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Original Article

Effect of High-Flow Nasal Oxygen vs. Conventional Oxygen Therapy on Extubation Outcomes and Physiologic Changes for Patients with High Risk of Extubation Failure in the Medical ICU: A Tertiary Center, Randomized, Controlled Trial

Ting-Yu Hu [a], Chao-Hsien Lee [a], Kuang-Hua Cheng [a], Mei-Chu Tan [a,b], Hsiao-Fang Hua [a,b], Li-Kuo Kuo [a,c *]

[a] *Department of Critical Care Medicine, Mackay Memorial Hospital, Taipei branch, Taiwan,* [b] *Department of Respiratory Therapy, Mackay Memorial Hospital,* [c] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*

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SUMMARY

Background: Postextubation respiratory failure is associated with increased mortality. The role of high-flow nasal cannula (HFNC) oxygen therapy in high-risk patients has not been clarified in post-extubation failure. This study aimed to determine whether HFNC reduces postextubation respiratory failure in high-risk patients compared with conventional oxygen therapy.
Methods: A single-center randomized controlled trial was conducted in Taiwan's 25-bed adult medical intensive care units (ICUs) from September 2014 to September 2016. Enrolled patients with high-risk postextubation failure were randomized to receive either HFNC or conventional oxygen therapy for 72 hours postextubation. Primary outcomes were rate and causes of postextubation respiratory failure within 72 hours. Secondary outcomes included the ICU length of stay, 28-day mortality, and 48-hour postextubation physiologic values.
Results: Of 56 patients, 29 received HFNC and 27 received conventional oxygenation therapy. Fewer patients developed respiratory failure in the HFNC (0/29, 0%) than in the Conventional Group (7/27, 25.9%) (odds ratio 0.408 [95% confidence interval, 0.29–0.57], p = 0.0038). There was no significant difference in the ICU length of stay, 28-day postextubation mortality, multiorgan failure, or the 48-hour postextubation physiologic variables. However, there was a trend toward better oxygenation in the HFNC Group (102.4 ± 25.4 vs. 86.6 ± 26.4 mmHg, p = 0.148).
Conclusion: Among patients at high risk for extubation failure, HFNC reduced the risk of postextubation respiratory failure compared to conventional oxygen therapy.

1. Introduction

Acute respiratory failure with mechanical ventilation (MV) accounts for 30%–40% of intensive care unit (ICU) admissions.[1] Successful liberation from MV and extubation are important for outcome improvement.[2] Extubation failure in adult patients ranges from 10% to 20% and reintubation is associated with increased ICU mortality and poor outcomes.[2–4]

After extubation, prophylactic noninvasive ventilation (NIV) is beneficial for patients at high risk for postextubation failure in several studies.[5,6] However, mask discomfort, gastric distention, or patient intolerance may be concerning for postextubation NIV use.[6] Recently, a promising method for oxygen therapy management with high-flow nasal cannula (HFNC) has shown clinical benefits.[7] HFNC can generate low levels of positive end-expiratory pressure to reduce lung atelectasis, enhancing better gas exchange, flushing nasopharyngeal dead space and reducing the effort of breathing.[7]

Regarding postextubation failure, HFNC has shown some benefit in recent studies compared with conventional oxygen therapy for critically ill patients,[8,9] at low risk for extubation failure[10] and at high risk for postextubation failure.[11] However, Fernandez et al. reported that HFNC showed no benefit in preventing postextubation failure over conventional therapy in high-risk non-hypercapnic patients. Thus, this study aimed to test the hypothesis that HFNC can reduce postextubation respiratory failure compared with conventional oxygen therapy for high-risk patients.

2. Materials and methods

The randomized clinical trial (Clinicaltrials.gov NCT02290548) was conducted in Taiwan's 25-bed adult medical ICUs of MacKay Memorial Hospital (MMH), Taipei, from September 2014 to September 2016. The study was approved by the institutional review committees at MMH in Taiwan (IRB No. 14MMHIS164), and all included patients and their surrogates provided written informed consent.

2.1. Eligible participants

All adult patients admitted to the ICU with acute respiratory failure mechanically ventilated for > 48 hours were screened for enrollment. Patients were eligible for inclusion if they had successfully passed a spontaneous breathing trial (SBT) for the scheduled

* Corresponding author. Department of Critical Care Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei City 10449, Taiwan.
E-mail address: lmn4093@gmail.com (L.-K. Kuo)

extubation according the statement of the Sixth International Consensus Conference on Intensive Care Medicine on the subject of weaning.[4] We excluded patients < 20 years of age and those with tracheotomy, pregnancy, facial trauma with intolerable postextubation facial mask or HFNC use, acute gastrointestinal bleeding, as well as those planning to use NIV after extubation. Patients were included for meeting at least one of the following high-risk extubation failure criteria: age > 65 years,[6,12] congestive heart failure,[6] COPD,[2] bronchiectasis or old pulmonary tuberculosis with lung destruction, idiopathic pulmonary fibrosis,[2] end-stage renal disease (ESRD) under maintenance dialysis,[6,13] respiratory muscle weakness related to neuromuscular disease,[13] inadequate respiratory tract secretion management ability,[6,13] body mass index > 30 (calculated by the weight in kilograms divided by the height in meters squared), adult respiratory distress syndrome, or invasive MV use of > 7 days.[6]

At baseline, demographics and causes of respiratory failure were recorded. At extubation and at 48 hours postextubation, physiologic variables were recorded.

2.2. Weaning protocol

The ICU patients were assessed daily for their readiness for weaning by rapid shallow breathing index (RSBI, fR/VT: respiratory frequency/tidal volume), MIP (maximal inspiratory pressure), and cuff leak test (CLT), after they met the criteria proposed in the weaning protocol.[4]

Patients fulfilling these criteria for tolerance of spontaneous ventilation underwent a SBT. The SBT was performed with a T-tube for 30–120 minutes. The standard criteria for a failed SBT were used.[4] Ventilators were reconnected for rest after SBT failure, and a new SBT could be performed if they fulfilled the criteria again. Patients who passed the SBT were directly extubated and randomized. Within 24 hours prior to extubation, systemic steroids were given if the CLT was $\leq$ 110 mL.

2.3. Randomization and masking

After extubation, patients were assigned to receive either HFNC or conventional oxygen therapy in a 1:1 ratio with a randomized block design. The baseline timepoint was defined as the end of SBT and immediately before extubation. Medical management of both study groups were performed by the same medical, nursing, and respiratory therapy team.

2.4. Intervention

Conventional oxygen therapy was administered continuously through nasal prongs (delivering 1–4 L/min oxygen flow rate) or Venturi facial mask with oxygen and flow titrated (delivering the FiO_2 between 35% and 100%) and with humidification. Both conventional oxygenation therapy modes were exchangeable according to patient's demand and were supplied as long as patients needed.

HFNC (Optiflow; Fisher & Paykel Healthcare, East Tamaki, New Zealand) was applied immediately after extubation. The humidified temperature was initially set to 37 °C and adjusted to the patient's comfort. The gas flow initially began at 40 L/min with adjustment in 5–10 L/min scales (up to 60 L/min).

The FiO_2 of both groups were titrated to maintain the pulse oxygen saturation (SpO_2) level at greater than 92% (88%–95% in patients with compensated hypercapnia).[14] Both therapies were applied for at least 72 hours or up until ICU discharge as the patients needed. After 72 hours postextubation, HFNC could be maintained or shifted to conventional therapy as patients demand. All patients in both groups were followed until hospital discharge.

2.5. Outcomes and clinical assessment

The primary outcome was respiratory failure within 72 hours postextubation and the use of rescue devices. Postextubation respiratory failure was defined as, or with the persistence of, any of the following: hypercapnia (pH < 7.35 with $PaCO_2$ > 45 mmHg), hypoxemia (SpO_2 < 90% or PaO_2 < 60 mmHg with $FiO_2 \geq 0.5$), respiratory rate greater than 35 breaths/min, tachycardia (heart rate > 140 beats/min or sustained increase or decrease of 20%), signs of respiratory muscle fatigue, increased work of breathing (e.g., paradoxical abdominal movement, use of accessory muscle, or intercostal retractions), and/or low level or deterioration of consciousness or agitation.[4] Respiratory variables and hemodynamic variables were continuously monitored. Rescue management for postextubation respiratory failure was allowed for any oxygen therapy, NIV, or reintubation.

Secondary outcomes included the time to postextubation failure within 72 hours to use rescue devices, multiple organ failure, ICU length of stay, 28-day all-cause mortality after extubation, and 48-hour postextubation respiratory and hemodynamic values.

2.6. Statistical analysis

Statistical analysis was performed with SAS version 9. (SAS Institute Inc., Cary, NC USA).

Data were analyzed with an intention-to-treat principle. Categorical variables were compared by chi-squared or Fisher's exact test. Student's *t*-test was used to compare continuous variables. The level of significance was set at 0.05 and at a 2-sided level.

Multivariable logistic regression was used to determine the factors associated with postextubation respiratory failure. Surrogates with a $p < 0.15$ in univariate analysis were entered into the multivariate model. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics of the recruited patients

During the study period, 62 patients were screened (Figure 1). Six patients were excluded. Eventually, 56 patients had been randomized with 29 patients receiving HFNC and 27 receiving conventional oxygen therapy. No loss of follow-up or drop-out occurred.

The two groups were similar in basic characteristics at inclusion (Table 1). The most common factor for high-risk postextubation respiratory failure was age > 65 years (46/56, 82.1%). Steroids, sedation, and pain control use prior or peri-extubation were similar in both groups.

The baseline physiologic parameters were similar in both groups (Table 1). Before SBT, the weaning indexes were measured and the mean RSBI was 75.8 $\pm$ 31.4 (less than the classical cut-off value of 105), and the mean CLT was 271.3 $\pm$ 142.3 mL (more than the general cut-off value of 110 mL).[15]

3.2. Primary outcomes

The postextubation respiratory failure with HFNC (0/29, 0%) was significantly lower than that of the Conventional Group (7/27, 63.3%) (OR 0.408 [95% CI, 0.29–0.57], p = 0.0038) (Table 2).

The causes for postextubation respiratory failure are shown in

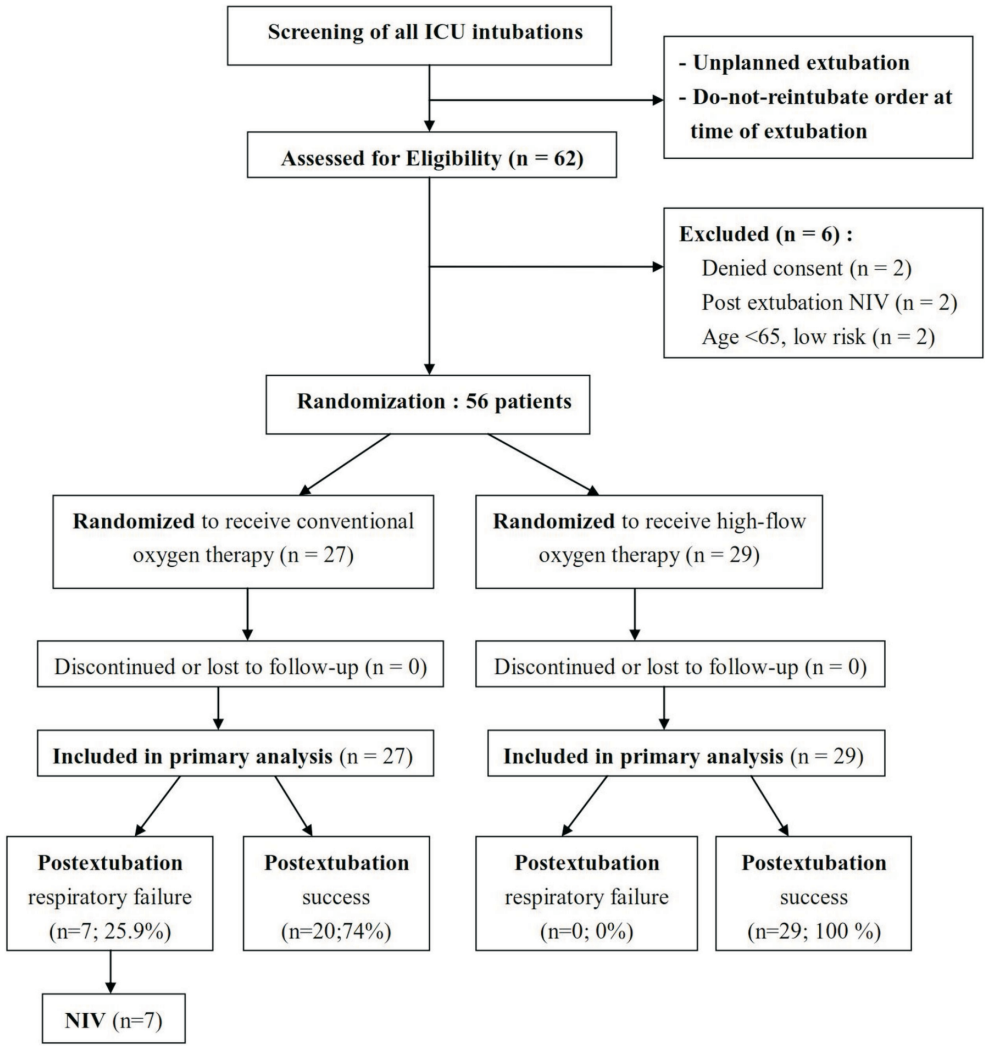

Figure 1. Participant flow diagram for the study of postextubation high-flow nasal cannula vs. conventional oxygen therapy for high-risk postextubation respiratory failure patients. NIV, noninvasive ventilation.

Table 2. Intolerable dyspnea or hypoxia (6/7, 85.7%) and respiratory acidosis (1/7, 14.3%) were the two main reasons for respiratory failure in the Conventional Group. No patients suffered from postextubation upper airway obstruction or stridor. Rescue therapy using NIV without intubation was needed in all seven respiratory failure patients of the Conventional Group (7/7, 100%).

3.3. Secondary outcomes

Median time using rescue therapy was 3.5 hours (interquartile range [IQR], 0.5–15.5) in the Conventional Group. The length of ICU stay and 28-day all-cause postextubation mortality were similar between the groups. Other secondary outcomes including sepsis and multiorgan failure were similar in both groups.

At 48 hours after extubation, the respiratory and hemodynamic variables were similar (Table 2). The HFNC Group had a trend toward better PaO_2 compared to the Conventional Group (102.4 ± 25. 4 vs. 86.6 ± 26.4 mmHg, p = 0.148).

3.4. Factors associated with postextubation failure

We used the demographics and cause of respiratory failure listed in Table 1 for variables in univariate regression analysis comparing failed (n = 7) to successful (n = 49) extubation groups. The baseline variables tested in the multivariable regression model were HFNC therapy, chronic renal disease, diabetes mellitus, and body mass index > 30, and all the variables associated with postextubation respiratory failure that had p values less than 0.15. The OR of HFNC therapy (OR < 0.001 [95%, CI < 0.001–∞], p = 0.937) favored and had the trend toward that the HFNC Group was associated with lower postextubation respiratory failure than the Conventional Group, but not statistical significantly. The factor of chronic renal disease was associated with postextubation respiratory failure (OR 19.621 [95% CI, 1.63–236.33], p = 0.019) (Table 3).

4. Discussion

In critically ill patients at high risk of respiratory failure after extubation, our study showed that the postextubation respiratory failure rate was significantly lower in the HFNC Group than in the Conventional Group. Comparing to HFNC therapy, conventional oxygen therapy resulted in a greater need for rescue therapy with NIV within 72 hours postextubation.

From a literature review, the overall extubation failure rate ranges from 10% to 15%, but the rates are > 20% in patients at high risk of extubation failure.[3,6] Prior to our study, there was only one published report in 2017 investigating the outcomes of non-hypercapnic high-risk patients receiving HFNC or conventional oxygena-

Table 1
Basic characteristics of study participants (N = 56).

Characteristics	Oxygen therapy, No. (%)			Mean (SD)	p
	Conventional (n = 27)	High-flow (n = 29)	Total (n = 56)		
Age (years), mean ± SD	74.9 ± 11.4	72.9 ± 13.1		73.9 ± 12.2	0.546
Sex					0.294
Male	17 (62.9)	22 (75.9)	39 (69.6)		
Female	10 (37.4)	7 (24.1)	17 (30.4)		
APACHE II, median (IQR)			25.7 ± 5	25.7 ± 5	0.868
ICU admission	25 (22–30)	27 (23–29)			
APACHE II > 12, ICU admission	27 (100)	29 (100)	56 (100)		n/a
Length of MV before extubation, median (IQR), d	7 (5–11)	9 (6–12)		9.5 ± 6.2	0.316
Corticosteroids starting < 24 hours before or within 4 hours of postextubation	12 (44.4)	6 (20.7)	18 (32.1)		0.057
Sedation use before or after extubation	0 (0)	1 (3.45)	1 (1.8)		1.000
Benzodiazepines	0 (0)	1 (3.45)	1 (1.8)		
Dexmedetomidine	0 (0)	0 (0)	0 (0)		
Propofol	0 (0)	0 (0)	0 (0)		
Pain control before or after extubation	1 (3.7)	0 (0)	1 (1.8)		0.482
Comorbidities					
COPD	6 (22.2)	6 (20.9)	12 (21.4)		0.889
Heart failure	10 (37)	9 (31)	19 (33.9)		0.636
Liver cirrhosis	2 (7.4)	0 (0)	2 (3.6)		0.228
Cerebrovascular disease	7 (25.9)	8 (27.6)	15 (26.8)		0.889
Chronic renal disease	10 (37)	12 (41.4)	22 (39.3)		0.74
Bronchiectasis, old pulmonary TB, IPF	2 (7.4)	0 (0)	2 (3.6)		0.228
Diabetes mellitus	12 (44.4)	13 (44.8)	25 (44.6)		0.977
Hypertension	17 (63)	17 (58.6)	34 (60.7)		0.74
Cancer	4 (14.8)	4 (13.8)	8 (14.3)		1.00
Acquired immune deficiency syndrome	0 (0)	0 (0)	0 (0)		n/a
Rheumatoid disorder	1 (3.7)	0 (0)	1 (1.8)		0.482
High-risk factors for reintubation					
Age > 65 years	21 (77.8)	25 (86.2)	46 (82.1)		0.411
Prolonged MV use > 7 days	11 (40.7)	18 (62.1)	29 (51.8)		0.11
COPD	6 (22.2)	6 (20.9)	12 (21.4)		0.889
Heart failure as the main indication for MV	5 (18.5)	8 (27.6)	13 (23.2)		0.422
Bronchiectasis or old pulmonary TB with destroyed lung or IPF	2 (7.4)	0 (0)	2 (3.6)		0.228
Neuromuscular disease related respiratory muscle weakness	0 (0)	1 (3.5)	1 (1.8)		1.00
End-stage renal disease under dialysis	3 (11.1)	4 (13.8)	7 (12.5)		1.00
Body mass index > 30	3 (11.1)	3 (10.3)	6 (10.7)		1.00
ARDS	1 (3.7)	3 (10.3)	4 (7.1)		0.612
Causes of respiratory failure at admission to ICU					
Pulmonary	15 (55.6)	18 (62.1)	33 (58.9)		0.62
ARDS	0 (0)	1 (3.5)	1 (1.8)		
Exacerbated COPD or asthma	3 (11.1)	2 (6.9)	5 (8.9)		
Respiratory tract infection	9 (33.3)	13 (44.8)	22 (39.3)		
Upper airway obstruction	1 (3.7)	0 (0)	1 (1.8)		
Others	2 (7.4)	2 (6.9)	4 (7.1)		
Cardiac	5 (18.5)	7 (24.1)	12 (21.4)		0.609
Neurologic	0 (0)	0 (0)	0 (0)		n/a
Gastrointestinal or hepatic	1 (3.7)	0 (0)	1 (1.8)		0.482
Renal	0 (0)	0 (0)	0 (0)		n/a
Others	6 (22.2)	4 (13.8)	10 (17.9)		0.497
Baseline physiologic variables from spontaneous breathing trial prior to extubation, mean ± SD					
Heart rate, beats/min	90.5 (± 14.9)	91.3 (± 11.9)		90.9 ± 13.3	0.808
Mean arterial blood pressure, mmHg	88.6 (± 15.4)	88.9 (± 15.7)		88.8 ± 15.4	0.951
PaO_2:FiO_2, mmHg	279 (± 90.6)	320 (± 89.6)		300.7 ± 91.6	0.097
$PaCO_2$, mmHg	38 (± 7.4)	42 (± 7.9)		40.1 ± 97.9	0.063
Arterial pH	7.5 (± 0.05)	7.5 (± 0.05)		7.5 ± 0	0.416
Rapid shallow breathing index	71.1 (± 28.5)	80.2 (± 33.7)		75.8 (± 31.4)	0.281
Cuff leak test	251.1 (± 131.7)	286.1 (± 150.4)		271.3 ± 142.3	0.421

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, adult respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; MV, mechanical ventilation; n/a, not applicable; SD, standard deviation; TB, tuberculosis.
Categorical variables were reported as percentages and continuous variables as mean (SD) or median (IQR [range]).

tion but the report showed an inconclusive benefit of HFNC.[11] In our study, the postextubation respiratory failure rate (25.9%) was similar to Fernandez et al.'s study for the conventional oxygen therapy group (27%), but had a relatively lower rate for the HFNC Group (0% vs. 20%). The difference may be explained by our patients being older (mean age: 73.9 ± 12.2 years) and with a higher Acute

Table 2
Primary and secondary outcomes in patients randomly assigned to high-flow nasal oxygen compared with conventional oxygen therapy.

Outcomes	Oxygen therapy, No. (%)			Difference between Groups (95% CI)	p
	Conventional (n = 27)	High-flow (n = 29)	Total (n = 56)		
Primary outcomes					
Postextubation respiratory failure[a]	7 (25.9)	0 (0)	7 (12.5)		0.0038*
Causes of postextubation respiratory failure					n/a
Intolerable dyspnea or hypoxia	6 (85.7)	0 (0)	6 (10.7)		
Respiratory acidosis	1 (14.3)	0 (0)	1 (1.8)		
Decreased level of consciousness	0 (0)	0 (0)	0 (0)		
Postextubation stridor or upper airway problems	0 (0)	0 (0)	0 (0)		
NIV or reintubation within 72 hours postextubation	7 (25.9)	0 (0)	7 (12.5)		0.0038*
Devices for extubation failure					
NIV	7 (100)	0 (0)	7 (12.5)		n/a
Tracheal intubation	0 (0)	0 (0)			
Other devices	0 (0)	0 (0)			
Secondary outcomes					
Time to failure within 72 hours, median (IQR), h	3.5 (0.5–15.5)	n/a			n/a
Multiorgan failure	16 (59.3)	19 (65.5)	35 (62.5)		0.629
ICU length of stay, median (IQR), (days)	9 (6–12)	10 (7–13)		-1.6 (-5.8 to 2.6)	0.453
Hospital mortality, postextubation	1 (3.7)	2 (6.9)	3 (5.36)		0.596
Respiratory variables, hemodynamic variables, 48 hours after extubation, mean ± SD					
Heart rate, beats/min	87 ± 14	90 ± 14		-4 (-14 to 7)	0.484
Mean arterial blood pressure, mmHg	91.4 ± 10.5	90.5 ± 13.5		0.8 (-8.9 to 10.6)	0.865
PaO_2, mmHg	86.6 ± 26.4	102.4 ± 25.4		-13.8 (-32.6 to 5.1)	0.148
$PaCO_2$, mmHg	37.2 ± 9.6	41.3 ± 7.5		-4 (-10.1 to 2.0)	0.184
Respiratory rate, breaths/min	22 ± 6	21 ± 5		0.5 (-31 to 4.1)	0.776

IQR, interquartile range; NIV, noninvasive ventilation; SD, standard deviation.
Categorical variables were reported as percentages, and continuous variables as median (IQR [range]) or mean (SD) or between groups difference.
[a] Odds ratio (OR) for postextubation respiratory, High-flow nasal group compared to conventional group: OR 0.408 (95% CI, 0.29 to 0.57), p = 0.0038.
* Significant values (p < 0.05) are presented.

Table 3
Multivariate logistic regression analysis for factors of postextubation failure.

Parameter	Estimate	Standard error	p	OR	95% confidence interval of OR
HFNC vs. Conventional Group	-13.5381	169.3	0.9363	< 0.001	< 0.001–> 999.999
Chronic renal disease	2.9766	1.2697	0.019*	19.621	1.629–236.333
Diabetes mellitus	1.1245	1.1737	0.338	3.079	0.309–30.721
Body mass index > 30	1.7938	1.9960	0.369	6.013	0.12–300.642

Baseline variables associated with postextubation failure in the univariate analysis with p < 0.15 were included in the multivariate analysis.
HFNC, high-flow nasal cannula; OR, odds ratio.
* Significant values (p < 0.05) are presented.

Physiology, Age, Chronic Health Evaluation II (APACHE II) score (25.7 ± 5) who benefited to a greater degree from applying HFNC, and our study gave longer HFNC (72 vs. 24 hours) compared to the 2017 study.[7,11] Second, hypoxia or intolerable dyspnea as the main cause of postextubation respiratory failure in our study (6/56, 10.7%) was an evident indication for HFNC use.[16] Low level of consciousness of the failure causes (18%) may explain less benefit from HFNC use postextubation in previous study.[11]

Lengthened HFNC therapy in critical illness could reportedly have better outcomes.[17] In our study protocol, HFNC therapy was designated for prolonged use for at least 72 hours after extubation, compared to most trials that involved postextubation HFNC use for 24–48 hours.[8-11,18] In our study, 48-hour postextubation oxygenation had improved in the HFNC Group, although not significantly (102.4 ± 25. 4 vs. 86.6 ± 26.4 mmHg, p = 0.148). Therefore, the relatively short duration for postextubation HNFC use in previous studies may increase the risks of delayed intubation.[19] Further large randomized controlled trials are needed to determine the optimal duration of HFNC for the prevention of postextubation failure.

4.1. Study limitations

First, because of the small number and slow enrollment rate of patients, the possibility of selection bias cannot be excluded. Therefore, by using covariate adjustments in a logistic regression model, we could increase our statistical power.[20] Second, our study was conducted in a single medical ICU; thus, the results cannot be generalized. Third, there was a lack of assessment for subjective patient discomfort in our study.

5. Conclusion

In summary, high-flow nasal cannula oxygen therapy compared to conventional oxygen therapy reduced the postextubation failure rate in patients at high-risk for postextubation failure.

Disclaimer

The company Fisher & Paykel provided the high-flow oxygen therapy equipment for our research but had no other involvement in the study.

Declaration of interests

We declare no competing interests. The authors have no conflicts of interest relevant to this article.

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