0.425
Albumin, g/dL	2.5 ± 0.5	2.6 ± 0.4	0.456
Sodium, mmol/L	138.9 ± 5.5	136.7 ± 4.2	0.099
Potassium, mmol/L	3.9 ± 0.4	3.6 ± 0.6	0.082

Values are presented as mean ± SD.
NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; FiO_2, inspired fraction of oxygen.

require reintubation during their ICU stay. The rate of avoidance of reintubation was not significantly different between the two groups (66.7% for NIV vs. 79.4% for HFNC, p = 0.223). Device intolerance occurred in five patients (12.8%) with NIV, whereas there was no device intolerance in patients with HFNC (p = 0.057). Four of the five patients that did not tolerate NIV progressed to respiratory failure and were reintubated. In the HFNC group, seven patients progressed to severe respiratory failure, all of whom were reintubated and received invasive mechanical ventilation. A total of 20 patients (27.4%) were reintubated (33.3% in the NIV group vs. 20.6% in the HFNC group, p = 0.531). The rates of reintubation and application of invasive mechanical ventilation were not significantly different between the two groups. The reasons for reintubation were similar in the two groups: refractory hypoxemia was the most common cause (6/39, 46.2% for NIV vs. 4/34, 57.1% for HFNC, p = 0.531). There was no difference in the rate of tracheostomy between the two groups (6/13, 46.2% in the NIV group vs. 4/7, 57.1% in the HFNC group, p = 1.0). The duration of ICU stay from extubation was significantly shorter in the HFNC group than in the NIV group (6.8 ± 9.6 days vs. 10.4 ± 11.1 days, p = 0.013), but the duration of ICU stay from the onset of PERF to general ward in ICU survivors did not differ significantly between the groups (7.8 ± 9.2 days in the NIV group vs. 4.6 ± 5.6 days in the HFNC group, p = 0.856). The length of hospital stay was similar between the two groups (52.9 ± 38.7 days in the NIV group vs. 48.7 ± 40.5 days in the HFNC group, p = 0.367). There was no significant difference in the rate of ICU-acquired pneumonia after extubation (20.5% in the NIV group vs. 17.6% in the HFNC group, p = 0.756), ICU (20.5% in the NIV group vs. 8.8% in the HFNC group, p = 0.164), or in-hospital mortality (41% in the NIV group vs. 23.5% in the HFNC group, p = 0.112) between the two groups.

Subgroup analysis of outcome variables according to the presence of hypercapnia

Further outcomes analyses according to the presence of hypercapnia were performed since the baseline level of $PaCO_2$ differed significantly between the NIV and

Table 3. Comparison of clinical outcomes between the NIV and HFNC groups.

Variable	NIV group (n = 39)	HFNC group (n = 34)	*p* value
Avoidance of reintubation	26 (66.7)	27 (79.4)	0.223
Total reintubation rates	13 (33.3)	7 (20.6)	0.223
Reasons for reintubation			0.531
Refractory hypoxemia	6 (46.2)	4 (57.1)	
Refractory hypercapnia	3 (23.1)	0	
Excess respiratory secretions	1 (7.7)	1 (14.3)	
Cardiopulmonary arrest	2 (15.4)	1 (14.3)	
Changes in mental status	0	1 (14.3)	
Lack of improvement in signs of muscle fatigue	1 (7.7)	0	
Tracheostomy	6/13 (46.2)	4/7 (57.1)	1.000
ICU stay, day	20.6 ± 14.2	13.4 ± 10.3	0.015
Post-extubation ICU stay, day	10.4 ± 11.1	6.8 ± 9.6	0.013
ICU stay after PERF in ICU survivors, day	7.8 ± 9.2	4.6 ± 5.6	0.856
Hospital stay, day	52.9 ± 38.7	48.7 ± 40.5	0.367
ICU-acquired pneumonia after extubation	8 (20.5)	6 (17.6)	0.756
ICU mortality	8 (20.5)	3 (8.8)	0.164
Hospital mortality	16 (41)	8 (23.5)	0.112

Values are presented as mean ± SD or number (%).
NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; ICU, Intensive Care Unit; PERF, post-extubation respiratory failure.

Table 4. Analysis of outcome variables according to arterial carbon dioxide pressure.

Outcome	$PaCO_2$ < 45 mmHg			$PaCO_2$ ≥ 45 mmHg		
	NIV group (n = 22)	HFNC group (n = 28)	*p* value	NIV group (n = 17)	HFNC group (n = 6)	*p* value
Avoidance of reintubation	14 (63.6)	24 (85.7)	0.070	12 (70.6)	3 (50)	0.363
ICU mortality	6 (27.3)	1 (3.6)	0.034	2 (11.8)	2 (33.3)	0.270
In-hospital mortality	9 (40.9)	4 (14.3)	0.033	7 (41.2)	4 (66.7)	0.371

Values are presented as number (%).
$PaCO_2$, partial pressure of carbon dioxide; NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; ICU, Intensive Care Unit.

HFNC groups (Table 4). In the 50 patients with $PaCO_2$ < 45 mmHg, patients with HFNC showed a lower ICU mortality rate (3.6% vs. 27.3%, p = 0.034) and in-hospital mortality rate (14.3% vs. 40.9%, p = 0.033), as well as a trend toward a lower incidence of reintubation than those with NIV (85.7% vs. 63.6%, p = 0.07). In the 23 patients with a $PaCO_2$ > 45 mmHg, there were no significant differences in the above outcome variables between the two groups.

DISCUSSION

In patients with PERF, our study showed that HFNC exhibited a similar efficacy to NIV in terms of avoidance of reintubation in patients with PERF. In addition, HFNC was better tolerated, and associated with a shorter ICU stay, compared to NIV. In patients without hypercapnia (as indicated by a $PaCO_2$ < 45 mmHg at the onset of PERF), HFNC was associated with lower ICU and in-hospital mortality rates than NIV.

Extubation is a critical step in patients who receive

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invasive mechanical ventilation. Despite recent advances in mechanical ventilation, PERF develops in ~10% to 20% of patients who meet weaning criteria [1,2]. Reintubation due to PERF is associated with poor outcomes and a mortality rate of up to 50% [3,5,6]. Therefore, an effective intervention is required to prevent or reverse PERF to avoid reintubation. Previously, NIV was considered a promising therapy and recommended in patients with PERF [7]. However, two randomized studies failed to show beneficial effects of NIV in patients who develop respiratory failure after extubation. Indeed, the mortality rate was higher in the NIV group in two studies [8,9]. The benefit of NIV as a treatment for PERF was evident only in patients with hypercapnic respiratory failure [18,19].

Heated and humidified HFNC was recently introduced to ICUs. It supplies up to 100% heated and humidified oxygen at a maximum flow rate of 60 L/min via a nasal prong or cannula. By delivering a continuous high flow of oxygen, the pharyngeal dead space is washed out, nasopharyngeal resistance is reduced and some positive end expiratory pressure is generated, all of which contribute to a reduction in the work of breathing [10,11]. The heated humidification facilitates secretion clearance and expectoration of bronchial secretions. It also increases patient comfort because high-flow oxygen is delivered via a nasal cannula, and does not interrupt eating, drinking or talking. In addition, HFNC therapy has not been associated with pneumonia or barotrauma. A few reports have demonstrated the clinical benefits of HFNC, as shown by alleviation of symptoms and improvement of respiratory parameters such as respiratory rate, arterial blood oxygen partial pressure or saturation in patients with acute respiratory failure [12-15]. Two studies have reported that HFNC is equal or more effective than a simple mask in extubated patients in terms of tolerance and delivering oxygen [20,21]. However, the clinical efficacy of HFNC in PERF patients has not been reported to date. The present study indicates that HFNC is not inferior to NIV. Especially in patients with PERF without hypercapnia (i.e., PERF with dominant hypoxia), clinical outcomes such as duration of ICU stay and in-hospital mortality rate were more favorable with HFNC than with NIV. The clinical outcomes of PERF patients with hypercapnia did not differ significantly between HFNC and NIV.

There were several limitations to this study. First, because of its retrospective design and the small number of enrolled patients, the possibility of selection bias cannot be excluded. Second, as a single-center cohort was analyzed, the results cannot be generalized. Third, the group of patients with hypercapnic PERF was small, and so the results of comparison of HFNC and NIV in such cases should be verified.

In conclusion, HFNC may be at least equivalent to NIV in patients with PERF in terms of avoiding reintubation. HFNC oxygen therapy is associated with shorter ICU stay in patients with PERF. In subjects without hypercapnic PERF, ICU and in-hospital survival rates were improved by HFNC.

KEY MESSAGE

1. High-flow nasal cannula (HFNC) oxygen therapy was associated with shorter Intensive Care Unit stay in patients with post-extubational respiratory failure compared with noninvasive ventilation (NIV).
2. HFNC may not be inferior to NIV in terms of avoiding the need for reintubation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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