A Retrospective Study of Short-term versus Long-term Use of High Flow Nasal Cannula after Extubation in the Intensive Care Unit

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ABSTRACT: **Background:** The use of a high flow nasal cannula (HFNC) was examined for different clinical indications in the critically ill.

Objectives: To describe a single center experience with HFNC in post-extubation critical care patients by using clinical indices.

Methods: In this single center study, the authors retrospectively evaluated the outcome of patients who were connected to the HFNC after their extubation in the intensive care unit (ICU). At 48 hours after the extubation, the patients were divided into three groups: the group weaned from HFNC, the ongoing HFNC group, and the already intubated group.

Results: Of the 80 patients who were included, 42 were without HFNC support at 48 hours after extubation, 22 and 16 patients were with ongoing HFNC support and already intubated by this time frame, respectively. The mean ROX index (the ratio of SpO_2 divided by fraction of inspired oxygen to respiratory rate) at 6 hours of the weaned group was 12.3 versus 9.3 in the ongoing HFNC group, and 8.5 in the reintubated group ($P = 0.02$). The groups were significantly different by the ICU length of stay, tracheostomy rate, and mortality.

Conclusions: Among patients treated with HFNC post-extubation of those who had a higher ROX index were less likely to undergo reintubation.

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KEY WORDS: extubation, high flow nasal cannula (HFNC), intensive care unit (ICU), reintubation, ROX index

Post-extubation hypoxemia and extubation failure are associated with increased morbidity and mortality [1]. Post-extubation hypoxemia may be treated with several oxygen delivery methods including conventional oxygen therapy (COT, flows < 15 liters/minute), non-invasive ventilation (NIV) and more recently, the high flow nasal cannula (HFNC) [2,3]. Few prospective studies have been performed on the use of HFNC for post-extubation hypoxemia. However, a recent meta-analysis has pooled the data available for this clinical scenario, demonstrating that in the post-extubation setting, use of the HFNC was associated with a reduced rate of escalation of respiratory support and intubation when compared to COT but not when compared to NIV [3].

Several studies have also suggested that use of the HFNC may be associated with some improvement in comfort and dyspnea [4-6] but a systematic view of the topic found that the existing data is too heterogeneous to draw such conclusions [7]. As delayed intubation has been associated with worse patient outcomes [8], in the current study we examined whether any differences could be identified between the physiological and laboratory variables observed during use of the HFNC in patients with failed and successful extubation and to validate the ROX index (the ratio of SpO_2 divided by fraction of inspired oxygen to respiratory rate) [9] for predicting the need for reintubation.

PATIENTS AND METHODS

This retrospective observational study was conducted in the general intensive care unit (ICU) at the Shaare Zedek Medical Center in Jerusalem, Israel (ethics approval #0163-16SZMC). The need for informed consent was waived.

SETTING

At the time of the study, the Shaare Zedek Medical Center was a 1000-bed hospital with 11 general ICU beds and 22 additional specialized adult ICU beds. During the study period the medical record transitioned from manual to electronic.

PARTICIPANTS

Lacking specific ICD coding for treatment with the HFNC, the records of all patients admitted to the ICU during the study period were reviewed by a single investigator (TH) to identify relevant cases. Patients were included in the study if they were adults (> 18 years old) treated with the HFNC after their extubation first attempt in the general ICU (1 December 2012 to 31 December 2015). HFNC devices (Optiflow™ Fisher & Paykel,

New Zealand) were used in the general ICU in 2011; therefore, to ensure that the learning curve did not affect the study results, patients were only included from 2012 onward.

VARIABLES

The primary outcomes were the clinical and laboratory variables and the ROX index [9] of patients who succeeded versus patients who failed extubation. Secondary outcomes included ICU and hospital lengths of stay, complication rates (i.e., atelectasis, pneumonia), and the rates of tracheostomy and death during admission.

DATA SOURCES AND MEASUREMENT

All data were collected from the clinical files of the patients. The data collected included patient demographics and medical history, the primary cause of admission, condition at the time of ICU admission and whether the patient had undergone tracheostomy, and/or survived to hospital discharge. Also collected were the following: times of ICU admission, intubation, extubation, initiation and termination of HFNC support, reintubation, and hospital discharge or death. Ventilator settings (including HFNC settings), patient vital signs (heart rate, blood pressure, oxygen saturation as measured by pulse oximeter [SaO_2]), and arterial blood gas data (pH, PaO_2, $PaCO_2$) were collected from seven time points. These time points constituted part of the routine monitoring of these patients: immediately before and after extubation. If there was a delay between extubation and initiation of HFNC support then just before initiation of support, immediately after initiation of HFNC support, and at 2, 6, and 24 hours post-initiation of HFNC support.

ADDRESS OF BIAS

Manual review of patient files for evidence of the use of HFNC effectively eliminates any potential bias introduced by coding. Our unit has no criteria for initiating treatment with the HFNC; therefore, support was provided in accordance with physician discretion. This predisposes our dataset to selection bias. The data collected regarding medical history and outcomes of our patients were intended to enable comparison of our cohort to others. The amount of missing data was reported and was minimal and did not required adjustment. Bias in laboratory data was unlikely given the stringent international standards adhered to in our institution. Recording bias may be an issue with manual documentation of physiological data.

SAMPLE SIZE CALCULATION

We thought that it would take us approximately 4 years to recruit the patients. Based on the intubation rate in Roca et al. [9] we planned a study with 20 non-responders (reintubations) and 60 responders (weaned patients) over a period of 4 years. We assumed a ROX index standard deviation of 1.5 with a normal distribution. A sample of 80 patients would allow detection of a true difference in the mean response of responders and non-responders of ± 1.1 with a power of 80% and a type I error probability of 0.05 for the null hypothesis that mean ROX index of the responders and non-responders are similar with HFNC treatment.

QUANTITATIVE VARIABLES

We addressed all physiological and laboratory variables as continuous. Based on clinical impression we classified the study patients into three groups: those weaned from the HFNC within 48 hours of extubation, those who received treatment with the HFNC for more than 48 hours after extubation, and those who had been reintubated within this time frame (i.e., failed extubation). The ROX index was calculated for the 2, 6, and 24 hours after HFNC initiation as SaO_2/respiratory rate/FiO_2.

STATISTICAL ANALYSIS

Descriptive statistics were first used to characterize the study cohort. Due to the small number of cases and the non-normal distribution of the variables we used mainly nonparametric analyses for between-group comparisons. For comparisons of categorical data, we used the two-sided Fisher exact test. For continuous data we used the Mann-Whitney test for group comparison. A P value < 0.05 was considered significant. Statistical analyses were performed using Statistical Package for the Social Sciences software version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Overall 83 patients were identified who had been treated with the HFNC following extubation in the ICU. Three files were excluded for lack of data; hence, the study cohort was comprised of 80 patients.

DESCRIPTION OF THE STUDY COHORT AS A WHOLE

The majority of study participants were males (n=35, 65%) and their mean age was 65.8 years (median 69.5, interquartile range [IQR] 55–81). Almost half of the cohort had congestive heart failure (n=32, 40%), about a third (n=29, 36.3%) had diabetes mellitus, slightly less than a quarter (n=19, 23.8%) had chronic obstructive pulmonary disease, and one in 10 (n=8, 10%) was a smoker. Their mean Charlson score was 3.9 (median 4, IQR 2–6) [Tables 1 and 2]. The indications for intubation were diverse, including surgery (n=41, 51.3%), sepsis (n=19, 23.8%), primary respiratory failure (n=12, 15%), heart failure (n=2, 2.5%), and other reasons (n=6, 7.5%). Support with the HFNC was initiated a median of 2 hours (IQR 0–13) after extubation.

DESCRIPTION OF THE STUDY GROUPS

Overall 42 (52.5%) were weaned from the HFNC within 48 hours (weaned group), 22 (27.5%) were treated with the HFNC for more than 48 hours (ongoing HFNC group), and 16 (20%)

Table 1. Demographics

	Total (n=80)	Weaning (n=42)	HFNC ongoing (n=22)	Reintubation (n=16)	Sig
Sex (% female)	35.0% (28)	40.5% (17)	31.8% (7)	25.0% (4)	0.51
Diabetes mellitus	36.3% (29)	28.6% (12)	40.9% (9)	50.0% (8)	0.27
Chronic obstructive pulmonary diseases	23.8% (19)	28.6% (12)	18.2% (4)	18.8% (3)	0.57
Chronic heart failure	40.0% (32)	35.7% (15)	36.4% (8)	56.3% (9)	0.33
Obstructive sleep apnea	7.5% (6)	4.8% (2)	13.6%(3)	6.3% (1)	0.43
Pulmonary hypertension	7.5% (6)	4.8% (2)	9.1% (2)	12.5% (2)	0.57
Hyperlipidemia	30.0% (24)	23.8% (10)	40.9% (9)	31.3% (5)	0.36
Pneumonia	15.0% (12)	11.9% (5)	22.7% (5)	12.5% (2)	0.49
Trauma	8.8% (7)	14.3% (6)	0.0% (0)	6.3% (1)	0.15
Smoking	10% (8)	14.3% (6)	4.8% (1)	6.3% (1)	0.42
Hypertension	40.0% (32)	40.5% (17)	31.8% (7)	50.0% (8)	0.53
Neuromuscular disease	17.5% (14)	14.3% (6)	22.7% (5)	18.8% (13)	0.69
Obesity	13.8% (11)	11.9% (5)	18.2% (4)	12.5% (2)	0.78
Benign prostate hypertrophy	12.5% (10)	19.0% (8)	4.5% (1)	6.3% (1)	0.17
Psychiatry	11.3% (9)	11.9% (5)	9.1% (2)	12.5% (2)	0.93
Pulmonary embolism	3.8% (3)	2.4% (1)	0.0% (0)	12.5% (2)	0.11

HFNC = high flow nasal cannula

Table 2. Demography and variables

		Total (n=80)	Weaning (n=42)	HFNC ongoing (n=22)	Reintubation (n=16)	Sig
Age	Mean	65.8 ± 2.2	66.5 ± 3.0	64.2 ± 4.5	65.9 ± 4.9	0.90
	Median	69.5	68.5	69.5	71.0	
	Range	20–95	2–94	20–95	20–87	
	Q1	55.0	55.0	49.3	57.3	
	Q3	81.0	82.3	80.0	80.8	
	IQR	26.0	27.3	30.8	23.5	
Charlson score	Mean	3.9 ± 0.3	3. 7 ± 0.4	3.9 ± 0.5	4.3 ± 0.6	0.70
	Median	4.0	4.0	4.0	4.0	
	Range	0-10	0-9	0-10	0-8	
	Q1	2.0	2.0	1.8	3.0	
	Q3	6.0	6.0	5.3	6.0	
	IQR	4.0	4.0	3.5	3.0	
Body mass index	n	72	38	18	16	0.79
	Mean	26.5 ± 0.9	27.0 ± 1.3	25.6 ± 1.5	26.4 ± 1.7	
	Median	25.6	26.7	24.9	25.6	
	Range	14.7–49.7	14.7–49.7	16.9–39.5	17.2–44.92	
	Q1	21.3	21.1	19.2	21.7	
	Q3	29.4	29.5	30.5	27.6	
	IQR	8.1	8.4	11.2	5.9	

HFNC = high flow nasal cannula, IQR = interquartile range

were reintubated within less than 48 hours (reintubated group). Most reintubations were performed within a day of extubation. The three groups were similar in the prevalence of various co-morbidities, age, Charlson score, and body mass index [Tables 1 and 2]. There was also no difference between the groups in the indications for mechanical ventilation ($P = 0.36$).

Support with the HFNC was initiated at a median of 1 hour (IQR 0–6.3) for the weaned group, 2 hours (IQR 0–16.3) for the ongoing HFNC group, and 12.5 hours (IQR 3.3–27.8) for the reintubated group. Although clinically meaningful, this finding was not statistically significant ($P = 0.06$). Support with the HFNC length lasted a median of 23 hours (IQR 18–31.3) for the weaned group, 66.5 hours (IQR 53.3–95.5) for the ongoing HFNC group and 14.5 hours (IQR 8.3–22.5) for the reintubated group. The difference between the groups is both statistically ($P = < 0.01$) and clinically meaningful. The median initial flow setting was 30 L/min in all the groups and the FiO_2 was 0.6, 0.6, and 0.55 (for the weaned, ongoing, and reintubated groups, respectively) with no statistical difference.

PRIMARY OUTCOME

Heart rate and blood pressures (systolic, diastolic, and mean) did not differ in the groups at any of the time points studied. The respiratory rate differed at 6 hours. Patients in the weaned group had a median respiratory rate of 19 beats per minute (bpm) (IQR 14–22) at this time, whereas the ongoing HFNC group had 22 bpm (IQR 16.8–24.5) and the reintubated group had 24.5 bpm (IQR 17.8–29.3) ($P = 0.02$), see the appendix (available on the online version only). No meaningful difference was found in the arterial blood gas parameters (pH, PaO_2, $PaCO_2$) other than in the O_2 saturation at 24 hours ($P = 0.03$) [Appendix]. The ROX index differed significantly between the groups at two of the studied time points. At 6 hours, the mean ROX index of the weaned group was 12.3 vs. 9.3 in the ongoing HFNC and 8.5 in the reintubated group ($P = 0.02$); and at 24 hours the values were 15.6, 10.1, and 8.1 for the three groups, respectively ($P = 0.003$) [Figure 1]. The statistically significant differences observed at 24 hours in both O_2 saturation and the ROX index should be viewed with caution given the small number of patients included in the analysis in the reintubated group. Most of the patients in this group had been reintubated by this time and were no longer being treated with the HFNC.

SECONDARY OUTCOMES

The three groups differed significantly in their overall ICU length of stay ($P < 0.01$) but not in their hospital length of stay. No difference was observed in the rate of complications (i.e., atelectasis or nosocomial pneumonia). However, the odds of undergoing tracheostomy were almost twice as high

Table 3. Complications

Complications	Total (n=80)	Weaning (n=42)	HFNC ongoing (n=22)	Reintubation (n=16)	Sig*
Secondary pneumonia	22.5% (18)	14.3% (6)	31.8% (7)	31.3% (5)	0.18
Tracheotomy	12.5% (10)	4.8% (2)	9.1% (2)	37.5% (6)	**0.003**
Mortality	22.5% (18)	9.5% (4)	36.4% (8)	37.5% (6)	**0.01**

*Bold indicates significance

HFNC = high flow nasal cannula

in the ongoing HFNC group and almost eight times higher in the reintubated group than in the weaned group ($P = 0.003$). Mortality was more than three times higher in both the ongoing HFNC and reintubated group than in the weaned group ($P = 0.01$) [Table 3].

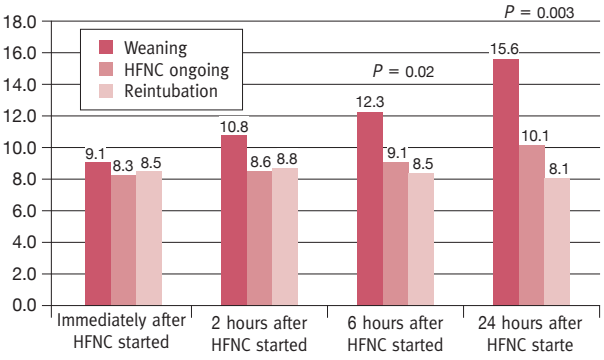
DISCUSSION

Patients who had been weaned entirely from the HFNC within 48 hours of initiation of HFNC treatment had shorter lengths of stay in the ICU and better outcomes (i.e., less tracheostomies and mortality) than those who were still struggling on the HFNC or had undergone reintubation by this time. However, some physiological parameters (respiratory rate, oxygen saturation, and ROX index) of patients who were successfully weaned from the HFNC were already better than those of their failing counterparts within 6 hours. In addition, although this finding was not statistically significant, there may be some correlation between early connection to the HFNC by the discretion of the treating physician and better outcomes.

Our study is unique in its focus on identifying the patients failing HFNC treatment. To this end, we studied physiological parameters at pre-specified time points up to 24 hours, we validated the ROX index at this time point, and we divided the patients into three groups based on a relatively late 48-hour endpoint. Brotfain et al. [10] retrospectively studied the data from the first and sixth hours. Stéphan and colleagues [11] prospectively gathered information at 1, 6, and 12 hours after extubation. To the best of our knowledge, only one other study has validated the ROX score thus far. [9].

Our findings differ from those of several studies that have shown a reduction in respiratory rate shortly after initiation of HFNC therapy [12-14]. They also differ from studies that have shown a reduction in heart rate after initiation of treatment [13,15]. Patients after prolonged ICU intubation may have very different causes of hypoxemia and tachypnea than patients presenting to the ED with acute respiratory failure (e.g., respiratory muscle atrophy and fibrotic changes post hypoxemic lung injury and prolonged mechanical ventilation). Indeed Stéphan and co-authors did not find a change in the respiratory rate of

Figure 1. ROX index means of different points of time



HFNC = high flow nasal cannula

post-cardiothoracic surgery extubated patients who were connected to HFNC. In addition, the reintubation rate in our study was similar to that observed in this large randomized controlled trial that included only high-risk patients post-cardiothoracic surgery [11].

Our study, due to its retrospective nature and design, cannot answer the question whether the use of HFNC actually decreases the need for reintubation. Stéphan et al. [11] prospectively showed non-inferior reintubation rates with the HFNC compared to NIV in patients after cardiac surgery. Parke et al. [16] prospectively showed less reintubation with the HFNC compared to conventional oxygen therapy, in the post-cardiothoracic surgery patients. Brotfain and colleagues [10] retrospectively showed less reintubations with the HFNC compared to conventional oxygen therapy in general ICU patients. Maggiore et al. [17] prospectively showed lower intubation rates with the HFNC compared to the HFNC in general ICU patients with relative hypoxemia ($PaO_2/FiO_2 < 300$) immediately before the extubation. Conversely, the OPERA trial found no difference in reintubation rates in patients after abdominal surgery treated with the HFNC versus conventional oxygen therapy [18]. Finally in obese patients post-cardiac surgery Corley et al. [19] showed no decrease in reintubation rate with the HFNC versus COT.

This conflicting evidence raises the question of patient safety, specifically how to identify the failing patient before occurrence of respiratory collapse. This issue is highlighted by the higher mortality of patients who failed HFNC treatment in our study. This difference of outcome probably is multifactorial in nature; however, it might be related to a later connection to the device or poor selection of the patients. In patients with hypoxemic respiratory failure secondary to H1N1 influenza pneumonitis, non-responders to the HFNC had lower PaO_2/FiO_2 and required higher oxygen levels at 6 hours of treatment [12]. In patients with pneumonia, Roca et al. [9] proposed using the ROX index with a cutoff of < 4.88 at 12 hours being indicative of a higher odd of intubation. This index has not previously

been studied in post-extubation ICU patients. Our findings support the use of this tool but there may need to be a different cutoff for this population. Furthermore, our results may suggest establishing a decision point at the sixth hour post-HFNC connection, in this setting.

LIMITATIONS

The current study included a relatively small number of patients from a single medical center. It is also limited by its retrospective design, which made it highly dependent on the data available in the medical records. As a result, the cohort is highly mixed and no specific protocols were used regarding when to connect the patient or what settings to use, both were solely based on the discretion of the treating physician. Still, the three groups were relatively similar. There are also inevitable gaps between the time of blood gas sampling and documentation of the physiological variables as these are mostly performed by the same nurse. It is also impossible to draw any conclusions regarding causality in retrospective studies.

CONCLUSIONS

Among patients treated with the HFNC post-extubation at the discretion of the treating physician, those who had a higher ROX index were also less likely to undergo reintubation. Prolonged use of the HFNC was associated with higher mortality rates and both prolonged use of the HFNC and reintubation were associated with a higher likelihood of death during admission. A larger prospective study should be conducted to define the appropriate setting and patients who would benefit from this modality.

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Capsule

Microglia modulate memories

Synaptic reorganization and circuit rewiring leads to loss or weakening of connections between neurons and may result in the erasure of previously formed memories. Microglia eliminate excessive synapses in the developing brain and regulate the dynamics of synaptic connections between neurons throughout life. However, it is still unclear whether forgetting is related to microglia activity and how microglia regulate memory erasure in the adult brain.

Wang et al. discovered that microglia eliminated synaptic components in the adult hippocampus and that depleting microglia or inhibiting phagocytosis of microglia prevented forgetting. Synapse elimination by microglia may thus lead to degradation of memory engrams and forgetting of previously learned contextual fear memory.

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