RESEARCH PAPER

Impact of High-flow Nasal Cannula Therapy in Quality Improvement and Clinical Outcomes in a Non-invasive Ventilation Device-free Pediatric Intensive Care Unit

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Objective: To analyze the change in quality indicators due to the use of high-flow nasal cannula therapy as a non-invasive ventilation method in children with respiratory distress/failure in a non-invasive ventilation device-free pediatric intensive care unit. **Methods**: Retrospective chart review of children with respiratory distress/failure admitted 1 year before (period before high-flow nasal cannula therapy) and 1 year after (period after high-flow nasal cannula therapy) the introduction of high-flow nasal cannula therapy. We compared quality indicators as rate of mechanical ventilation, total duration of mechanical ventilation, rate of re-intubation, pediatric intensive care unit length of stay, and mortality rate between these periods. **Results**: Between November 2012 and November 2014, 272 patients: 141 before and 131 after high-flow nasal cannula therapy were reviewed (median age was 20.5 mo). Of the patients in the severe respiratory distress/failure subgroup, the rate of intubation was significantly lower in period after than in period before high-flow nasal cannula therapy group (58.1% *vs*. 76.1%; *P* <0.05). The median pediatric intensive care unit length of stay was significantly shorter in patients who did not require mechanical ventilation in the period after than in the period before high-flow nasal cannula therapy group (3d *vs*. 4d; *P*<0,05). **Conclusions**: Implementation of high-flow nasal cannula therapy in pediatric intensive care unit significantly improves the quality of therapy and its outcomes.

Keywords: *Endotracheal intubation, Mechanical ventilation, Respiratory distress/failure.*

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High-flow nasal cannula therapy (HFNC), is a non-invasive form of oxygen delivery, wherein heated, humidified, and blended oxygen/air reduces damage to the upper airway mucosa, increases ciliary activity, decreases viscosity of secretions and may reduce airway edema that makes it a comfortable way of oxygenation [1-4]. Most studies on HFNC therapy have been performed in neonates or in the post-extubation period in children or infants with bronchiolitis. They have reported some advantages, such as easy application and tolerability [5-8]. A few studies have been conducted in pediatric intensive care units (PICUs), with most of these concentrating on bronchiolitis [9-12]. Studies evaluating the effectiveness of HFNC in children with various etiologies of respiratory distress between 1 month and 18 years of age in PICUs are very limited [13-15].

The aim of our study was to analyze the effectiveness of HFNC therapy as a non-invasive ventilation (NIV) method in quality improvement and clinical outcomes of children aged 1 month to 18 years with various etiologies of respiratory distress/failure in the PICU.

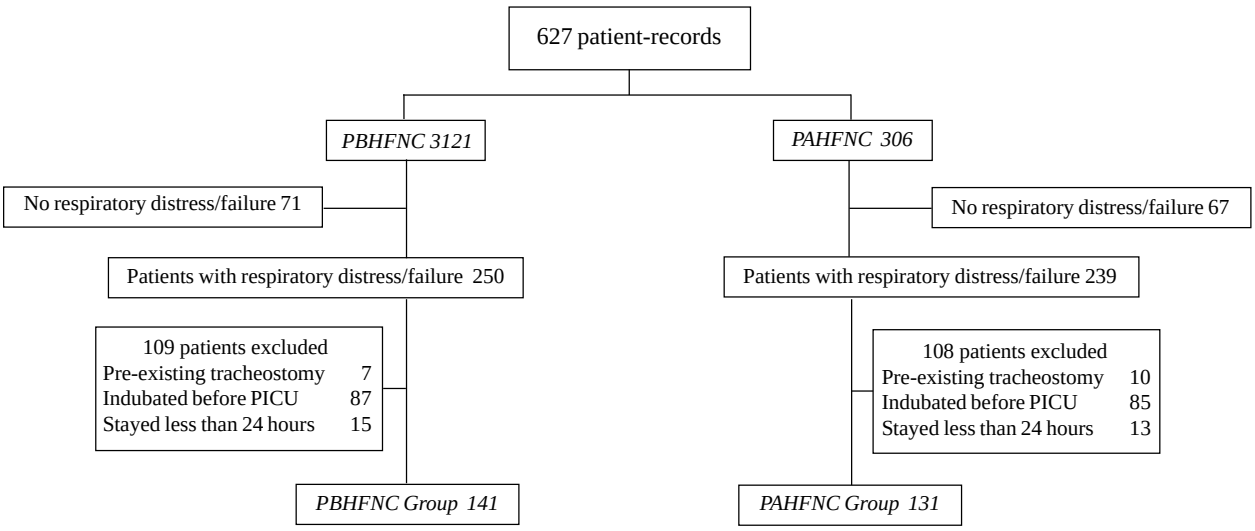
Methods

This study was a retrospective chart review of children with respiratory distress/failure admitted 1 year before and 1 year after the introduction of HFNC therapy. Our PICU is in Tepecik Teaching and Research Hospital in Ýzmir, Turkey. It is a 10-bed tertiary mixed surgical and medical unit. There was only invasive mechanical ventilation (MV) as a ventilation method in our PICU before the implementation of HFNC. In this period, nasal cannula oxygen, hood, simple face mask, and non-rebreather mask were used. HFNC therapy was first used on November 1, 2013. After the introduction of HFNC, all patients received HFNC as the primary respiratory support for respiratory distress/failure according to our HFNC protocol. No other non-invasive ventilation device was used in our PICU and there was no HFNC in our Pediatric Emergency Department (PED) during the study period. The nursing staff, the intensive care specialists,

the standard care, the admission criteria, the decision for intubation and the respiratory support methods given other than HFNC were similar in these periods.

In the protocol, the oxygen flow rates used were 5-50 L/min depending on the patient response (respiratory rate, heart rate, SpO_2, perfusion, comfort) with a FiO_2 between 0.3 and 1. The inspired oxygen concentration was titrated to achieve $SpO_2 > 94\%$. SpO_2/FiO_2 ratio was used to determine the requirement for oxygen. The flow rate was set at 5 L/min for infants or 15 L/min for children at the beginning, and was titrated (±5 L/min) to achieve reduction of the oxygen requirement to FiO_2 of 30% and to improve the work of breathing, respiratory rate, and heart rate. The flow rate used in infants was 5-20 L/min and for children, 15-50 L/min. HFNC was discontinued if there was clinical deterioration (oxygen requirement, work of breathing, respiratory rate, or heart rate) in the first 30 min and the patients were intubated and ventilated mechanically. If there was no change in the first 30 min, the patients were followed for 30 min longer. The HFNC system (Fisher & Paykel Healthcare Airvo 2) comprises a humidifier (MR290) and a continuous flow circuit (900PT531 for infants, 900PT501 for children). We selected the nasal prong size that best fitted the nostrils (Optiflow, OPT318, OPT842, OPT844, OPT846).

We evaluated whether the clinical outcomes improved due to using HFNC therapy. We chose five quality measurements that indicate success, failure or ineffectiveness: the rate of MV, total duration of MV, rate of re-intubation, PICU length of stay (LOS) and rate of mortality. The patients with respiratory distress or failure between 1 month to 18 years of age who stayed more than 24 h in the PICU were included to the study. The definition of "respiratory distress" was hypoxemia (SpO_2<94%), tachypnea, increased work in breathing (chest wall retraction, use of accessory respiratory muscles, nasal flaring/grunting, feeding difficulties). Poor perfusion (cyanosis, mottling, poor neurological status, reduced muscle tonus), apnea or PaO_2 < 50 mmHg in room air, respiratory acidosis (pH<7.35), PaO_2<60 mmHg when FiO_2 60%, and $PaCO_2$ > 60 mmHg in arterial blood gas analysis were deemed "respiratory failure". The patients admitted between November 1, 2012 and November 1, 2014 to our PICU were evaluated. Thus, 1 year before HFNC therapy was defined as the period before HFNC and 1 year after the introduction of HFNC therapy was defined as the period after HFNC. Patients were excluded if they had had a tracheostomy, if they were intubated before PICU admission, or if they stayed less than 24 h in the PICU. We estimated the severity of respiratory distress by using a score, which can be used for a large range of ages and etiologies of respiratory distress [16]. Pediatric index of mortality 2 (PIM 2) and pediatric risk of mortality (PRISM) scores were routinely used in the PICU. Calculations of these scores were made using web-based calculators (*http://www.sfar.org/article/316/scoring-systems-for-icu-and-surgical-patients*).



PBHFNC: Period before high-flow nasal cannula therapy, PAHFNC: Period after high-flow nasal cannula therapy, PICU: Pediatric intensive care unit.

FIG. 1 *Study algorithm.*

TABLE I THE COMPARISON OF DEMOGRAPHIC FEATURES, CLINICAL PARAMETERS, AND OUTCOMES BETWEEN THE TWO GROUPS.

Characteristic(median / interquartile range or n, %)	*Total (n=272)*	*PBHFNC (n= 141)*	*PAHFNC (n= 131)*	*P*
Age in months	20.5 (5- 75)	22 (4.5- 49)	18 (5- 70)	0.414
Sex (*n*, %), female	116 (42.6)	55 (39)	61 (46.5)	0.183
Weight, kg	10 (6- 16)	10 (5- 15)	13 (7- 16)	0.051
PIM2 (%)	21.8 (8-45)	23.2 (8-45)	20.4 (8-42)	
PRISM (%)	32.3 (12-60)	31.3 (12-60)	33.4 (12-58)	0.382
Chronic disease (+)	154 (56.6)	77 (54.6)	77 (58.8)	0.488
Primary diagnosis at admission				
Intoxication	5 (1.8)	3 (2.1)	2 (1.5)	
Sepsis	89 (32.7)	49 (34.8)	40 (30.5)	
Trauma	9 (3.3)	4 (2.8)	5 (3.8)	
Post-op	12 (4.4)	5 (3.5)	7 (5.3)	0.877
Neurological	5 (1.8)	2 (1.4)	3 (2.3)	
Respiratory	121 (44.5)	63 (44.7)	58 (44.3)	
Gastrointestinal	1 (0.4)	0	1 (0.8)	
Metabolic	11 (4)	7 (5)	4 (3.1)	
Hemato-oncological	4 (1.5)	1 (0.7)	3 (2.3)	
Cardiovascular	15 (5.5)	7 (5)	8 (6.1)	
Etiologies for respiratory distress/ failure				
Bronchiolitis	41 (15.1)	23 (16.3)	18 (13.7)	
Pneumonia	69 (25.4)	35 (24.8)	34 (26)	
Upper airway obstruction	12 (4.4)	6 (4.3)	6 (4.6)	
Other pulmonary diseases	41 (15.1)	23 (16.3)	18 (13.7)	
Extrapulmonary ALI/ARDS	80 (29.4)	45 (31.9)	35 (26.7)	
Neuromuscular disease	22 (8.1)	6 (4.3)	16 (12.2)	
Asthma	7 (2.6)	3 (2.1)	4 (3.1)	0.338
Severity of respiratory distress				
Mild	16 (5.9)	10 (7.1)	6 (4.6)	
Moderate	70 (25.7)	43 (30.5)	27 (20.6)	0.089
Severe	186 (68.4)	88 (62.4)	98 (74.8)	
MV (+)	137 (50.4)	72 (51.1)	65 (50)	0.861
Duration of MV (d)	4 (1-11)	4 (1-11)	4 (1-11)	0.440
Re-intubation (+)	32 (11.8)	15 (21.1)	17 (27.4)	0.397
LOS in PICU (d)	8 (2-20)	8.5 (2-18)	7 (3-23)	0.079
Death (+)	46 (16.9)	25 (17.7)	21 (16)	0.709

PBHFNC: Period before high-flow nasal cannula, PAHFNC: Period after high-flow nasal cannula. ALI: Acute lung injury, ARDS: Acute respiratory distress syndrome. PIM2: Pediatric index of mortality 2, PRISM: Pediatric risk of mortality. MV: Mechanical ventilation, LOS in PICU: Length of stay in pediatric intensive care unit.

Primary diagnosis of patients were categorized (intoxication, sepsis, trauma, post-op, neurological, respiratory, gastrointestinal, metabolic, hemato-oncological and cardiovascular) and analyzed. We classified the patients into seven categories according to etiology of their respiratory distress/failure: bronchiolitis, pneumonia, upper airway obstruction, extra pulmonary acute lung injury (ALI), asthma, neuromuscular diseases, and other pulmonary diseases. We divided the patients in to two groups according to the severity of respiratory distress/failure: patients with mild-moderate and severe respiratory distress. The

demographic and clinical parameters (body weight, mortality scores, presence of chronic disease, primary diagnose, etiology of respiratory distress/ failure, severity groups, rate of MV, total duration of MV, rate of re-intubation, PICU LOS and rate of mortality) were compared between the two time-periods. We also analyzed the subgroups: mild-moderate respiratory distress group, severe respiratory distress group, patients with respiratory distress/failure due to pulmonary disease (bronchiolitis, pneumonia, upper airway obstruction, other pulmonary diseases and asthma), patients diagnosed as bronchiolitis, patients required MV, and patients who did not required MV. The study was approved by the local ethics committee.

The study databases were analyzed using the SPSS software (ver. 20.0; SPSS Inc., Chicago, IL). Numerical variables were analyzed using the Mann-Whitney U-test. Categorical variables were compared using the Chi-square or Fisher's exact test, as appropriate. Differences were considered significant at $P < 0.05$.

RESULTS

In total, 272 records (141 in the before the high-flow nasal cannula introdution) were reviewed (***Fig* 1**). In study group, 137 (50.3%) patients were intubated (72 in the before group, 65 in the after high flow nasal cannula group) and 46 (16.9%) patients died. There was no difference in the rate of mechanical ventilation or its duration, rate of re-intubation, PICU LOS, or mortality rate between the groups (***Table* I**). We found no difference in the primary diagnosis (diagnostic categories of patients at admission) or etiology of respiratory distress/failure between the intubated patients in the two groups.

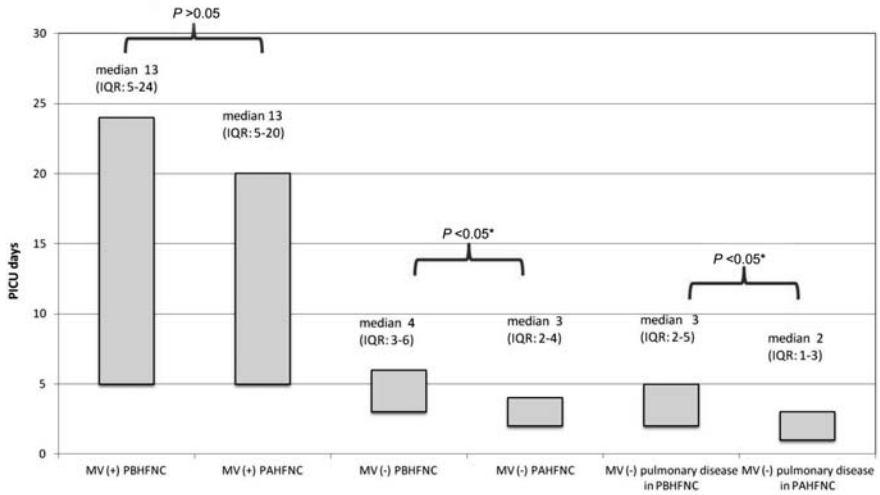
Of the severe respiratory distress group, the rate of intubation was significantly lower in the after high flow nasal cannula group (58.1% *vs.* 76.1%; $P< 0.05$) (***Web Table* I**).

In total, 137 (50.8%) patients required mechanical ventilation. The median PICU LOS was not significantly different in the patients who required mechanical ventilation between the before (median: 13 days; IQR: 5-24) and after high-flow nasal cannula (median: 13 days; IQR: 5-20) groups (P=0.7). Among the patients who did not require mechanical ventilation (134; 49.2%), the median PICU LOS in after high flow nasal cannula group was significantly shorter [median (IQR) 3 (2-4) d *vs.* 4 (3-6) d; P=0.018]. When we analyzed the patients with pulmonary disease who did not require mechanical ventilation, the median PICU LOS was also shorter in the former [median (IQR) 2(1-3) d *vs.* 3 (2-5) d; P=0.005] (***Fig*. 2**).

DISCUSSION

In this retrospective chart review, we found that the use of HFNC therapy reduced rate of mechanical ventilation in the children with severe respiratory distress/failure subgroup. Furthermore, we found that the use of HFNC as a primary support decreased the PICU LOS in children who did not require intubation or mechanical ventilation.

Our study had several limitations; the most important being inadequate sample size. This makes it difficult to



*MV: Mechanical ventilation, PICU: Pediatric intensive care unit, PBHFNC: Period before high-flow nasal cannula, PAHFNC: Period after high-flow nasal cannula, *statistically significant.*

FIG. 2 *Comparison of length of PICU stay between patients with and without MV support in the PBHFNC and PAHFNC groups.*

WHAT THIS STUDY ADDS?

- Implementation of high-flow nasal cannula therapy improved the quality of treatment and its clinical outcomes in children with respiratory distress/failure in non-invasive ventilation device-free PICU.

analyze the effectiveness of HFNC for specific diseases. The heterogeneity of the age of the study population was also a limiting factor. Another limiting factor was that the study was conducted retrospectively in a single center. We could not evaluate more changes in vital parameters, changes in laboratory findings, or patient comfort levels after initiating HFNC therapy, because of the retrospective nature of the study.

As in our study, Wing, *et al*. [17] found that the need for intubation and the use of mechanical ventilation in the PICU were decreased after the implementation of a hospital-wide guideline for HFNC use. Nonetheless, they found no difference in the PICU LOS, mortality rate, or duration of mechanical ventilation. HFNC was shown to be a safe and an effective form of respiratory support in the PICU, and the prognosis of patients could be predicted by simple bedside observations [13]. However, a meta- analysis determined no evidence for the safety or effectiveness of HFNC as a form of respiratory support in children [18]. In the literature, reduced intubation rates in patients with bronchiolitis have been reported after the use of HFNC [7,8]. However, in a meta-analysis, it was determined that there was insufficient evidence for the effectiveness of HFNC therapy for infants with bronchiolitis [19]. In our study, patients with bronchiolitis constituted 15% of all patients, and we did not find any significant impact on clinical outcomes in patients with bronchiolitis.

In conclusion, we showed that the implementation of HFNC therapy improved clinical outcomes in children aged 1 month to 18 years with various etiologies of severe respiratory distress/failure admitted to the non-invasive ventilation device-free PICU. To better understand the effectiveness of HFNC in the PICU, prospective randomized-controlled studies are needed.

Contributors: FKC: study design, analysis of data, manuscript preparation; ABA, MA: study design, analysis of data, review of manuscript; NZ, AB, YB, GG, FD, GI: literature search, data collection.
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WEB TABLE I COMPARISON OF SUBGROUPS IN PBHFNC AND PAHFNC ACCORDING TO PRIMARY AND SECONDARY OUTCOMES

Subgroups		*MV (+) n (%)*	*Duration of MV (days), median (IQR)*	*LOS in PICU (d) median (IQR)*	*Re-intubation (+), n (%)*	*Death (+) n (%)*
Mild-moderate respiratory	PBHFNC, *n*= 53	5 (9.4%)	3 (1-6)	6 (3-9)	0	2 (3.8%)
distress group	PAHFNC, *n*= 33	8 (24.2%)	3 (2-6)	6 (4-12)	1(%3)	3 (9.1%)
	P value	0.07	0.72	0.170	>0.99	0.37
Severe respiratory	PBHFNC, *n*= 88	67 (76.1%)	5 (2-12)	8 (2-25)	15 (22.7%)	23 (26.1%)
distress group	PAHFNC, *n*= 98	57 (58.1%)	5 (2-15)	9 (5-27)	16 (29.6%)	18 (18.4%)
	P value	0.01	0.42	0.93	0.39	0.20
Patients with	PBHFNC, *n*=23	3 (13%)	2 (1-2)	3 (1-4)	0	0
bronchiolitis	PAHFNC, *n*=18	0	-	3 (2-3)	-	0
	P value	0.243	-	0.714	-	-
Patients with pulmonary	PBHFNC, *n*=90	36 (40%)	4 (2-9)	3 (2-6)	6 (16.7%)	5 (5.6%)
disease	PAHFNC, *n*=80	31 (38.8)	5 (2-14)	4 (3-10)	7 (24.1%)	7 (8.8%)
	P value	0.87	0.31	0.07	0.45	0.42

MV: Mechanical ventilation, LOS in PICU: Length of stay in pediatric intensive care unit, IQR: Interquartile range; PBHFNC: Period before high-flow nasal cannula, PAHFNC: Period after high-flow nasal cannula.