The Turkish Journal of Pediatrics 2021; 63: 1012-1019
https://doi.org/10.24953/turkjped.2021.06.009

Original Article

Predictive factors of high-flow nasal cannula oxygen therapy failure in children with respiratory distress treated in a Pediatric Emergency Department

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ABSTRACT

Background. High-flow nasal cannula (HFNC) is widely used as a feasible and tolerable respiratory support method. However, patients should be closely monitored, especially when used with moderate-severe respiratory distress indications. Because these patients can easily develop respiratory failure and escalated care may be required. The aim of this study is to determine the predictive factors in patients treated with HFNC who received escalated respiratory support for HFNC failure.

Methods. A retrospective study of patients admitted with respiratory distress and treated with HFNC therapy between January 2014 and December 2018 was carried out. The variables evaluated were age, gender, vital signs before and two hours post HFNC therapy, underlying disease, use of steroid, salbutamol and antibiotic therapy, blood gase analysis and lactate values, hospitalization in pediatric intensive care unit, respiratory viral panel and need for escalation of respiratory support. HFNC failure was identified requiring noninvasive or invasive respiratory support despite HFNC therapy.

Results. 243 patients receiving HFNC therapy were included in this study. The median age was 11 months [interquartile range(IQR) 5–27]. The diagnosis of 183 patients (75.3%) were acute bronchiolitis and 60 patients (24.7%) were pneumonia. Of 243 patients, 29 (%11.9) received escalated care. 22 invasive and 7 non-invasive respiratory supports were provided. The lower pH on admission was found in the non-responder group. Moreover, heart rate and respiratory rate did not decrease two hours after HFNC therapy.

Conclusions. The careful monitoring of patients receiving HFNC therapy is critical. Because these patients are at risk for needing escalated care. We found that low pH values on admission and high pulse rate and respiratory rate observed at the second hour of follow-up period could be predictive factors for HFNC failure.

Key words: children, high-flow nasal cannula, respiratory distress, respiratory support.

Respiratory distress is an important reason for presentation to pediatric emergency departments (PED). Respiratory distress is usually reversible but when there is failure to treat it, it can cause respiratory arrest and even death. Various respiratory support methods are used in its treatment. It is not completely clear when and which respiratory support modalities including noninvasive or invasive ventilation will be used in these patients. The gold standard for a patient who needs respiratory support is endotracheal intubation, but there are many complications in this method such as volutrauma, barotrauma, ventilator-associated pneumonia.[1,2] Therefore, noninvasive ventilation is used, especially in patients with mild and moderate respiratory failure. High-flow nasal cannula (HFNC) is widely used for noninvasive respiratory support.

It started to be used as a noninvasive respiratory support method in the early 2000s, and its use in critical patient care has increased gradually, especially in recent years.[3] HFNC reduces

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Received 20th April 2021, revised 21st June 2021, 25th June 2021, accepted 30th June 2021.

anatomical dead space and resistance in the upper respiratory tract, provides continuous airway pressure, and reduces the work of breathing.[4,5] Also adjustable (FiO_2 21-100%) heated (34- 37°C) oxygen with nearly 100% humidity can decrease mucosal injury and patient discomfort from cold, dry air.[6]

There is still no guideline that determines which patient will be given HFNC therapy. It is generally preferred for similar indications to nasal continuous positive airway pressure (nCPAP). Although HFNC is a feasible method for patients, in some patients HFNC fails and other respiratory support is needed. Also preferring HFNC therapy may negatively affect the prognosis in patients who need invasive respiratory support.[7] For this reason, it is very important to predict in which patient the HFNC treatment will be insufficient. Previous studies have not been able to locate factors predicting failure of HFNC, although the quality of the evidence is very low. However, respiratory acidosis at admission could be related to treatment of failure.[8] In an another study involving patients who were treated with HFNC due to respiratory distress, it was shown that a baseline respiratory rate (RR) >90th percentile, pCO_2>50 mmHg, pH<7.3 could predict HFNC failure.[7]

Considering the increasingly widespread use of HFNC, it remains important to identify the factors that may predict failure in children. Therefore, the aim of this study was to determine the factors that may predict HFNC failure in patients who presented to the PED with respiratory distress.

Material and Methods

Study Design, Setting and Participants

This is a retrospective, observational study. Patients with respiratory distress treated by HFNC therapy within the first 24 hours of admission to the PED were included in this study. The characteristics of the patients admitted between January 2014 and December 2018 were reviewed retrospectively. Medical records of patients were accessed using patient files and computer database. Patients aged 28 days or under were excluded from the study. The study was reviewed and approved by the the Ethics Committee of Hacettepe University (GO 19/185). All patients were anonymous. The parents signed a consent form approving anonymous data use for academic purposes when the patients were admitted to hospital.

High-flow nasal cannula therapy

HFNC therapy was given to patients with moderate and severe respiratory distress. HFNC therapy was provided by Airvo2 (Fisher & Paykel Healthcare).

The initial FiO_2 and flow were determined by the clinicians, it was adjusted as 1-2 L/kg/min flow. The inspired oxygen concentration was adjusted to achieve a SpO_2 >94%.[9,10] All patients who had respiratory distress were monitored in an observation room in the PED. Patients needing an escalation of respiratory support were transferred to the pediatric intensive care unit (PICU).

Definitons

Increase in heart rate (HR) and RR, nasal flaring, grunting, restlessness and use of accessory muscles were accepted as respiratory distress.[11] Initial values of blood gases were dichotomized using pCO_2 greater than 50 mmHg or pH less than 7.3 as markers of severity of respiratory distress.[7]

"HFNC therapy failure" (non-responders) was defined as the need for escalation to an other ventilation support treatment: non-invasive or invasive mechanical ventilation.

The definitive diagnoses of patients were divided into two groups: acute bronchiolitis and bacterial pneumonia. The diagnosis of acute bronchiolitis was made using the guideline of the American Academy of Pediatrics at 2014.[12] Patients who had respiratory distress symptoms (increase in RR, retraction, wheezing)

following fever, cough, two to three days of upper respiratory tract infection findings, and hyperinflation on chest X-ray were considered as acute bronchiolitis. Patients who had sudden fever, cough, toxic appearance, tachypnea, crackles on auscultation, and alveolar infiltration and consolidation on chest radiography were accepted as bacterial pneumonia.[13]

Medical history was coded into 4 binary variables defined by a previous history of atopy (eczema, asthma, reactive airways disease, or allergic rhinitis), genetic abnormalities (chromosomal abnormality, single gene mutation, or ongoing workup), history of prematurity, neurological disease including global developmental delay, muscular dystropy.[7]

Predictive factors

Age (corrected age for premature infants), gender, vital signs before and two hours post HFNC therapy start, underlying disease, use of steroid, salbutamol and antibiotic therapy, blood gases analysis and lactate values, hospitalization to PICU, respiratory viral panel (RVP) and need of escalation of respiratory support were evaluated. All parameters were evaluated during admission and vital signs were evaluated at the admission and second hour of follow-up period. Vital signs at the second hour were examined because of healthier access to medical records and inspired by similar studies. Normal vital signs were evaluated according to pediatric advanced life support (PALS) criteria.[9]

Statistical Analyses

SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov–Smirnov) to determine whether they were normally distributed. Numerical measurements were presented with mean and standard deviation or medians with interquartile range (IQR) based on distribution; qualitative data with numbers and percentages. According to the distribution of numerical variables, paired samples t-test or Mann–Whitney U were performed to investigate the differences between groups. For categorical variables, a chi-square test or Fisher exact test was performed. The possible factors determined by univariate analysis were then analyzed with a multiple logistic regression model. p value < 0.05 was considered to be statistically significant.

Results

A total of 243 patients who received HFNC therapy were included in this study. 139 (57.2%) of the patients were male and 104 (42.8%) were female (Table I). The median age was 11 months (IQR, 5–27). The age, sex, rate of RSV (Respiratuar Sinsityal Virus) positivity and drug used (steroid, salbutamol, antibiotics) were similar between the two groups. The final diagnosis was acute bronchiolitis in 183 (75.3%) patient, pneumonia in 60 (24.7%) patients. An underlying disease was present in 65.8% of the patients.

There was prematurity in 24 patients, a history of atopy in 31 patients, genetic disease in 61 patients, and neurological disease in 44 patients.

HFNC was well tolerated by all study patients and sedation was not given for any patient. There were no cases of pneumothorax or any other adverse events or complications.

Despite HFNC therapy, 44 (17.6%) patients transferred to PICU from PED and 29 (11.9%) patients required escalation of respiratory support. For 22 patients invasive and 7 patients non-invasive respiratory support were provided. RVP samples were taken from 147 patients, a virus was isolated in 98 patients. The most common agent was RSV (14.4%). It is followed by Humanrhinovirus with 20 patients, Bocavirus with 17 patients, and Influenza with 16 patients. 25 patients were diagnosed with recurrent bronchiolitis.

When the two groups were compared, there was no correlation in terms of age, gender,

Table I. Characteristics of patients with and without HFNC therapy failure.

	Failure (n: 29)	Success (n: 214)	All patients (n: 243)	*p* value
Sex, n (%)				
Male	13 (44.8)	126 (58.9)	139 (57.2)	0.151
Female	16 (55.2)	88 (41.1)	104 (42.8)	
Diagnosis, n (%)				
Bronchiolitis	22 (75.9)	161 (75.2)	183 (75.3)	0.941
Pneumonia	7 (24.1)	53 (24.8)	60 (24.7)	
Comorbidity, n (%)				
Positive	21 (72.4)	139 (65.0)	160 (65.8)	0.427
Negative	8 (27.6)	75 (35.0)	83 (34.2)	
Drugs use, n (%)				
Salbutamol	23 (95.8)	189 (92.6)	212 (93.0)	0.563
Steroid	16 (72.7)	143 (74.1)	159 (74.0)	0.890
Antibiotic therapy	28 (100)	205 (98.1)	233 (98.3)	0.460
Respiratuar Sinsityal Virus, n (%)				
Positive	3 (10.3)	32 (14.9)	35 (14.4)	0.703
Negative	26 (89.6)	182 (85.1)	208 (85.6)	

underlying disease and diagnosis. However, in the non-responders it was found that the HR and RR in the second hour of treatment were higher and also the pH value was lower on admission (Table II).

The results of the logistic regression model are presented in Table III. 102 cases were excluded from the regression model because of missing data. Three continuous variables and one categorical variable were in this model. Just one variable was associated with increased risk for HFNC failure: RR at second hour of initiation.

Discussion

In this retrospective study, possible predictive factors for escalation of respiratory support were determined in patients who received HFNC treatment in a PED. This study is one of the few studies identifying predictors of HFNC failure. Our results show that HFNC is a feasible respiratory support method that can be applied in all age groups of children. However, some patients may need escalation of respiratory support. The failure rate in our study was 11.9% and low pH values on admission and high pulse rate and respiratory rate observed at the second hour of follow-up could be a predictive factor.

Recently, there are no established guidelines for the initiation of oxygen therapy in pediatric patients. HFNC therapy has been extensively used in the last decade and studies continue regarding its use. Many studies have focused on its use in patients with bronchiolitis and HFNC therapy has been confirmed to be beneficial in severe bronchiolitis.[14-16] The physiological benefits generated by the supply of heated and humidified air are proven.[17-19] The reduction in intubation rate is another important benefit confirmed in studies.[20,21] Wing et al.[3] found that the need for intubation and mechanical ventilation decreased after the use of HFNC in their study on patients transferred from PED to PICU with acute respiratory failure. In a similar study, McKiernan et al.[22] examined patients admitted to PICU with bronchiolitis and showed that HFNC treatment reduced the rate of intubation by reducing respiratory rate and work of breathing. But still there is no clear consensus about which patients are the best candidates for this noninvasive respiratory support and which factors can predict HFNC failure.

Table II. Association between patient characteristics and HFNC therapy failure.

	Failure (n: 29)	Success (n: 214)	All patients (n: 243)	*p* value
Age, months (IQR)	8 (3.5-42.5)	11.5 (5-25.5)	11 (5-27)	0.593
Under 2 years (%)	19 (65.5)	160 (74.7)	179 (73.6)	0.289
SpO_2 % (SD)	84.3 (10.7)	86.8 (8.4)	86.5 (8.7)	0.279
HR, bpm (SD)	160.4 (18.4)	158.9 (23.6)	159.1 (23)	0.815
RR, rpm (SD)	63.0 (24.4)	63.0 (16.8)	63 (17.7)	0.924
SpO_2 at 2nd hour, % (SD)	91.4 (12.9)	96.7 (2.5)	96.1 (5.1)	0.337
HR at 2nd hour, bpm (SD)	145.4 (23.0)	133.9 (16.0)	135.2 (17.2)	0.014
RR at 2nd hour, rpm (SD)	56.9 (19.1)	47.6 (11.0)	48.6 (12.4)	0.017
pH (SD)	7.30 (0.07)	7.35 (0.06)	7.34 (0.06)	0.005
pCO_2 (mmHg) (SD)	51.4 (23.6)	44.6 (10.8)	45.5 (13.4)	0.170
SO_2 (mmHg) (SD)	66.5 (25.7)	66.8 (18.6)	66.7 (19.7)	0.694
pO_2 (mmHg) (IQR)	45.7 (30.2-57.2)	37.6 (30.6-48.8)	38.4 (30.6-49.8)	0.236
HCO_3 (mEq/L) (SD)	24.4 (8.8)	23.7 (5.1)	23.8 (5.7)	0.990
Lactate (mmol/L) (IQR)	1.8 (1.1-4.3)	1.6 (1.2-2.1)	1.6 (1.2-2.2)	0.137
Hb (g/dL) (SD)	11.4 (2.04)	11.4 (1.6)	11.4 (1.6)	0.792
WBC (/mm³) (IQR)	11.2 (9.2-19.2)	12.0 (8.7-15.3)	12.0 (8.8-15.5)	0.791
PLT (/mm³) (IQR)	362.0 (291.5-452.5)	349.0 (273.5-436.0)	349.5 (275.7-437)	0.665
ESR (mm/h) (IQR)	12.5 (3.5-24.2)	12.0 (2.7-25.0)	12.0 (3-24.7)	0.918
CRP (mg/dL) (IQR)	1.96 (1.07-4.74)	1.10 (0.45-3.04)	1.26 (0.47-3.42)	0.109
Severe respiratory distress (%)	15 (51.7)	41 (19.2)	56 (23)	<0.001

CRP: *c-reactive protein*, ESR: erythrocyte sedimentation rate, Hb: haemoglobin, HR: heart rate, IQR: interquartile range, PLT: platelet, RR: respiratory rate, SD: standard deviation, WBC: white blood cell.

Table III. Selected predictor variables for multivariable model of high-flow nasal cannula failure.

Variable	OR	95% CI	*p* value
pH	0.002	0.000-30.692	0.209
HR at 2nd hour, bpm	0.896	0.793-1.013	0.080
RR at 2nd hour, rpm	1.058	1.012-1.106	0.012
RSV positive	0.565	0.101-3.168	0.516

HR: heart rate, RR: respiratory rate, RSV: Respiratuar Sinsityal Virus.

High-flow nasal cannula failure rate has been found in different studies. The reason for this may be that the definition of failure is handled in different ways in studies. In some studies, failure was defined as intubation and cardiopulmonary arrest[7], while in others needing escalated care (non-invasive or invasive mechanical ventilation) was defined as a nonresponder.[23] In addition, in some studies, inclusion of patients diagnosed with only bronchiolitis may be another factor.[24,25] Because bronchiolitis diagnosis has been found to be protective for non-responders.[7,26] In this study, non-responder rate was found to be 11.9%. Betters et al.[26] found this rate to be 6% in their study on the use of HFNC outside PICU. This rate was even lower in two randomized controlled trials.[24,25] The rate of these patients was between 6 and 19% in the literature.[20,26-29]

As expected, the predictive factors of HFNC failure also differed. Kelly et al.[7] found that a triage RR greater than 90th centile for age, initial venous blood gas demonstrating pCO_2 greater than 50 mmHg or initial venous pH less than 7.30 were independently associated with

PED in their study of patients under two years of age who underwent HFNC for PED with a higher subsequent need for intubation. In a prospective study investigating bronchiolitis patients who underwent HFNC for less than 12 months in PED, it was found that HR and RR did not decrease in the non-responder group.[28] In another retrospective study, bronchiolitis patients who were taken into intensive care unit in which possible predictive factors of HFNC failure were examined, and on admission RR and pCO_2 were found to be higher in the non-responder group.[29] In a retrospective study examining HFNC failure in patients who were undertaken outside PICU, high FiO_2 requirements, previous history of intubation, and cardiac co-morbidity were associative predictors of HFNC failure.[26] In this study we found that non-responders had lower pH on admission. Also after two hours initiation of HFNC therapy, RR and HR did not decrease. In addition, the pulse, RR and pCO_2 on admission were not related with HFNC failure.

Some patients are at risk for developing respiratory failure and need timely identification for escalated care because in our department HFNC therapy is used in patients with moderate to severe respiratory distress. The objective is not to be late for the necessary escalated care. Some scores used in PED are available for this decision such as the Pediatric Risk of Admission Score[30], the Pediatric Early Warning System Score (PEWS)[31], and the pediatric respiratory assessment measure.[32] Hansen et al.[33] used PEWS in their retrospective study to evaluate clinical response in patients receiving HFNC therapy in the pediatric ward. However, as it is known, clinical respiratory scales are generally used for specific diagnoses (e.g., bronchiolitis, pneumonia, etc.) and there is no validated score for patients receiving HFNC treatment. In our study involving patients treated with HFNC at different ages and diagnoses, no adverse effects such as air leak syndrome, bradycardia, bradypnea, emergency intubation, or cardiopulmonary resuscitation were observed. In a series of cases in the literature, three patients with air leak syndrome were reported.[34]

This study has several limitations. First of all it is not a randomized controlled trial. It is a retrospective study conducted in a single center. For this reason, clinical findings of some patients who were treated with HFNC may not have been reached. Moreover, it does not have a control group so we couldn't control for confounding factors. Another limitation is that the comorbidity is very high because our hospital is a tertiary care university hospital (65.8%). On the other hand, it may indicate that HFNC can be used easily regardless of the underlying disease or the patient's diagnosis. Additionally, the subgroups of patients in our study were not evaluated according to age groups or underlying disease, because there was a large range of ages but a relatively small number of patients, especially in patients with HFNC failure. Not surprisingly, in our study, HFNC failure rate was found to be lower. Possible reasons for that could be a small number of severe patients included in the study and rapid initiation of acute treatment in the PED.

We concluded in this retrospective study that HR and RR didn't decrease in the non-responders group two hours after HFNC initiation and the pH were lower on admission in venous blood gases. However, the need for multicenter randomized controlled studies on this subject is evident to determine predictive factors of HFNC failure.

Ethic approval

The written consents from the patient families were obtained according to the Declaration of Helsinki (1964) and the study was approved by the ethics committee of Hacettepe University (GO 19/185; approval date, March 2019).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: OA, AZB, OT; data collection: OA, AZB, OT; analysis and interpretation of results: OA, EAA, OT; draft manuscript preparation: OA, EAA, OT. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

There is no funding source.

Conflict of interest

OA, EAA, AZB, OT declared that they have no conflict of interest.

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