Review / Derleme

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Safety and Efficacy of High-flow Nasal Cannula Therapy in the Pediatric Emergency Department

Çocuk Acil Servisinde Yüksek Akışlı Nazal Kanül Tedavisinin Güvenilirliği ve Etkinliği

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Abstract

The objective of this review was to provide a summary of the current literature on heated humidified high-flow nasal cannula therapy (HFNC), discuss the mechanism of action, describe how HFNC is used, indications for use, and safety and efficacy in the pediatric emergency department (PED). A computer-based literature search through January 2019 was conducted using MEDLINE (PubMed) and Google Scholar. We included all original studies on HFNC use in pediatric patients in the PED. Our search identified fourteen studies that met the search criteria and all were reviewed by the authors. The majority of patients (1867, 67%) included in these studies were children with acute bronchiolitis. While, most of the studies concluded that HFNC was more effective than standard oxygen therapy in reducing respiratory rate, heart rate, endotracheal intubation rate and pediatric intensive care unit (PICU) admission, the limited data suggest that HFNC had similar effect to continuous positive airway pressure in patients with acute bronchiolitis. There is no general practice about the initiation and weaning of HFNC yet. Although a small number of adverse effects have been reported, HFNC therapy was usually safe. HFNC is a useful treatment modality for children with acute bronchiolitis. In the acute setting, it was shown to decrease respiratory rate, heart rate, RS, need for endotracheal intubation, and PICU admission. However, there is limited data on the initiation process, flow rate, and standardized protocol for weaning patients off HFNC. Further studies are needed to address these issues.

Keywords: Child, emergency department, oxygenation, heated humidifier, humidification, high flow gas

Öz

Bu derlemenin amacı, çocuk acil serviste (ÇAS) kullanılan ısıtılmış nemlendirilmiş yüksek akımlı nazal kanül oksijen (YANKO) tedavisi ile ilgili literatürün gözden geçirilmesi ve bu tedavinin etki mekanizmasının, kullanım endikasyonlarının, etkinliğinin ve güvenilirliğinin tartışılmasıdır. MEDLINE (PubMed) ve Google Scholar kullanılarak Ocak 2019'a kadar olan tüm yayınlar tarandı. ÇAS'de gerçekleştirilen YANKO kullanımı ile ilgili tüm orijinal çalışmalar derlemeye dahil edildi. Arama kriterlerini karşılayan literatürdeki on dört çalışma incelendi. Bu çalışmalara dahil edilen hastaların çoğu (1867, %67) akut bronşiyolitli çocuklardı. Çalışmaların çoğu, YANKO'nun solunum hızı, kalp atım hızı, endotrakeal entübasyon ve yoğun bakım (YB) yatış oranını azaltmada standart oksijen tedavisinden daha etkili olduğunu belirtmekle birlikte, bazı çalışmalar bu tedavinin akut bronşiyolitli hastalarda en az diğer non-invaziv ventilasyon yöntemleri kadar etkili olduğunu göstermiştir. YANKO tedavisinin başlatılması ve kesilmesi konusunda henüz bir görüş birliği olmamakla birlikte, bu yöntemin güvenle kullanılabileceği belirtilmektedir. YANKO tedavisi, özellikle akut bronşiyoliti olan çocuklar için kullanışlı bir tedavi yöntemidir. Acil serviste solunum sıkıntısı nedeniyle tedavi edilen çocuklarda solunum sıkıntısını, endotrakeal entübasyon ve YB yatış oranını azalttığı gösterilmiştir. Bununla birlikte, başlangıç süreci, akış hızı ve hastaları tedaviden ayırma ile ilgili sınırlı veri vardır. Bu konuların ele alınacağı daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Çocuk, acil servis, oksijenizasyon, ısıtılma, nemlendirme, yüksek akışlı oksijen

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Introduction

Respiratory distress is one of the most common and most important complaints in children presenting to the pediatric emergency department (PED).[1] Viral bronchiolitis, a common seasonal illness causing respiratory distress in children, leads to over 300.000 PED visits annually in the USA.[2,3] As such, the management of acute respiratory distress has evolved over the past four decades. Whereas supplemental oxygen has been the mainstay for managing respiratory distress in children with bronchiolitis, many other treatments such as albuterol, epinephrine, and systemic corticosteroids, nebulized hypertonic saline, heliox have been investigated.[4] While supplemental oxygen is provided via mask or nasal cannula for children with mild or moderate respiratory distress, non-invasive or invasive ventilation support is often required for severe cases. In recent years, high-flow nasal cannula (HFNC), a non-invasive ventilation (NIV) modality, has become the preferred initial treatment method for children with respiratory distress.[5] The use of HFNC was previously limited to in neonatal intensive care units and pediatric intensive care units (PICU).[6] Given its proven safety and efficacy, it is currently used with increasing frequency in PEDs and general pediatric wards.[7] HFNC delivers heated and humidified high flow (>2 L/min) oxygen that maintains positive airway pressure. The heated humidified air/oxygen mixture does not irritate the respiratory mucosa.[8] HFNC provides ventilation in anatomical dead space and decreases upper airway resistance. Thus, it facilitates the excretion of carbon dioxide (CO_2) and supports ventilation perfusion balance.[9,10]

Current literature has shown that HFNC decreased the need for endotracheal intubation and PICU admission rates in children with bronchiolitis.[11] Furthermore, it has been reported that HFNC was as effective as other non-invasive ventilatory support modalities in these patients.[12] To date, there are no clear guidelines on when to initiate HFNC, which air/oxygen flow rate is effective, how and when to wean patients off the HFNC system, or its use in the PED setting.[13-15]

The objective of our review was to provide a summary of the current HFNC literature, discuss the mechanism of action, describe how HFNC is used, indications for use, safety, and efficacy.

Methods-Literature Search

We conducted a systematic literature search of the databases MEDLINE (PubMed) and Google Scholar up to January 2019. We first searched for all articles with the keywords high flow nasal cannula or HFNC and articles including children 0-18 years of age. Then, we limited the search to articles conducted in emergency department, and to English and Turkish language studies in human.

All original publications on children with respiratory distress who received HFNC in the PED were included. Studies completed on hospitalised children were excluded.

Study Characteristics

A total of 120 relevant records were retrieved with reference to our search criteria. After duplicates and irrelevant studies were removed, 64 studies were further scrutinized. Of these, 14 publications on children treated with HFNC in the PED were identified. Study design, outcome and key results are summarized in Table 1. Seven studies included only children with bronchiolitis[16-22], six studies had children with respiratory distress due to any disease[23-28] and one study was on children with acute asthma exacerbations.[29] Five studies enrolled children up to 24 months of age[19,20,22,24,27], four enrolled children up to 18 years of age[23,25,26,28], four included children up to 12 months of age only[16-18,21], and one enrolled children aged 1 to 14 years.[29]

In five studies, HFNC devices were used with 2 L/kg/min flow rate for infants or children up to 10 kg[17,21,25,28,29], five studies did not report a specific flow rate[18,20,24,26,27], in one study, 1 L/kg/min flow rate was utilized[19] and in one study, both 1 L/kg/min flow rate and 2 L/kg/min were used.[22] In another study a flow rate of 1-8 L/min was used[16], and in the last study a flow rate of 4-10 L/min was used for children younger than 24 months of age and 5-50 L/min flow rates in older children.[23]

Four studies compared HFNC to standard oxygen therapy[18,19,21,29], three evaluated reasons for HFNC therapy failure[24,25,28], and two studies evaluated the effects of HFNC on intubation and PICU admission rates.[17,23] While two studies tried to determine the safety and efficacy of HFNC therapy[20,26], one study compared 1 L/kg/min flow rate with 2 L/kg/min[22], one study compared HFNC to continuous positive airway pressure (CPAP)[27], and another one measured nasopharyngeal pressures at varying flow rates.[16]

Basic Components of HFNC System

HFNC, a closed system, generally comprises a flow oxygen/air blender which regulates the pressurized oxygen and air; a water reservoir that is interdependent to an heater and humidifier; a heater and humidifier; an insulated heated circuit that checks and protects the temperature and relative humidity of the conditioned gas delivered to the patient; and a special nasal cannula (Figure 1).[10]

HFNC system heats the gas to near the body temperature up to 37 °C, humidifies and delivers to the patient via nasal

cannula. Although, currently a couple of HFNC circuits and devices are produced by different manufacturers, they have same basic action mechanisms.[7]

Mechanism of Action

HFNC is defined as heated and humidified mixture of air and oxygen administered via nasal cannula at a higher flow (>2 L/min) than the patient's inspiratory flow.[8] It is adopted that flow rates >6 L/min are high flow in children.[11] Some researchers regulate the flow rates according to body weight and while some of them recommend using 1 L/kg/min, others suggested 2 L/kg/min.[17,19,30] The flow rate is also chosen by age in some centers.[31] There has been no consensus about this issue yet.[14] Whichever flow rate is selected, HFNC has several advantages over conventional "low-flow" oxygen therapy in washout of nasopharyngeal dead space, gas exchange, oxygenation, decrease of inspiratory resistance and work of breathing, improvement of airway conductance and mucociliary clearance, reduction of the metabolic cost and providing an end-distending pressure to the lungs.[32]

The air in the nasopharynx and trachea includes high proportion of CO_2 at the end of exhalation during normal breathing. This air is changed with the fresh air on the next respiratory cycle that decreases the efficiency of gas exchange. But, in patients receiving HFNC therapy, the oxygen-rich fresh gas rapidly covers the nasal cavity, pharynx, and trachea, and CO_2-rich gas is washed out from the dead spaces, thus improves alveolar

Table 1. Overview of the 14 original studies including children receiving HFNC in the ED

Authors Year Type of study	Study group Sample size and treatment Age of patients	Flow rate	Main outcomes	Main findings
Arora et al.[16] 2012 Prospective observational	Infants with bronchiolitis 25 (all cases received HFNC*) Age <12 months	1-8 L/min	NP ǂpressures at varying flow rates of HFNC	Increasing flow rate of HFNC up to 8 L/min were associated with linear increase in NP pressure
Wing et al.[23] 2012 Retrospective observational case control	42% had asthma 24% had bronchiolitis 19% had pneumonia 15% had other illnes 848 (228 cases received HFNC) Age 0-18 years	2-10 L/min for pre-adolescent, 5-50 L/min for adolescents	The rate of intubation and median PICU† LOS‡ with and without using HFNC	Using HFNC decreased 50% the need of intubation but didn't significant influence in mortalite and median PICU LOS
Kelly et al.[24] 2013 Retrospective observational	46% had bronchiolitis 28% had pneumonia 26% had other illnes 498 (all cases received HFNC) Age <2 years	Not given	Patient characteristics that predict success or failure of HFNC	RR¥ greater than 90th percentile for age, initial venous $PaCO_2$# greater than 50 mmHg, or pH less than 7.30 were associated with failure of HFNC therapy. A diagnosis of acute bronchiolitis was protective with respect to intubation following HFNC
Mayfield et al.[17] 2014 Prospective-retrospective observational case control	Infants with bronchiolitis 94 (61 cases received HFNC, 33 cases were treated with low-flow oxygen) Age <12 months	2 L/kg/min Max 10 L/min	Comparing HFNC with standard low-flow nasal oxygen in the clinical impact, in PICU admission and in adverse events	Non-responders requiring PICU admission could be identified early of HFNC treatment. There was four times lower risk to need PICU admission in HFNC group than standard therapy group. No serious adverse events
Long et al.[25] 2016 Prospective observational	69% had bronchiolitis 24% had pneumonia 7% had other illnes 71 (all cases received HFNC) Age 3-20 months	2 L/kg/min for the first 10 kg, then 0.5 L/kg/min thereafter	Evaluating HFNC use, failure rates, predictors of failure and adverse events	The therapy failure was 39%. Initial mean RR and HR¤ were higher in the non-responders group. One patient with asthma developed air leak syndrome
Milani et al.[18] 2016 Prospective observational	Infants with bronchiolitis 36 (18 cases received HFNC, 18 cases were treated with low-flow oxygen) Age <12 months	L/min=8 mL/kg x RR x0.3	Comparing the RR, respiratory effort, ability to feed, LOS, the duration of oxygen supplementation in the two groups	Improvements in the RR, respiratory effort and ability to feed were significantly faster in the HFNC group than the low-flow oxygen group. The HFNC group needed oxygen for 2 days less and LOS was 3 days shorter than in the low flow oxygen group
Söğütlü et al.[26] 2016 Prospective observational	66% had pneumonia 34% had bronchiolitis 32 (all cases received HFNC) Age 0-17 years	1-40 L/min	Improving in the RR, HR and SpO_2≠ and comparing patients with pneumonia and patients with bronchiolitis	The RR, HR and SpO_2 values were improved at the 1st hour after treatment. There was no significant difference between two diagnostic groups in clinical improving

*High-flow nasal cannula, ǂNasopharyngeal. †Pediatric intensive care unit, ‡Length of stay, ¥Respiratory rate, #Partial corbon dioxide, ¤Heart rate, ≠Peripheral capillary oxygen saturation, HFNC: High-flow nasal cannula, NP: Nasal prong, PICU: Pediatric intensive care unit, LOS: Length of stay, HR: Heart rate, RR: Respiratory rate, ED: Emergency department

Table 1. Overview of the 13 original studies including children receiving HFNC in the ED (continued)

Kepreotes et al.[18] 2017 Randomised controlled	Infants with bronchiolitis 202 (101 cases received HFNC, 101 cases were treated with low-flow oxygen) Age <24 months	1 L/kg/min	Comparing HFNC with standard low-flow nasal in time to weaning off oxygen, treatment failure and serious adverse events,	Time to weaning off oxygen did not differ significantly between two groups. The therapy failure was higher in the standard therapy group. No serious oxygen-related adverse events
Davison et al.[19] 2017 Retrospective observational	Infants with bronchiolitis 61 (all cases received HFNC) Age <24 months	0.6 to 3.3 L/kg/min	Improving in some physiological parameters (HR, RR, WOB[Θ]) and evaluating adverse events	The WOB, RR and HR reduced with using HFNC. No adverse events related to HFNC therapy
Vitaliti et al.[25] 2017 Randomised controlled	77.5% had bronchiolitis 17.5% had pneumonia 5% had asthma 60 (20 cases received HFNC, 20 cases were treated with CPAP[ϋ], 20 cases were treated with standard pharmacological treatment) Age 1-24 months	1-3 L/kg/min	Evaluating efficacy (RR, SpO_2, pH, $PaCO_2$, PaO_2[Þ] and PaO_2/FiO_2) and safety of HFNC and CPAP. Comparing the 2 NIV methods with standard pharmacological treatment	Both CPAP and HFNC were efficient in improving the clinical parameters, however CPAP was more effective than HFNC. CPAP had a better clinical course in LOS and in use of medication compared with HFNC and standard treatment
Franklin et al.[20] 2018 Multicenter randomised controlled	Infants with bronchiolitis 1472 (739 cases received HFNC, 733 cases treated with standard oxygen) Age <12 months	2 L/kg/min Max 25 L/min	Comparing HFNC with standard low-flow nasal oxygen in terms of treatment failure, LOS, duration of oxygen therapy, intubation PICU admission and adverse events	HFNC therapy had significantly lower rate of treatment failure than standard oxygen therapy. No significant differences were observed in the LOS, the duration of oxygen therapy, the intubation and the PICU admission. One patient from each group occured pneumothorax
Er et al.[26] 2018 Retrospective observational	60% had pneumonia 40% had bronchiolitis 154 (all cases received HFNC) Age 5-23 months	2 L/kg/min for infants and 1 L/kg/min for older children Max 25 L/min	Assessing early determining factors of unresponsiveness to HFNC therapy	On admission, lower SpO_2, SpO_2/FiO_2 ratio, venous pH, and higher pCO_2 were related with unresponsiveness. Also the reduction of RR, respiratory score, and SpO_2/FiO_2 ratio at the first hour was greater in the responsive group
Ballestero et al.[17] 2018 Prospective randomised	Patients with asthma 62 (30 cases received HFNC, 32 cases treated with standard oxygen) Age 1-14 years	2 L/kg/min for the first 10 kg, then 0.5 L/kg/min thereafter Max 60 L/min	Comparing HFNC with conventional oxygen therapy in the respiratory score, hospital discharge, LOS, need for additional therapies and side effects	HFNC was superior than conventional oxygen therapy for reducing respiratory distress within the first 2 hours. There were no significant differences in hospital discharge, LOS and need for additional therapies. No side effects occurred
Yurtseven et al.[22] 2019 Prospective observational	Infants with bronchiolitis 168 (88 cases received 1-L/kg/min HFNC flow rate and 80 cases 2-L/kg/min) Age <24 months	One group 2 L/kg/min and other group 1 L/kg/min Max 25 L/min	Comparing the HFNC flow rate of 1 L/kg/min (1 L) with 2 L/kg/min (2 L) in patients with severe bronchiolitis presenting to the pediatric emergency department	HFNC therapy with a 2 L/kg/min flow rate was not clinically more effective than 1 L/kg/min in patients with severe bronchiolitis. 1 L/kg/min ensured earlier impact and was well tolerated

[Θ]Work of breathing, [ϋ]continuous positive airway pressure, [Þ]Partial oxygen, HFNC: High-flow nasal cannula, NP: Nasal prong, PICU: Pediatric intensive care unit, LOS: Length of stay, HR: Heart rate, RR: Respiratory rate, ED: Emergency department

ventilation and reduces the effects of rebreathing.[33] It is stated that this mechanism is especially important in small children, since they have higher extrathoracic anatomical dead space.[34] In a study using computational fluid dynamics simulations of the CO_2 concentration within the upper airway model in a patient receiving HFNC, a nasopharyngeal washout phenomenon was observed and the amount of CO_2 cleared from the nasal cavity was found to increase in a flow-dependent manner over the range of flows simulated.[35] Another study utilizing neonatal piglets with lung injury has also indicated that HFNC could serve as a means of oxygenation support independent of supplemental oxygen administration by way of nasopharyngeal dead space elimination.[36]

The nostrils and the nasal passages have a large surface area and cause high resistance in the human airway.[37] HFNC delivers a flow that is equal to or exceeding the patient's peak inspiratory pressure via an appropriately placed nasal cannula, there by bypassing this area that has the highest resistance in the respiratory tract and preventing nasopharyngeal collapse which normally happens during spontaneous breathing.[38] Heated humidified gas also reduces airway resistance, increases mucus clearance and prevents atelectasis through improving mucociliary function.[39] These effects of HFNC can also play a role in decreasing the inspiratory resistance.

The respiratory muscles work hard in children with severe respiratory distress and increase energy consumption. If

this condition persists for a long time, respiratory muscle insufficiency may occur and intubation may be required. HFNC provides heated oxygen-rich gas, thereby the energy cost of heating the inspired gas to body temperature disappears, achieving more energy and preventing respiratory muscles failure.[33]

Creating positive end expiratory pressure (PEEP) is one of the most important mechanisms of action of HFNC and especially with this effect, it is accepted as a NIV modality.[33,38] Several studies have shown that HFNC ensure PEEP in both children and adults.[32] Particularly, PEEP in closed-mouth state has been reported to be markedly higher than in open-mouthed state.[16] In their study including 21 infants with acute respiratory syncytial virus bronchiolitis, Milesi et al.[40], found that only flows ≥6 L/min provided positive pharyngeal pressure throughout the respiratory cycle. PEEP can also prevent atelectasis and help lung recruitment, thus improve ventilation-perfusion stability, alveolar ventilation and oxygenation.

Initiation and Weaning

If we consider using HFNC therapy for any patient, we need to set up basically 2 variables: FiO_2, and flow rate. Another variable, the gas temperature, is usually kept constant about 1-2 °C below body temperature. FiO_2 is adjusted at 0.4 initially and can rise to 0.5-0.6 provided oxygen saturation (SpO_2) is >92%. In follow-up, FiO_2 is arranged up or down to achieve the target SpO_2, typically 92%-97%.[7] While there is no general acceptance about optimal initial HFNC flow rate, HFNC therapy is usually started with 4-6 L/min flow rate or more in non-newborn children.[41] The studies have generally suggested two types of HFNC flow rate preference; age-based protocol and weight-based protocol.[30,31] Hutchings et al.[42], who have reported one of the best age-based protocols of HFNC flow rate, have recommended 6 L/min for patients up to 1 month, 8 L/min for 1-12 months, 10 L/min for 1-4 years and 12 L/min for 5 years and over. Other age-based studies have advised 2 L/min for patients <6 months, 4 L/min for 6-18 months and 8 L/min for those aged 18-24 months; or 8-12 L/min for infants and 20-30 L/min for children.[31,41] Studies, which have suggested the HFNC flow rate to be according to weight, have mostly proposed flows such as 1 L/kg/min or 2 L/kg/min.[17,19,21] Although, some physiological studies reported that a flow rate ≥2 L/kg/min was required to achieve optimal effects, clinical studies have not supported this data.[15,22,38,40] Moreover, it has been indicated that a flow ≥2 L/kg/min was associated with a higher rate of discomfort and with a longer stay in the PICU.[15] In other age-based studies; while Long et al.[25] have used 2 L/kg/min HFNC flow rate for the first 10 kg, then 0.5 L/kg/min for every kilogram thereafter, Er et al.[28] have chosen 2 L/kg/min for infants and 1 L/kg/min for older children. According to our experience, HFNC therapy can be started with 6 L/min and adjusted up to 10 L/min for children with bronchiolitis.

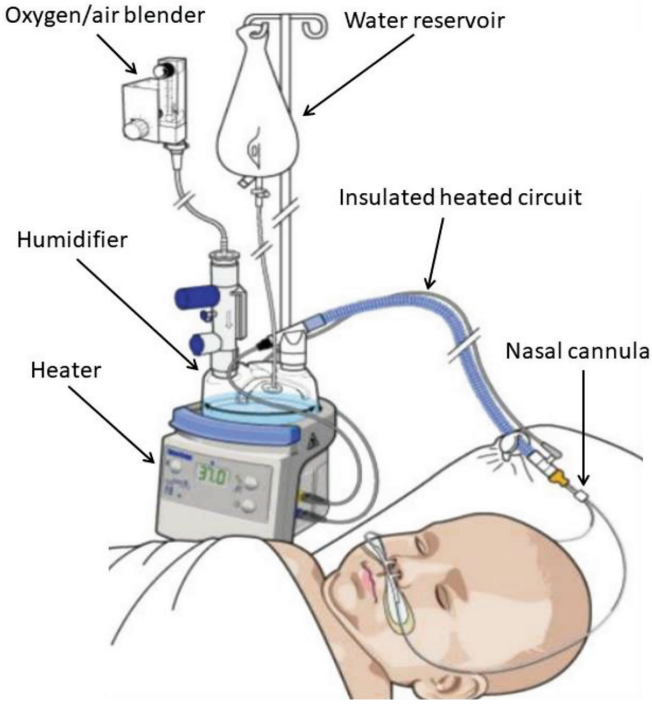

Figure 1. Components of the HFNC system: A oxygen/air blender, water reservoir, humidifier, heater, insulated heated circuit, and nasal cannula
HFNC: High-flow nasal cannula

Weaning is another uncertainty in the HFNC therapy. Few suggestions are available about it. Betters et al.[43], who have reported one of the most detailed weaning protocol, created a respiratory assessment score (RAS) based on six components [respiratory rate (RR), chest movement, intercostal retractions, xiphoid retractions, nasal flaring, and expiratory grunt], and scored each category 0, 1, or 2, for up to a total of 12 points. They assessed their patients for RAS every 12 hours. Patients, who have 6 or lower RAS, were weaned and started low-flow nasal cannula settings. Patients with a RAS of 7 or 8 had HFNC flow reduced by half, and patients scoring more than 8 were maintained on initial settings and evaluated during the next 12-hour shift. Although, this protocol could be appropriate in PICU, it may not be useful for ED, since patients are evaluated at long intervals. Hutchings et al.[42] suggested another HFNC weaning protocol that based on only their local guidelines. According to their approach, FiO_2 should be initially weaned to 0.4 before reducing flow rates by 0.5 L/min/h for neonates and 1 L/min/h for all other children provided the respiratory score remains under the initial trigger level. HFNC therapy is ceased when the flow rate reaches a value that is below than the initial oxygen saturations over 92% and a FiO_2 of 0.4 or less. This protocol could be more useful in EDs.

Oral Feeding in Patients Receiving HFNC

Children with respiratory distress usually present to the ED with insufficient oral intake that may increase the patient's agitation and exacerbate respiratory distress. This issue is more common particularly in infants. That is why, feeding is vital for patients on HFNC. However, no guidelines are available about enteral nutrition in children on HFNC. In a prospective, observational cohort study, Sochet et al.[44] observed that in full-term children with bronchiolitis without chronic medical conditions, enteral nutrition was well tolerated during all their HFNC flow rates and respiratory rates, and the delaying nutrition was related with a longer length of hospital stay. Slain et al.[45] also found similar results and showed that children receiving HFNC therapy, who received early enteral nutrition, had a shorter PICU length of stay and lower hospital charges, and in these patients feeding-related adverse events were rare. According to the studies and our practice, enteral nutrition and especially breastfeeding should not be withheld in this population as much as possible.

Clinical Effects

The first expectation from HFNC therapy is that it improves ventilation and oxygenation. Many studies have reported that HFNC provides a decline in RR and heart rate (HR) and improvement of SpO_2 and blood gas parameters.[41,46,47] In a prospective randomized study conducted on children with respiratory distress (age 1-24 months) in the ED, it has been reported that HFNC was efficient in improving SpO_2, arterial blood gas PaO_2, and PaO_2/FIO_2 significantly.[27] In other studies, it has been found that there was a significant reduction in RR and HR with HFNC therapy.[20,22]

HFNC treatment achieved wide popularity especially with reports showing to reduce the rate of intubation and PICU admission. Most previous studies reported that the overall rate of intubation and PICU admission declined in patients with bronchiolitis by HFNC therapy.[48-50] In a study conducted with nearly 850 children in the ED, Wing et al.[23], have showed that there was an 83% reduction in the odds of intubation in patients receiving HFNC compared with patients could not get HFNC. However, in a unique, multicenter, randomized controlled trial (RCT), comparing HFNC with standard oxygen therapy, Franklin et al.[21], have found no difference in intubation rate between two groups. Mayfield et al.[17], in a prospective pilot study conducted with 61 infants aged <12 months with bronchiolitis in the ED, have determined that children receiving HFNC therapy were four times less likely to need PICU admission than those receiving standard treatment. In another RCT including children with moderate bronchiolitis in the ED and comparing HFNC with standard therapy, Kepreotes et al.[19] have stated that, 61% of children who experienced treatment failure on standard therapy were rescued with high-flow heated humidified oxygen.[19]

Potential Side Effects and Safety

Although it is accepted that HFNC treatment is generally safe, some complications have been reported. Hegde and Prodhan[51] have presented 3 patients who had serious air leak syndrome complicating HFNC therapy in a case series which is still the most important publication on this subject. Additionally, in 12 clinical studies which were conducted in the ED, 2180 patients receiving HFNC were examined and totally 4 (0.18%) (3 pneumothoraces and 1 superficial burn) complications were detected.[16-29] Air leak syndrome has been reported in 6 patients after HFNC therapy. Of these 6 patients; two were infants with bronchiolitis, two had pneumonia (one a 16-year-old child, other one infant), one a 4-year-old child treated for asthma and the last one a 22-month-old boy was postextubation. However, all these patients had potential risks for air leak syndrome due to severe respiratory distress. Actually we do not know exactly whether they developed air leak syndrome before HFNC treatment. The findings of Franklin et al.[21] study, in which they compared HFNC therapy with standard oxygen therapy, support this suspicion. In this study, they evaluated 1472 patients (739 patients in HFNC group and 733 in standard-therapy group) and found that one case of pneumothorax occurred in HFNC group and one in standard-therapy group.

Abdominal distension can sometimes be seen in children on HFNC therapy and the therapy is discontinued because of that.[47,52] In a prospective observational study including 71 children aged 0-18 years receiving HFNC in ED, Long et al.[25] have reported that three patients developed abdominal distension.[25]

Infection development is also possible with HFNC therapy. Jhung et al.[53] have reported an outbreak of Ralstonia mannitolilytica related with use of a contaminated oxygen delivery device (Vapotherm 2000i) in the US in 2005. The device was modified by the producer right after. Since that time no further infectious complications have been reported.

Other mild complications, such as mucosal injury, epistaxis, and skin irritation, may also occur with HFNC therapy, but these complications are more common with CPAP therapy.[54] ten Brink et al.[52] conducted a prospective observational study with 72 children receiving HFNC in PICU and found that mucosal injury occurred in only one of them.

The Predictors of Unresponsiveness to HFNC

Treatment failure can be expected more frequently in patients receiving HFNC with more severe respiratory distress.[24,25,55] Although Wraight and Ganu[56] have found that heart disease was associated with a higher failure rate, they have reached this data with only 4 patients. Therefore, this result was not reliable. In a large study conducted with children younger than 2 years in the ED, it was reported that patients who were non-responders to HFNC therapy had a respiratory rate higher than the 90th percentile for age, an initial venous partial pressure of CO_2 ($PaCO_2$) >50 mmHg, and an initial venous pH>7.30.[24] In another retrospective cohort study of children aged 0-18 years with respiratory distress on HFNC in the ED, Er et al.[28] have showed that while the unresponsive group had lower SpO_2, SpO_2/FiO_2 ratio, and venous pH, and higher $PaCO_2$ on initiation, the diagnosis had no effect on the responsiveness to HFNC therapy. The authors suggested that patients receiving HFNC should be evaluated rapidly with blood gas and cardiorespiratory values. In this way, hypercarbia, respiratory acidosis, severe tachypnea and tachycardia can be determined early. That will enable us to identify patients who would not respond, and thus other treatment options would not be delayed.

Use of HFNC in the Pediatric Emergency Department

HFNC has recently become an indispensable treatment option for PED patients.[7] It has been most commonly used for children with bronchiolitis which were included in almost all studies conducted in the ED.[16-28] In all studies, in which HFNC therapy was compared with standard oxygen therapy, HFNC therapy was superior to standard oxygen in reducing the rate of intubation and PICU admission.[17,23] In the largest one ever, Franklin et al.[21] have found that the rate of treatment failure in infants receiving HFNC was 12% whereas in the standard-therapy group it was 23% (61% of those responded to HFNC rescue therapy). They have also determined that no significant difference was detected in mortality, length of hospital stay or the duration of oxygen therapy. The findings of Kepreotes et al.[19] study supported these results. In other prospective observational study comparing the effects of CPAP and HFNC in children with respiratory distress (age=1-24 months) in the emergency operative unit, Vitaliti et al.[27] have demonstrated that both CPAP and HFNC therapies were efficient in improving the clinical conditions of subjects with mild-to-moderate respiratory distress when compared with a control group, but clinical response in patients receiving CPAP was more favorable and rapid than in children treated with HFNC. In a retrospective cohort study, including 498 children younger than 2 years old receiving HFNC in the ED, in whom the most common final diagnosis was acute bronchiolitis (46%) followed by pneumonia (28%) and asthma (8%), Kelly et al.[24] have reported that the intubation rate was lower in patients having acute bronchiolitis than in others. But, the evidences of Long et al.[25] study have not supported this result. They have found that the failure rate was 43% and 35% in patients with acute bronchiolitis and pneumonia, respectively.

Another frequent reason for ED visits is acute asthma exacerbation which can require HFNC therapy. In studies involving children with acute asthma exacerbation in the ED, it has been shown that HFNC therapy had beneficial effects in these patients.[23,25,28] In a prospective randomized pilot study including children aged 1-14 years presenting to ED with moderate-to-severe asthma exacerbations, Ballestero et al.[29] compared HFNC with standard oxygen therapy and demonstrated that while HFNC was superior in reducing respiratory distress within the first 2 hours of treatment refractory to first line medication, it was not effective in decreasing the overall rates of PICU or ward admission. They also have reported that no side effects associated with HFNC use were observed.

HFNC may also support children having respiratory distress associated with other diseases, such as pneumonia, sepsis, croup, cardiac failure and apnoea, in the ED.[23-25,27] In a recent retrospective cohort study, Er et al.[28] evaluated 95 children aged 0-18 years with pneumonia receiving HFNC in the ED and found that the rate of therapy success was 81% in these patients. They also determined that HFNC provided improving significantly in the RR, HR, and respiratory score decreased at the first hour.

Conclusion

The majority of the studies on the use of HFNC in the PED were small observational studies and conducted in infants with bronchiolitis. The results of these studies have shown that HFNC was a feasible, safe and well-tolerated method for delivering oxygen and also reduced the rate of intubation and PICU admission.

However, there have been many points such as the initiation, the optimal flow rate, oral feeding and weaning that need to be clarified regarding this treatment. Although the initiation is controversial in older children, HFNC may be started with 6 L/min flow rate and then increased up to 12 L/min flow rate for children with bronchiolitis. FiO_2 is adjusted at 0.4 initially and can be rised to 0.5-0.6 provided oxygen saturation is >92%. Enteral nutrition and breastfeeding should be continued in these children. The following weaning protocol can be recommended: FiO_2 should be initially weaned to 0.4 before reducing flow rates by 0.5 L/min/h for neonates and 1 L/min/h for all other children providing the respiratory

score remains under the initial trigger level. HFNC therapy is stopped when the flow rate reaches a value that is below than the initial with the oxygen saturations over 92% and a FiO_2 of 0.4 or less.

Until further evidence is found, HFNC can be used as a respiratory support method in children. Despite beneficial effects of HFNC, still there is no comprehensive HFNC guideline and it has not been recommended by the international guidelines yet. Future researches are needed.

Ethics

Peer-review: External and Internal peer-reviewed.

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