Does High-Flow Nasal Cannula reduce re-intubation among high-risk patients in real practice?

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Abstract— **Background: Re-inbutation in high- risk patients leading for prolonged hospital stays and increased in mortality rate. HFNC after extubation had better outcome for lowering rate of re-intubation in low-risk patients rather than conventional oxygen therapy, but no sufficient of clinical evidence in high-risk groups.**

Objective: To demonstrate that HFNC reduces re-intubation rate in high-risk patients compared with conventional oxygen therapy.

Methods: A single-center, prospective cohort study was conducted between January and December 2023. Total 200 patients with one or more from the high- risk criteria for extubation were enrolled. The primary outcome was re-intubation within 72 hours. Secondary outcomes included time to re-intubation, post-extubation respiratory failure, ventilator-associated pneumonia (VAP), hospital length of stay (LOS) and mortality rate.

Results: A total of 200 patients were enrolled, with 100 receiving HFNC and 100 receiving COT. More patients in the HFNC group had cerebrovascular disease, airway patency issues, poor expectoration, and a longer duration of mechanical ventilation, which correlated with a higher incidence of respiratory tract infections, the leading cause for the need for mechanical ventilation. Re-intubation was required in 14% of the HFNC group and 11% of the COT group, but the time to re-intubation did not differ between the groups. The incidence of ventilator-associated pneumonia (VAP) was higher among re-intubated patients in the HFNC group (13% vs. 5%), leading to prolonged hospital stays and increased mortality rates, although these differences were not statistically significant.

Conclusion: Among patients at high risk for re-intubation, HFNC did not reduce the risk of re-intubation within 72 hours compared to COT.

Keywords: **HFNC, COT, Re-intubation, High-risk patients**

I. INTRODUCTION

Extubation failure leading to re-intubation with varying rate in low-risk patient range from 5% to 13% [1,2,3] while in high risk groups ,rates can be as high as 22% to 24% [4,5] .Re-intubation and post-extubation respiratory failure (PERF) are closely associated with ventilator-associated pneumonia (VAP),prolonged hospital stays and increased mortality rates, which have been reported to exceed 40% in some studies among high risk groups.[6,7] Oxygen therapy following extubation is the mainstay treatment to maintain adequate oxygenation and to prevent the recurrence of acute respiratory failure. The conventional low-flow oxygen system (LFOS) includes nasal cannulas and facial masks, has been widely used due to its availability and patient comfort. However, the high-flow oxygen system (HFOS), comprising noninvasive ventilation (NIV) and high-flow nasal cannulas (HFNC) is preferred due to its physiologic benefit. [5,14,15] Studies have shown that HFOS can effectively improve hypoxia and reduce the work of breathing, making it a favorable option for post-extubation care. In high-risk patients, some studies suggest that treatment with NIV leads to better outcomes [8,9] and may prevent post-extubation respiratory failure [5,18] compared to standard conventional oxygen, but others [10] suggest otherwise. NIV has a definite indication only in hypercapnic patients [11] and its associated complications still limit its use. HFNC has achieved a higher success rate of oxygen therapy [13] compared to conventional oxygen therapy (COT). In two well-designed studies, HFNC demonstrated a lower intubation rate in a combined population of critically ill patients [14] and significantly reduce the re-intubation rate in low-risk patients.[15] However, in high-risk patients compared to COT, HFNC did not reduce the risk of re-intubation [16,17] , and the protective effect against post-extubation respiratory failure remain inconclusive.[15,17] A large-scale randomized controlled trial comparing HFNC with NIV has reported that HFNC was non-inferior to NIV in preventing re-intubation in high-risk patients. Our study aim to determine whatever high-flow oxygen therapy immediately after planned extubation would reduce re-intubation rates compared to standard oxygen therapy in patients at high-risk for re-intubation.

II. METHODS

A. Study designs and patients

A single-center, prospective, observational cohort study was conducted at the Medical Ward of Trang Hospital between January and December 2023.Approval for involvement of human subjects was obtained from the Trang Hospital Institutional Review Boards (IRB) written informed consent was obtained from patients or their relatives. All patients who required mechanical ventilation for more than 24 hours and passed a spontaneous breathing trial (SBT) were eligible for inclusion. Patients had at least one of the following high-risk criteria for extubation failure [4,5] : age ≥ 65 years, heart failure as cause of intubation, non-hypercapnic moderate-to-severe COPD, APACHE II score > 12 points at extubation, body mass index > 30 kg/m2, weak cough and copious secretions, more than one SBT failure, more than 7 days of mechanical ventilation and multiple comorbidities were included. Exclusion criteria were patients with tracheostomy, HIV infection, inability to follow commands, patients with do-not-resuscitate orders, and those who declined participation.

B. Intervention

Patients meeting the criteria for a spontaneous breathing trial (SBT) underwent the local protocol. After the SBT, if the extubation criteria were met patients attempted extubation. Patients were assigned to either HFNC or COT post-extubation depending on the opinion of the doctor in charge. In the HFNC group, HFNC oxygen therapy (AIRVO; Fisher & Paykel Healthcare, Auckland, New Zealand) was applied immediately after extubation with a flow of 60 L/min and a temperature set at either 34’C or 37’C. In the COT group, nasal oxygen cannula with a flow rate range from 3-5 L/min. or a mask with a reservoir bag with a flow of 8-10 L/min. was used. In both groups, the oxygen supply was continuously adjusted to maintained oxygen saturation, SpO2 ≥ 92% for at least 24 hours after extubation.

The primary outcome variable was re-intubation within 72 hours. Secondary outcomes included time to re-intubation, post-extubation respiratory failure, ventilator-associated pneumonia (VAP), hospital length of stay (LOS) and mortality rate. Re-intubation was performed in any of the following clinical situations: refractory hypoxemia, excessive secretions, respiratory muscle fatigue, or alter mental status. Post-extubation respiratory failure was defined as any of the following as respiratory acidosis (pH < 7.35 with PaCO2 > 45 mmHg), hypoxemia (SpO2 < 90% or PaO2 < 60 mmHg with FiO2 ≥ 0.5), tachypnea ≥ 35/min., sign of respiratory muscle fatigue, alter mental status or agitation.

C. Statistical analysis

Based on data from a randomized controlled trial comparing HFNC and COT [12,14,15] in high-risk patients, the mean intubation rate was 5.9% in the HFNC group and 11.9% in the COT group. And expected extubation failure rate of 12 % with an absolute expected improvement in HFNC group of 6% was calculated for a planned sample of 63 patients for each arm, with an alpha error of 5% and a power of 80%. Statistical analyses using SPSS for Window (version 23). Continuous variables were presented as mean and standard variation or median and interquartile range. Discrete variables were presented as frequency or percentage. The Mann-Whitney U test was used for comparison of continuous variables, Fisher’s exact test was used for comparison of categorical variables. Kaplan-Meier survival analyses were done for re-intubation.

P-values < 0.05 were considered statistically significant.

III. RESULT

From January to December 2023, a total of 200 patients were included in the final analysis sample (100 patients in the HFNC group and 100 patients in COT group) (Fig.1).

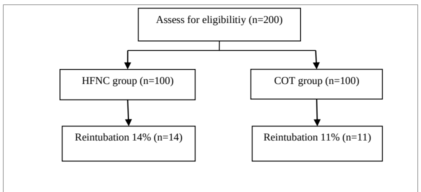

Fig. 1 Flow diagram presenting the number of patients included in the study. HFNC = high-flow nasal cannula, COT=conventional oxygen therapy

Baseline clinical characteristics for both groups are shown in Table 1. More than 60% of both groups were male, with a slightly higher percentage of obesity in high flow nasal cannula (HFNC) group (Body mass index ≥ 30 kg/m2:12% in the HFNC group and 6% in the COT group, p 0.216). The HFNC group had more patients with cerebrovascular disease, poor expectoration, airway problems, and a longer duration of mechanical ventilation compared to the conventional oxygen therapy (COT) group. The most common criteria for high-risk were APACHE II score > 12, age > 65 years and Chronic obstructive pulmonary disease (COPD). More than half of the patients in both groups had more than one comorbidity, with a higher percentage in HFNC group: 66% in HFNC and 52% in COT group, p = 0.061. Physiologic variables from spontaneous breathing trial prior to extubation showed that the PaO2/FiO2 ratio in high-flow nasal cannula group was lower than in the conventional oxygen therapy group. The most common diagnoses leading to the need for mechanical requirement were respiratory tract infection, followed by exacerbation of COPD and sepsis. All patients tolerated high-flow therapy for up to 72 hours during the observation period, with some discontinuing it while eating, but still maintaining an average oxygenation level of over 92%.

Table 1. Patient Baseline Characteristics.

Variables	Oxygen Therapy		p-value
	COT (n=100)	HFNC (n=100)	
Age, y	67.6 ± 15.1	70.9 ± 13.3	0.096[a]
Men	62 (62)	65 (65)	0.769[b]
Body mass index, kg/m2	22.4 ± 4.6	22.4 ± 5.4	0.978[a]
LMV at time of extubation, days	4.4 ± 4.9	7.1 ± 5.2	0.000[a]
APACHE II score at time of extubation	17.4 ± 6.6	17.0 ± 5.9	0.685[a]
Corticosteroid > 12 hrs. before extubation	48 (48)	44 (44)	0.670[b]
High-risk factors for re-intubation			
Age > 65 y	63 (63)	71 (71)	0.292[b]
APACHE II score > 12	77 (77)	80 (80)	0.731[b]
Body mass index > 30 kg/m^2	6 (6)	12 (12)	0.216[b]
Poor expectoration/airway patency problem	17 (17)	31 (31)	0.031[b]
Congestive heart failure	20 (20)	5 (5)	0.001[b]
COPD	42 (42)	39 (39)	0.773[b]
LMV > 7 days	14 (14)	27 (27)	0.035[b]
> 1 comorbidities	52 (52)	66 (66)	0.061[b]
Underlying medical condition			
Diabetes mellitus	29 (29)	30 (30)	1.000[b]
Hypertension	56 (56)	65 (65)	0.247[b]
Chronic renal disease	30 (30)	32 (32)	0.879[b]
Liver cirrhosis	2 (2)	2 (50.0)	1.000[c]
Heart disease	23 (23)	29 (29)	0.420[b]
Cerebrovascular disease	10 (10)	26 (26)	0.005[b]
Malignancy	2 (2)	4 (4)	0.683[c]
Diagnosis at admission			
Respiratory tract infection	13 (13)	49 (49)	0.000[b]
Exacerbation of COPD	36 (36)	21 (21)	0.019[b]
Sepsis	29 (29)	25 (25)	0.524[b]
Congestive heart failure	20 (20)	5 (5)	0.001[b]
Neurogenic	2 (2)	0	
Physiologic variables from SBT			
PaO_2/FiO_2, mm H	320.8 ± 148.2	281.9 ± 101.1	0.031[a]
$PaCO_2$, mm Hg	36.0 ± 7.4	37.9 ± 10.3	0.142[a]
Arterial pH	7.4 ± 0.1	7.4 ± 0.1	0.520[a]

Data are presented as number (%) or mean ± standard deviation, a=Independent t-test, b= Pearson Chi-Square test, c=Fisher's exact test, p-value<0.05
HFNC = High flow nasal cannula, COT = Conventional oxygen therapy, LMV = Length of mechanical ventilation
APACHE II = Acute Physiology and Chronic Health Evaluation II , COPD = Chronic obstructive pulmonary disease
CHF = Congestive heart failure , SBT = Spontaneous breathing trial

Table 2. Primary and Secondary Outcomes.

Variable	Oxygen Therapy		Difference Between Groups (95% CI)	p-value
	COT(n=100)	HFNC(n=100)		
Primary Outcome				
Re-intubation, No.(%)	11 (11.0)	14 (14.0)	0.6 to 3.1	0.521[a]
Secondary Outcomes				
Post-extubation respiratory failure (PERF), No.(%)	11 (11.0)	14 (14.0)	0.6 to 3.1	0.521[a]
Ventilator-associated pneumonia (VAP), No.(%)	5 (5.0)	13 (13.0)	0.9 to 8.3	0.048[a]
Cause of Post-extubation respiratory failure, No.(%)				
Hypoxia	0	0	NA	NA
Respiratory acidosis	0	0	NA	NA
Unbearable dyspnea	11 (11.0)	11 (11.0)	0.4 to 2.4	1.000[a]
Inability to clear secretion	0	3 (3.0)	NA	0.246[b]
Decreased level of consciousness	0	0	NA	NA
Reasons for re-intubation, No.(%)				
Cardiorespiratory arrest	2 (2.0)	1 (1.0)	0.0 to 5.5	1.000[b]
Agitation	1 (1.0)	2 (2.0)	0.2 to 22.6	1.000[b]
Inability to clear secretion	1 (1.0)	3 (3.0)	0.3 to 29.9	0.621[b]
Hemodynamic impairment	4 (4.0)	7 (7.0)	0.5 to 6.4	0.352[b]
Upper airway obstruction	3 (3.0)	1 (1.0)	0.0 to 3.2	0.621[b]
Multiorgan failure, No.(%)	43 (43.0)	47 (45.0)	0.7 to 2.1	0.570[a]
Time to reintubation, median(IQR), hr	1.3 ± 7.5	2.7 ± 9.3	-3.8 to 0.9	0.240[c]
Hospital length of stay, median(IQR) , d	9.6 ± 9.8	14.5 ± 12.7	-8.1 to -1.8	0.002c
Hospital mortality	3 (3.0)	7 (7.0)	0.6 to 9.7	0.194[a]

Data are presented as number (%) or mean ± standard deviation, a=Pearson Chi-Square test, b=Fisher's Exact Test, c=Independent t-test, d=Binary Logistic Regression.
PERF = Postextubation respiratory failure , VAP = Ventilator-associated pneumonia

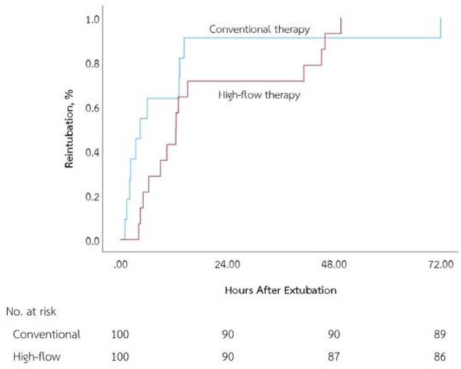

Figure 2. Kaplan-Meier Analysis of Time from Extubation to Re-intubation

Re-intubation was performed in 14 patients (14%) in the HFNC group, and 11 patients (11%) in the COT group (P = 0.521) (Table 2). The median time for re-intubation was 2.7 ± 9.3 hours (HFNC) and 1.3 ± 7.5 hours (COT). Post-extubation respiratory failure developed in all re-intubation patients (100%) in both groups, mostly caused by unbearable dyspnea. In the HFNC group, hemodynamic instability was the most common reason for re-intubation (n=7, 7%), compared with the COT group (n=4, 4%). Upper airway obstruction occurred in 1 patient (1%) in the HFNC group and in 3 patients (3%) in the COT group. In HFNC group, ventilator-associated pneumonia (VAP) developed more frequency than in the COT group (n=13 (13%) in the HFNC group vs. n=5 (5%) in the COT group), leading to prolonged hospital stays and increased mortality in this group, although the difference was not statistically significant.The multivariable logistic regression model identified only the length of mechanical ventilation (p=0.020) as independently associated with post-extubation respiratory failure.

IV. DISSCUSSION

In real world practice we frequency use high-flow nasal cannula (HFNC) for oxygenation after extubation, even in high-risk patients. Some studies [14,17] have shown that physicians prefer HFNC over low-flow oxygen therapy (LFOT) in patients older than 65 years, those with moderate to severe COPD, and with neurological disease, similar to our observational study. Yeun Cho et al [20] and Fernandez et al [21] conducted studies among high-risk groups and found inconclusive evidence regarding the potential benefit of HFNC over conventional therapy in reducing the risk of reintubation within 72 hours and preventing post-extubation respiratory failure. Our study yielded similar results, as we also observed a higher percentage of reintubation in the HFNC group, which with had a greater median age and more comorbidities compared to the COT group. Among the reintubated patients in HFNC group, the most common diagnosis leading to intubation were e respiratory tract infection, primarily in advanced age, those who were bed ridden, and individuals with underlying cerebrovascular disease, leading to inadequate secretion clearance. Others reasons included exacerbation of COPD (n=1,7.1%), end-stage renal disease (ESRD) with volume overload (n=1,7.1%), and septic shock (n=1,7.1%). Advanced age is an important factor associated with an increased risk of extubation failure. About 20-35% of elderly patients experience reintubation. [22,23] Age-related physiologic changes, such as stiffening of thoracic cage, increased residual volume, weakened diaphragmatic and respiratory muscle strength, decreased sensitivity of the cough center in the brain, and a decline in cardiac function [24], all contribute to the complexities behind reintubation. The physiologic effects of high-flow nasal cannula (HFNC) oxygen therapy after extubation [25] aim to prevent reintubation. Studies have found that HFNC provides substantial respiratory support, unload respiratory muscles, unloading diaphragm and shown a positive airway pressure effect and prevention of atelectasis, however problem in elderly patients especially in cerebrovascular disease they were not instructed to keep their mouths closed while breathing, so the PEEP effect may have been attenuated. [26]

A systematic review and meta-analysis [27] of patients in the intensive care unit on mechanical ventilation identified additional risk factors for reintubation beyond those included in our study, such as pneumonia, shock,low albumin and low hemoglobin status. These factors were also found in the reintubated patients in our study.Parren A et al [28] reported that respiratory pump insufficiency and cardiovascular dysfunction have been described as the primary physiological mechanism involved in extubation failure, affecting 42.9% (n=6) of patients in HFNC group who experienced reintubation. Surat Tongyoo et al [29] conducted a study among elderly sepsis patients in Thailand, comparing HFNC and non-invasive ventilation (NIV) to prevent reintubation. They found no significant difference between the two groups in preventing reintubation after 72 hours, with mean ages of 66 year for HFNC and 65.5 year for NIV.

Lee M et al [17] and Kang et al [20] indicated that delayed intubation due to high-flow therapy for more than 48 hours is associated with worse outcomes. They found that post-extubation respiratory failure (PERF) and reintubation are related to ventilator associated pneumonia (VAP), prolonged hospital stays, and increased mortality rate. In our study, the median time to reintubation was longer in HFNC group compare to the COT group (19 hours vs. 10 hours 32min.). However, the rate of delayed intubation after 48 hours was not significantly different between the groups: 7.1% (n=1) in the HFNC group and 9.1% (n=1) in COT group. All reintubated patients in both groups developed post-extubation respiratory failure (PERF) requiring mechanical ventilation. The HFNC group experienced a higher incidence of VAP compared to the COT group (71.4%, n=10 vs. 45.5%, n=5) but the rate of multiple organ failure (MOF) was not significantly different (50% in the HFNC, n=7 vs.54.5% in COT group, n=6). Complication following reintubation prolonged the length of hospital stay in both groups, with a higher mortality rate observed in the HFNC (0.07%, n=7) compared to the COT group (0.01%, n=1).

Data from Fernandez et al [21] in 2017 highlighted the role of non-invasive ventilation (NIV) as rescue treatment for post-extubation respiratory failure, but research supporting this was limited at that time. Only a few studied suggested that high-risk patients might have better outcome after extubation if routinely treated with NIV [8,9], and the literature supports the use of NIV in hypercapnic patients. [4] A recent study by Hernandez et al [30] in 2022 compared the effect of NIV versus high-flow nasal cannula (HFNC) in patients defined as very high-risk for extubation failure (those with ≥ 4 risk factors or obese patients with a BMI > 30/m2 and fewer than 4 risk factors). The conclusion was that among critically ill adults at very high-risk for extubation failure, NIV with active humidification was superior to HFNC for preventing reintubation. This study employed various strategies to enhance comfort during NIV treatment, including interface optimization, daily rest periods [31], and actively humidifying the inspired gases. [32] As a result, the tolerance for NIV in this study was significantly improved, with a median usage time of around 20 hours per day within the first 48 hours after extubation. [33] The beneficial finding from this recent study, combined with data from real-life practice from our study, may assist physicians in determining the most appropriate modality for post-extubation support in high-risk patients groups. Adjustments may be made for suitable cases, considering systemic support, environmental care, resource availability, and financial implications.

V. CONCLUSION

Compare with conventional oxygen therapy (COT), high-flow nasal cannula (HFNC) did not reduce rate of reintubation within 72 hours of planned extubation, length of hospital stay, or mortality rate among high-risk patients for extubation failure.

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