The Turkish Journal of Pediatrics 2018; 60: 126-133
DOI: 10.24953/turkjped.2018.02.002

Original

Comparison between high-flow nasal oxygen cannula and conventional oxygen therapy after extubation in pediatric intensive care unit

Başak Akyıldız[1], Sedat Öztürk[1], Nazan Ülgen-Tekerek[1], Selim Doğanay[2], Süreyya Burcu Görkem[2]

Departments of [1]Pediatric Intensive Care and [2]Radiology, Erciyes University Faculty of Medicine, Kayseri, Turkey.
E-mail: basaknurbesra@gmail.com

Received: 26th May 2017, Revised: 12th July 2017, 7th August 2017, Accepted: 30th August 2017

SUMMARY: Akyıldız B, Öztürk S, Ülgen-Tekerek N, Doğanay S, Görkem SB. Comparison between high-flow nasal oxygen cannula and conventional oxygen therapy after extubation in pediatric intensive care unit. Turk J Pediatr 2018; 60: 126-133.

The aim of this study was to compare the efficiency, safety, and outcomes of the high-flow nasal oxygen cannula (HFNC) and conventional oxygen therapy (COT) after extubation in children. A randomized controlled trial was conducted in a 13 bed pediatric intensive care unit. One-hundred children who underwent extubation were eligible for the study. Patients were divided into HFNC (n=50) and COT (n=50) groups. Basal variables including heart rate (HR), noninvasive blood pressure, respiratory rate (RR), SpO_2, SpO_2/FiO_2 (SF) ratio, and end tidal CO_2 ($EtCO_2$) were obtained initially and recorded at 15, 30, and 45 minutes and at 1, 6, 12 hours, 24 and 48 hours after extubation. SF ratio and SpO_2 increased during the first hour in the HFNC group (p=0.005 and p=0.03, respectively). HR and RR decreased during follow-up in the HFNC group (p=0.001 and p=0.048, respectively). There was no statistically significant difference for PCO_2 after extubation between the two groups. PCO_2 (p=0.008) and $EtCO_2$ (p=0.018) values at 24-h were different between two groups. At follow-up, HR decreased only in the HFNC group (p=0.001) and was different at 12 and 48 hours (p=0.047 and p=0.01, respectively). Initial modified radiologic atelectasis scores (m-RAS) were higher for the HFNC group and decreased steadily (p=0.001). Extubation failure rates were 4% and 22% for the HFNC and COT groups, respectively (p=0.007). In conclusion, HFNC is better than COT, especially for the restoration of the respiratory and radiologic parameters. Although more expensive, the use of HFNC may have more advantages to reduce the risk of extubation failure in critically ill children compared with COT.

Key words: children, conventional oxygen therapy, extubation, high-flow nasal oxygen cannula.

High-flow devices include venturi masks and large-volume aerosol systems, high-humidity face tents and high-humidity tracheostomy collars. High-flow nasal cannula oxygen cannula (HFNC) is a new technological device used in high-flow systems. It consists of an air-oxygen blender that generates flow between 2-70 L/min and a heated humidification system.[1,2] This may provide several advantages such as reducing the work of breathing, washing out pharyngeal dead space, reducing nasopharyngeal resistance, creating some positive end expiratory pressure, creating constant FiO_2, and facilitating secretion clearance from humidified gas.[1,2] HFNC demonstrated beneficial effects in many respiratory failure settings.[1-4] Although the use of HFNC is increasingly popular for noninvasive support in neonatal and adult intensive care units, there are limited studies indicating beneficial effects of HFNC during

This manuscript was presented at the 13th Congress of Child Emergency and Intensive Care, 5th October 2016, Izmir, Turkey; and was published in abstract form in the proceedings of the Congress.

the postextubation period in the literature.[5-8]

We aimed to compare the efficiency, safety and outcome of HFNC and conventional oxygen therapy (COT) after extubation period in critically ill children.

Material and Methods

A randomized controlled study was performed in a 13 bed pediatric intensive care unit during September 2014 and February 2016. The study was approved by the Ethics Committee of Erciyes University Medical Faculty. Consent was obtained from at least one parent or legal guardian before enrollment.

One hundred and six children who underwent on extubation process were included prospectively in the study. Six patients were excluded from the study. Exclusion criteria were: intubation for less than 24 hours, spontaneous breathing trial (SBT) failure, age older than 18 years and younger than 1 months, diaphragmatic hernia or paralysis, cyanotic congenital heart disease with unrepaired or palliated right to left intracardiac shunt, and presence of a tracheostomy tube. After successful SBT, one-hundred patients were extubated. Patients were divided into two groups by simple randomization: HFNC (n=50) and COT (n=50).

Outcomes

The primary outcomes were the changes of respiratory, hemodynamic and radiologic parameters in both groups. Basal variables including heart rate, noninvasive blood pressure, respiratory rate (RR), SpO_2, SpO_2/FiO_2 (SF) ratio, and end tidal CO_2 ($EtCO_2$) were initially obtained. These variables were also recorded at 15, 30 and 45 minutes; and at 1, 6, 12, 24 and 48 hours in the immediate-extubation period. Modified radiological atelectasis score (m-RAS) were recorded at baseline and at 24 and 48 hours after extubation period.

Secondary outcomes were reintubation rate and reasons of reintubation. In the follow-up, the decision of reintubation was made by the treating clinician. The decision to reintubate was based via the most significant factors recorded such as hypoxemia, presence of copious secretions, signs of respiratory-muscle fatigue, decreased level of consciousness (fall in GCS of more than 2), hypotension despite adequate volume and vasopressor therapy, etc.[9]

Device description

Vital signs including SpO_2, heart rate, systolic blood pressure and diastolic blood pressure data were recorded using GE 650 monitors.

The HFNC system (Optiflow, Fischer&Paykel Healthcare) is a humidifier with an integrated flow generator that delivers high flow and warmed respiratory gases to spontaneously breathe through a variety of patients interfaces. After applying the appropriate nasal cannula and circuit tubing with a Fisher and Paykel® MR850 humidifier, we used a flow rate of 1 L/min/kg and FiO_2 of 40% and if there was no clinical improvement we titrated flow up to 2 L/kg/min or a maximum 25 L/min and FiO_2 to maintain $SpO_2 \geq 92$ %.

The Capnostream 20 system was used to monitor $EtCO_2$ levels via the Filter Line H set CO_2 sampling line and airway adapter and also the respiratory pattern after extubation.

COT was delivered by either nasal cannula or a simple face mask with the same target SpO_2. In this group, oxygen was delivered with a flow meter from wall oxygen and humidification with a closed sterile water system at room temperature. Similar to the HFNC group FiO_2 and flow were titrated to maintain $SpO_2 \geq 92\%$.

SpO_2/FiO_2 (SF) ratio was directly calculated in the HFNC group according to recorded SpO_2 and FiO_2 during the time interval. In the COT group, SpO_2 was recorded directly during the time interval. To estimate FiO_2 during oxygen therapy via a nasal cannula and simple face mask, we calculated FiO_2 using a previously published formula.[10]

Demographic data including age, gender, initial diagnosis, PRISM III, PELOD, mechanical ventilation indication and duration, and admission diagnosis were also evaluated.

Procedures

Spontaneous breathing trial: The eligibility criteria for participation in SBT are as follows:

1. Improvement or resolution of underlying disease during follow-up.

2. Adequate gas exchange indicated by a PaO_2 level greater than 60 mmHg while breathing with FiO_2 concentration of 0.4 or lower with no need for increased ventilator support during the previous 24 hours.

3. Core body temperature lower than 38.5°C.

4. Alert mental status after removal of sedative agents.

5. No clinical need for increased ventilator support during the previous 24 hours.

6. No need for vasoactive agents except for low-dose dopamine (5 μg/kg/min; patients who received milrinone, epoprostenol, or nitroprusside were considered for extubation if other criteria were met)

7. Able to swallow secretions.

Patients underwent a 2-hours trial of spontaneous breathing with pressure support ventilation. Pressure support was set according to endotracheal tube (ETT) size (3.0 –3.5 mm -pressure support of 10 cmH_2O, 4.0–4.5 mm pressure support of 8 cm H_2O, and 5.0 mm pressure support of 6 cmH_2O). At the end of the SBT, exhaled tidal volume >5 ml/kg body weight, SpO2>95% and respiratory rate in acceptable range for age were considered successful completion of the SBT. Extubation failure was defined as the needing reintubation within 48 hours of extubation.[11,12] In both study groups, patients were reintubated according to selection criteria.

Atelectasis scoring

Chest radiographs were scored using a m-RAS system by two pediatric radiologists at baseline and at 24 and 48 hours immediate-extubation period. This scoring system was first referenced by Parke et al. in 2014.[13] The pediatric radiologists who assessed the m-RAS system were blinded to treatment allocations.

Statistical analysis

Numerical variables were expressed as mean±SD or median (minimum, maximum) when appropriate. Comparisons between groups for data with a normal distribution were performed using Student's t-test, and the comparisons between groups for data without a normal distribution were performed using the Mann-Whitney U test. Changes over time of the recorded variables were evaluated by mixed model linear analysis due to missing values for repeated measurements. Categorical variables were compared using x^2 test. A p value <0.05 was considered significant.

Results

One-hundred children were analyzed. The mean age was 27±19.95 months for the HFNC group and 52.9±34.4 months for the COT group (p=0.706); 49 patients (49 %) were boys. There were no significant differences in PRISM III, PELOD scores, mechanical ventilation duration, and diagnosis at admission between two groups. Baseline characteristics and demographic data of the patients were summarized in Table I.

Table I. Baseline Characteristics of the Patients.

Variable	Groups		p
	HFNC	COT	
Age, months	27±19.95	52.9±34.4	0.706
Male, N (%)	26 (52%)	23 (46 %)	0.548
PRISM III	17.78±6.66	18.3±7.23	0.72
PELOD	15.9±6.9	16.4±7	0.981
Duration of MV, days	5 (3-10)	6 (2-10)	0.225
Reintubation, N (%)	2 (4)	11 (22)	0.007
Reintubation time, hours	16 (10-24)	12 (6-24)	0.066
Diagnosis at admission, N (%)			
Respiratory	25 (50)	30 (60)	
Infectious	13 (26)	10 (20)	
Neurologic	7 (14)	3 (6)	0.349
Cardiologic	5 (10)	5 (10)	
Others	0 (0)	2 (4)	

COT: conventional oxygen therapy; HFNC: high-flow nasal oxygen cannula; MV: mechanical ventilation; PELOD: Pediatric Logistic Organ Dysfunction Score; PRISM III: Pediatric Risk of Mortality Score.

Primary outcomes

SpO_2 values were statistically higher starting at 60 minutes in the HFNC groups, (p=0.05) (Table II). In the HFNC group, SF values were statistically higher starting at 45 minutes and during intergroup comparison (p=0.005). Compared to baseline values, SF values were lower in the COT group and higher in the HFNC group at the end of the study (p=0.009 and p<0.001). There were no statistically significant differences in PCO_2 during the extubation period in both groups (p=0.300 and p=0.357). PCO_2 and $EtCO_2$ at 24-hour were significantly lower in the HFNC group, compared to COT group (p=0.008 and p=0.018, respectively). $EtCO_2$ was statistically significant lower during intergroup comparisons in the HFNC group (p=0.018). During the follow-up, heart rate decreased only in the HFNC group

Table II. Clinical and Laboratory Data After Extubation Period.

	Time									
Variables	Extubation	15-min	30-min.	45-min	60-min.	6-h	12-h	24-h	48-h	p
SpO_2	92.5±1.4	93.9±1.2	95.2±1.1	95±0.9	95±0.2	97±1.3	98±0.6	98±0.4	98±0.8	0.02
	94.1±0.8	94±0.9	94.08±0.3	94±0.8	94±0.7	94±0.7	94±1.2	93±1.1	93±2.6	0.06
p*	0.51	0.43	0.08	0.09	0.03	0.02	<0.01	<0.01	0.001	
SF	237±8	254±6.2	263±6.4	274±7	285±7	290±6.7	301±7.1	316±7.9	335±7.4	<0.001
	260±8	251±6.2	249±6.4	245±7	242±7	238±6.7	234±7.1	231±8	232±7.6	0.009
p*	0.40	0.784	0.122	0.005	0.001	0.001	0.001	0.001	0.001	
PCO_2 (mm Hg)	36.4±1.16		37.5±1.12		37.4±1.14	36.7±1.13	36.9±1.2	36.2±1.2	37.3±1.13	0.300
	38.8±1.15		39.1±1.12		40±1.14	39.9±1.13	39.7±1.21	41±1.27	40.5±1.19	0.357
p*	0.142		0.290		0.103	0.051	0.105	0.008	0.063	
$EtCO_2$ (mm Hg)	35.2±8	36.3±6.2	37.3±6.4	36.6±7	36±7	36.3±6.7	36.1±7.1	35.3±7.9	36.3±7.4	0.018
	37.4±8	37.6±6.2	37.7±6.4	37.8±7	38.6±7	38.3±6.7	38.3±7.1	39.3±8	39.1±7.6	0.391
p*	0.165	0.389	0.813	0.447	0.095	0.210	0.163	0.018	0.126	
RR (/min)	35.4±1.8	35.3±1.7	34.7±1.7	34.4±1.7	34±1.8	34.1±1.8	32.9±1.7	32.7±1.7	32±1.8	0.048
	40.7±1.8	41±1.7	41±1.7	41±1.6	41.7±1.8	43±1.8	42.5±1.7	43±1.8	43.6±1.8	0.340
p*	0.04	0.023	0.009	0.006	0.003	0.001	0.001	0.001	0.001	
HR (/min)	134.8±3	138.8±3	132.2±4	131±3	129±3	127±3	124±3	126±3	124±3	0.001
	132±3	138±3	132±3	131±3	133±3	131±3	130±3	132±3	134±3	0.103
p*	0.535	0.952	0.308	0.685	0.354	0.298	0.047	0.111	0.01	
SBP (mm Hg)	99.2±2.5	99.6±2.5	96.7±2.9	97.9±2.4	98.7±2.4	99.7±2.4	98.1±2.5	99.9±2.6	96.5±2.7	0.058
	95.8±2.6	95.2±2.5	96.3±2.9	94.5±2.4	94.2±2.4	95.4±2.4	95±2.6	93.4±2.7	95.7±2.7	0.340
p*	0.341	0.218	0.910	0.333	0.190	0.211	0.358	0.085	0.828	
DBP (mm Hg)	59.7±1.7	61±1.6	61.7±1.5	60.7±1.6	62±1.5	63±1.4	61±1.4	62.5±1.6	60.8±1.8	0.302
	59.4±1.7	60.3±1.6	61±1.5	60.4±1.6	60.3±1.5	60.1±1.4	59.6±1.4	59.6±1.7	61±1.9	0.943
p*	0.876	0.747	0.722	0.878	0.455	0.141	0.408	0.215	0.973	

First and second row indicate HFNC and COT groups for each variable, respectively.
COT: conventional oxygen therapy; DBP: diastolic blood pressure; HFNC: high-flow nasal oxygen cannula; HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure; SF: SpO_2/FiO_2
p: intragroup comparison, p*: intergroup comparison.

(p=0.001); and was lower in HFNC group at 12 and 48 hours, compared to COT group (p=0.047 and p=0.01, respectively). Systolic and diastolic blood pressure levels did not change during the immediate-extubation period in both groups. Comprehensive analyses of clinical and laboratory parameters for the two groups were presented in Table II.

The initial m-RAS was higher in the HFNC group, compared to COT group (1.391±0.9 vs. 0.997±0.09, p=0.003). At follow-up m-RAS decreased steadily in the HFNC group; and at 48 hours it was significantly lower in the HFNC group, compared to the COT group (p=0.001). Changes of m-RAS were presented in Table III.

Secondary outcomes

After the extubation, 11 patients (22%) in the COT and 2 patients (4%) in the HFNC group, were reintubated. Hypoxia or oxygen desaturation, hypercapnia with respiratory acidosis, decreased level of consciousness, and inability to clear secretions occurred in 4, 3, 2, and 4 patients, respectively. The incidence of reintubation was statistically lower in the HFNC group (p=0.007). The median reintubation time was 16 hours (10-24 hours) in HFNC group; and 12 hours (6-24 hours) in COT group (p=0.066).

Discussion

Administration of oxygen via nasal cannula and face mask is a traditional method used for hypoxemic respiratory failure after extubation period.[6,14,15] However, inadequate heating and inadequate humidification leads to dry nose, dry throat and nasal pain and ultimately to extubation failure.[16] Reintubation due to extubation failure is associated with increased risk for infection, lung and airway injury, length of stay, and sedation-related complications with related high costs.[17] During this period noninvasive mechanical ventilation (NIV) may be an alternative method to ameliorate respiratory failure and reintubation.[18,19] This method requires a different type of mask and different sedation to deliver adequate ventilation. Two studies comparing NIV to COT in critically ill patients at high risk of reintubation found that NIV was more effective.[20,21] However, 3-20% of patients require reintubation during NIV treatment.[8,18,22] Compared with NIV, HFNC is a newer noninvasive treatment method for respiratory failure. Under normal breathing conditions 30% of the tidal volume inhaled is anatomical dead space. At the beginning of inhalation, this dead space is filled with the gas remaining from the previous breath. HFNC systems may improve breathing efficiency by flooding the nasopharyngeal dead space with clean gas, thereby improving the minute ventilation. In this way the treatment provides better alveolar gas fractions and carbon dioxide elimination. Appropriate humidification and heating via HFNC reduce the work required for breathing and recovery of the respiratory pattern, heart rate and other factors.[23] However, like any respiratory system, this device has drawbacks. The noise level reaches approximately 80 dB, which is correlated with the flow and may be higher than that generated by other CPAP systems. The risk of air leak syndrome (pneumothorax, pneumomediastinum) could be associated with an inappropriate prong size that occludes the nostril lumen.[24] We did not encounter any problems regarding the use of HFNC. HFNC has been reported mostly for pediatric patients especially during the neonatal period and has shown many benefits.[4,25,26] To our knowledge this is the most comprehensive study evaluating the influence of HFNC and COT on extubation success

Table III. Changes of m-RAS After Extubation Period.

Groups	Time			
	Extubation	24-h	48-h	p
HFNC	1.391±0.9	1.221±0.17	0.607±0.1	0.001
COT	0.997±0.09	1.164±0.19	1.451±0.108	0.002
p*	0.003	0.824	0.001	

COT: conventional oxygen therapy; HFNC: high-flow nasal oxygen cannula; m-RAS: modified radiological atelectasis score. p: intragroup comparison, p*: intergroup comparison

associated with respiratory hemodynamic and radiologic parameters in a large pediatric population. We analyzed respiratory parameters including SpO_2, PCO_2, $EtCO_2$, SF ratio and respiratory rate. SF ratio is one of the most important respiratory parameters. Using SF ratio, we standardized the degree of hypoxemia which had different SpO_2 and FiO_2 in children without extra blood samples. The SF ratio has been especially useful for quantifying the PaO_2/FiO_2 ratio of hypoxemia in pediatric and adult patients.[27,28] We observed an increase in SPO_2 during the first 60 minutes and in the SF ratio during the first 45 minutes from the baseline values in the HFNC group. As compared with SpO_2, the SF ratio may be an early predictor of respiratory failure.

Respiratory rate and $EtCO_2$ levels decreased during follow-up in the HFNC group but there was no difference in PCO_2 levels in both groups. A new study reported better values in SpO_2 levels and no difference in PaO_2/FiO_2 with HFNC therapy after extubation.[5] The authors also detected decreased respiratory rates, and PCO_2 levels after extubation for the HFNC group as compared with noninvasive ventilation group. Similar to our study, Brotfain et al.[29] reported a better oxygenation with HFNC but $PaCO_2$ and respiratory rate were not different between the two groups. In a study by Testa et al.[8] they reported that HFNC had no impact on $PaCO_2$ in a series of 89 pediatric cardiac surgery patients. We also monitored $EtCO_2$ levels to evaluate the changes in respiratory status. $EtCO_2$ also provides additional information about cardiac performance and metabolic status.[30] Despite a good correlation between PCO_2 levels and $EtCO_2$ levels, $EtCO_2$ levels changed significantly only in the HFNC group. We considered this result attributable to leakage from the cannula, the influence of different flow rates and anatomical dead space. In our study, consistent with HFNC mechanisms, the response to hypoxemia was observed in an earlier period than the response to hypercapnia.

When we considered heart rate, noninvasive systolic blood pressure and diastolic pressure, heart rate decreased only in the HFNC group. There was no difference between the two groups in terms of systolic and diastolic blood pressure. Rittayamai et al.[6] reported similar results to our study; but conversely, there was no significant change in heart rate and blood pressure in the study by Tiruvoipati et al.[31]

Unlike the other studies, we also evaluated m-RAS in this study. In a study assessing atelectasis using chest radiograph after cardiac surgery, the m-RAS provided more detailed information about atelectasis and oxygenation requirements during follow-up [13]. We observed higher m-RAS for the HFNC group at the beginning, m-RAS decreased steadily in the HFNC group at 48 hours and were significantly lower than those of the COT group at follow-up. Ensuring adequate oxygenation and respiratory support is vital after extubation to prevent atelectasis; however, there is little evidence to guide clinicians in the objective selection and use of oxygen delivery devices.[13,32] HFNC systems also supply a certain degree of distending pressure for alveolar recruitment and prevent atelectasis. This pressure is variable (approximately 4-8 cm H_20) and related to nasal prong size, leaks and open mouth and the effectiveness of the humidity and heat.[26,33] During follow-up, we considered that lower m-RAS score was associated with improved pulmonary function and reduced atelectasis for the HFNC group.

Additionally, 13 patients were reintubated at follow-up. All patients required invasive mechanical ventilation in our study. Similar to NIV strategy, the greatest risk in using HFNC is that it may delay the recourse the mechanical ventilation. In children the risk of HFNC failure, defined as intubation requirement, ranges from 8% to 19%.[33] The incidence of reintubation was significantly lower for the HFNC group (4 %) than for the COT group (22 %). Testa et al.[8] reported that the incidence of treatment failure was 15% and two pediatric cardiac surgical patients were reintubated (1 patient in the HFNC group and 1 patient in the COT group). There was also no difference between the two groups regarding incidence of reintubation in this study.[8] However, a randomized controlled trial comparing the effects of the venturi mask and HFNC therapy showed less required reintubation following extubation in the HFNC group. It is estimated that a better lung compliance, decreased patient effort and improved secretion clearance may have played a role.[34]

Our study has several limitations. First, we

compared the effects of COT and HFNC therapy in nonhomogeneous group. Second, since HFNC system is more expensive than COT (HFNC costs approximately 114 USD per patient and is not included in intensive care payment system. During the study, COT was approximately 4.20 USD in our country.), the clinical application of HFNC may be advised for selected patients in PICU. As the third, we also titrated the flow rate according to patient's respiratory distress but we had no opportunity to measure subsequent changes in generated pressure.

In conclusion, HFNC is better than COT, especially for the restoration of the respiratory and radiologic parameters. Although more expensive, the use of HFNC may have more advantages to reduce the risk of extubation failure in critically ill children compared with COT.

Acknowledgments

This study was supported by Erciyes University Scientific Research Center (TTU-2014-5333).

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