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Respiratory support with heated humidified high flow nasal cannula in preterm infants

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The incidence of bronchopulmonary dysplasia (BPD) has not decreased over the last decade. The most important way to decrease BPD is by weaning the patient from the ventilator as soon as possible in order to reduce ventilator-induced lung injury that underlies BPD, and by using a noninvasive ventilator (NIV). Use of a heated, humidified, high flow nasal cannula (HHHFNC), which is the most recently introduced NIV mode for respiratory support in preterm infants, is rapidly increasing in many neonatal intensive care units due to the technical ease of use without sealing, and the attending physician's preference compared to other NIV modes. A number of studies have shown that nasal breakdown and neonatal complications were lower when using a HHHFNC than when using nasal continuous positive airway pressure (nCPAP), or nasal intermittent positive pressure ventilation. The rates of extubation failure during respiratory support were not different between patients who used HHHFNC and nCPAP. However, data from the use of HHHFNC as the initial respiratory support "after birth", particularly in extremely preterm infants, are lacking. Although the HHHFNC is efficacious and safe, large randomized controlled trials are needed before the HHHFNC can be considered an NIV standard, particularly for extremely preterm infants.

Key words: Bronchopulmonary dysplasia, High flow nasal cannula, Noninvasive ventilation, Preterm infant

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Introduction

The survival rates of preterm babies, particularly those at 24–26 weeks of gestational age (GA), have improved due to antenatal corticosteroid therapy, postnatal surfactant replacement therapy, and ventilator care. However, the incidence of bronchopulmonary dysplasia (BPD) in preterm babies has not declined over the last decade, with rates of 22% in Western countries[1] and 18% in Korea[2]. These results may be due to improved survival of very preterm infants with "new" BPD, which is caused by "arrested" development of alveoli and capillaries at early stages of lung development[3,4]. This is in contrast to the "classic" or "old" BPD that was described by Northway et al.[5] in relatively mature newborn babies receiving ventilator care.

Many studies have described ways to reduce the rate of BPD, starting from resuscitation at birth with noninvasive ventilator (NIV) and avoiding hyperoxia[6,7]. The most important way to prevent BPD is to wean the patient from the ventilator as soon as possible to reduce ventilator-induced lung injury causing BPD; and, using an NIV is crucial. NIV procedures have been increasingly adopted to reduce the use of invasive ventilators and the incidence of BPD. Frequently used NIVs in neonatal intensive care units (NICUs) are nasal continuous positive airway pressure (nCPAP), which is the most commonly used ventilator, nasal intermittent positive pressure ventilation (NIPPV), bi-level nCPAP (BiPAP), sigh CPAP

(SiPAP), and a heated, humidified high flow nasal cannula (HHHFNC)[8]. Sealing to the upper airway is critical in other NIV modes except HHHFNC, so the use of a skilled sealing technique with proper nursing care is essential, although nasal breakdown due to fitted nasal prongs occurs frequently[9]. Abdominal distension, called "CPAP belly," is common in patients using nCPAP, NIPPV, BiPAP, or SiPAP, which use fitted nasal prongs to deliver positive airway-distending pressure.

HHHFNC is the most recently introduced mode of NIV for respiratory support in preterm infants, and does not require sealing to the upper airway with fitted nasal prongs. Despite the lack of evidence supporting the efficacy and safety of HHHFNC in randomized controlled trials, it is commonly used in many NICUs due to the technical ease of use and the attending physician's preference for HHHFNC over other standard NIVs. Here, the mechanisms of action, efficacy, and safety of HHHFNC are described in comparison to nCPAP and NIPPV.

Mechanisms of action

Low flow nasal cannulas (flow rate less than 1 L/min) are used to deliver oxygen to preterm infants with BPD. The term "high flow nasal cannula" was described by Sreenan et al.[10]. HFNC, which is used to treat apnea of prematurity, can deliver airway-distending pressure comparable to that of nCPAP, and is as effective as nCPAP. However, flow rates >2 L/min cause mucosal dryness, airway dryness, and nosocomial infections, resulting in airway mucosal injury and airway obstruction due to mucous plugs[11,12]. Thus, a heated humidified gas delivery system was developed to overcome these shortcomings, and gas is delivered through a HFNC system, called a heated humidified high flow nasal cannula[13].

The Precision Flow (Vapotherm, Exeter, NH, USA) and the Optiflow Junior (Fisher & Paykel, Auckland, New Zealand) devices deliver gas temperatures up to 34°C and 33°C, respectively, and humidity up to 99% and 96%, respectively, at flow rates less than 4 L/min. As the flow rate increases, the temperature of the gas delivered is similar to that of a low flow rate; however, humidity decreases (up to 81.2% vs. 88.8%, respectively), when using the Precision Flow and Optiflow Junior devices at a flow rate of 8 L/min[14]. The temperature of gas delivered by the Precision Flow device at a flow rate of 0–8 L/min is lower than that of nCPAP (34.0°C vs. 34.5°C); however, humidity is significantly higher than that of nCPAP (83% vs. 76%)[15].

A HHHFNC can deliver positive airway-distending pressure to the lungs just as nCPAP does, if flow rate is greater than 2 L/min. However, unlike nCPAP, the pressure delivered by the HHHFNC is not constant or fixed, and varies widely according to the size of the nasal prongs, gas flow rate, size of the patient's airway, and airflow leakage through the nares or mouth[16,17]. Therefore, it is difficult to predict the pressure generated by a HHHFNC. More pressure can be generated if airflow leakage is decreased with nasal prongs, and if the flow rate is high. Sealing to the upper airway is critical for delivering positive airway-distending pressure during nCPAP. A chinstrap or pacifier is used to decrease airflow leakage through the mouth during nCPAP. However, unlike nCPAP, sealing the nasal prongs to nares is not necessary when using HHHFNC. Thus, the airway-distending pressure generated by HHHFNC is changed dynamically according to the infant's respiratory cycle, which is more physiological but is also a shortcoming[18].

Several studies have reported positive airway-distending pressure according to the flow rate of a HHHFNC. A flow rate of 2.5 L/min is equivalent to a positive airway pressure of 6 cmH_2O, and a flow rate of 1.6 L/min (preterm infants with body weight of 1,000 g) or 1.3 L/min (preterm infants with body weight of 500 g) is equivalent to positive airway pressure of 6 cmH_2O[10].

Although information on the mechanisms of action of a HHHFNC is limited, there are several proposed mechanisms[19]. (1) A HHHFNC delivers positive airway-distending pressure comparable to that of nCPAP. A linear relationship is observed between the flow rate of a HFNC and tracheal pressure in a neonatal piglet model. Tracheal pressure created by the HHHFNC is comparable to that of CPAP. Tracheal pressure is higher with a low-leak double prong (cannula fully occludes both nares) than with a high-leak single prong (cannula occludes only half the area of the nares). (2) A HHHFNC decreases airway resistance and improves gas exchange by washing out anatomic dead space in the upper airways due to the high gas flow. Anatomic dead space is relatively higher in infants, particularly in preterm infants (greater than 3 mL/kg in early infancy) compared to adults, but decreases with age[20]. Washing hypoxic and hypercapnic gas out of the dead space with oxygenated fresh gas is effective, particularly in preterm infants who have a larger anatomic dead space. (3) A HHHFNC improves gas conductance. (4) A HHHFNC reduces metabolic demands and reduces the burden of breathing due to the highly humidified heated gas.

Oxygenation has been shown to improve in a neonatal piglet model fitted with a HHHFNC, which may be due to increased flow rate, regardless of airflow leakage. Arterial oxygen tension (PaO_2) increases in a flow-dependent manner in a HHHFNC device as flow rate is increased to 2–8 L/min. A double prong with low leakage (cannula fully occludes both nares) improves oxygenation, while a single prong with high leakage (cannula occludes only half the area of the nares) improves CO_2 excretion or ventilation. However, PaO_2 did not increase with a CPAP device when it was 400 mmHg, as CPAP pressure was increased[19].

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Efficacy of HFNC compared to other NIV modes

1. Respiratory support after extubation

Holleman-Duray et al.[21] reported that the rate of reintubation after extubation failure is not different between HHHFNC and nCPAP groups in preterm infants 25–29 weeks of GA. Intraventricular hemorrhage (IVH), periventricular leukomalacia, necrotizing enterocolitis (NEC), retinopathy of prematurity, BPD, and mortality rates were also not different between the 2 groups. Ventilator duration was relatively shorter, and the rate of ventilator-associated pneumonia rather decreased in the HHHFNC group. Weight gain was greater in the HHHFNC group (P=0.016), which may have been due to reduced metabolic demands and burden of breathing because of the availability of highly humidified heated gas through the HFNC system[21].

Collins et al.[22] applied HHHFNC at a flow rate of 8 L/min and nCPAP at a pressure of 8 cmH_2O, and reported that extubation failure and weaning of invasive ventilator in patients with a HHHFNC was lower than that of nCPAP, but no difference was found in preterm (less than 28 weeks of GA) infants (22% in HHHFNC group vs. 34% in nCPAP group; odds ratio, 0.56, 95% confidence interval [CI], 0.26–1.22). Similar results were observed for extubation failure in relatively older infants who needed respiratory support after extubation (GA≥28 weeks; 15.1% in HHHFNC group and 11.4% in the nCPAP group; P=0.252); in this case, the investigators applied HHHFNC at a flow rate of 3 to 5 L/min and nCPAP at a pressure of 5 to 6 cmH_2O. Again, no differences were observed between the 2 groups on supplemental oxygen, incidence of BPD (20% in HHHFNC group vs. 16% in nCPAP group), or discharge from the hospital with oxygen[23].

In a noninferiority trial in Australia, Manley et al.[24] reported that HHHFNC is not inferior to nCPAP, while applying HHHFNC at a flow rate of 5 to 6 L/min and nCPAP at a pressure of 7 cmH_2O. The rate of extubation failure in patients with a HHHFNC is not inferior to that of nCPAP (34.2% in HHHFNC group vs. 25.8% in nCPAP group; risk difference, 8.4%; 95% CI, −1.9 to 18.7). Here, Manley et al.[24] found no differences were observed in BPD, pneumothorax, ventilator duration, or discharge from the hospital with oxygen. However, about half of the infants with HHHFNC treatment failure were successfully treated with nCPAP without reintubation[24]. After that study, the same authors reported results from follow-up studies, and concluded that HHHFNC is comparable to nCPAP for respiratory support after extubation in preterm infants. The rate of extubation failure was not different between the 2 groups[25].

On the other hand, Campbell et al.[26] reported that the rate of reintubation due to extubation failure, apnea, and bradycardia, were higher in the HFNC group (flow rate of 1.6 L/min) than in the CPAP group (pressure of 5 to 6 cmH_2O). However, the flow rate of HFNC was lower than that of other HHHFNCs, and they did not use the heated humidified gas.

Futhermore, Abdel-Hady et al.[27] reported that the HHHFNC group (flow rate of 2 L/min) showed longer duration of oxygen therapy and respiratory support compared to the nCPAP group (pressure of 5 cmH_2O).

HHHFNC was not different from nCPAP or NIPPV in respiratory support after extubation in a Cochrane meta-analysis[28].

2. Initial noninvasive respiratory support after birth

Only a few randomized controlled trials have been conducted to compare HHHFNC to nCPAP or NIPPV as initial respiratory support systems, particularly in extremely preterm infants.

Shoemaker et al.[29] reported that HHHFNC is superior to nCPAP as initial respiratory support in preterm infants less than 30 weeks of GA. The rate of intubation due to treatment failure was significantly less in the HHHFNC group (18% in HHHFNC group vs. 40% in nCPAP group). No differences in mortality rate, ventilator duration, BPD, or sepsis were observed between the HHHFNC and nCPAP groups[29]. However, the authors noted that ventilator duration decreased after introduction of the HHHFNC to the NICU (19.4 to 9.9 days). The use of HHHFNC increased to 64%, and use of nCPAP decreased to 4% after introduction of the HHHFNC, particularly in 95% and 12% of infants less than 30 weeks GA at the time during admission.

Yoder et al.[23] applied HHHFNC at a flow rate of 3 L/min to infants with a body weight 1,000 to <2,000 g, 4 L/min for those 2,000 to <3,000 g, and 5 L/min for those ≥3,000 g, and reported that treatment failure requiring intubation within 72 hours as a primary mode of respiratory support in infants greater than 28 weeks GA was not different between HHHFNC and nCPAP groups (10.8% in HHHFNC group vs. 8.2% in nCPAP group, P=0.344). However, the duration of respiratory support was longer in the HHHFNC group than in the nCPAP group.

Ciuffini et al.[30] reported preliminary results indicating that the incidence of treatment failure requiring intubation within 72 hours as a primary mode of respiratory support in 29- to 36-week GA infants were slightly higher in the HHHFNC group than that in the nCPAP group, although the differences were not statistically significant (12.9% in HFNC group vs. 5.4% in nCPAP group, P= 0.11).

Kugelman et al.[31] compared HHHFNC to NIPPV, and found that treatment failure as a primary mode of respiratory support for respiratory distress syndrome at birth was not different between the HHHFNC and NIPPV groups (28.9% in HHHFNC group vs. 34.2% in NIPPV group) in preterm infants (less than 35 weeks GA, and birth weight greater than 1,000 g). However, the failure rate was about 30%, which is much higher than that reported in other studies, although the mean GA was not significantly different (GA: 31.8±2.3 weeks vs. 32.0±2.3 weeks in HHHFNC and NIPPV groups, respectively).

In the INSURE study, "intubation, surfactant administration, and rapid extubation (InSurE)" (or extubated to nCPAP in cases of respiratory difficulty) did not decrease mortality or BPD in comparison with surfactant and mechanical ventilation[32]. Of those who had been successfully extubated or changed to nCPAP after InSurE due to respiratory difficulty, 41.7% required reintubation. However, Ovalle et al. reported that 30% of infants who received a HHHFNC after InSurE required reintubation, leading the authors to suggest that a HHHFNC could be comparable to nCPAP to prevent reintubation in patients treated with InSurE. Further randomized controlled trials are needed[33,34].

Safety

Collins et al.[22] reported that nasal trauma was significantly lower in the HHHFNC group than in the nCPAP group in preterm infants less than 32 weeks of GA (P<0.05). In a similar study, Collins et al.[35] reported that nasal trauma (scored by erythema, bleeding, or ulceration at 6 sites on the nose; score of 2.8 in the HHHFNC group and 11.7 in the nCPAP group) in preterm infants less than 32 weeks GA was significantly lower in the HHHFNC group than in the nCPAP group (P<0.001). The difference was more pronounced in preterm infants less than 28 weeks GA.

Nasal breakdown was significantly lower in the HHHFNC group than in the nCPAP group (9% in HHHFNC group vs. 16% in nCPAP group, P=0.047)[23]. No difference was observed during episodes of apnea of prematurity between the groups. Abdominal distension, which is common in patients receiving nCPAP (CPAP belly), and full enteral feeding days (>120 mL/kg/day) were not different, leading to the conclusion that a HHHFNC is comparable to nCPAP, particularly from a safety perspective (abdominal distension: 10% vs. 8%; full enteral feeding days: 18 vs. 17 days in HHHFNC and nCPAP groups, respectively).

Manley et al.[24] reported a significant reduction in nasal trauma in the HHHFNC group compared to that in the nCPAP group (39.5 % in HHHFNC group vs. 54.3% in nCPAP group, P=0.01) in preterm infants less than 32 weeks GA; however, the findings for neonatal outcomes such as mortality rate, pneumothorax, BPD, IVH, NEC, and ventilator duration, were not different. Nasal trauma decreased significantly in the HHHFNC group, but the incidence of nasal trauma in both groups was higher than that reported by other studies; this may have been due to the subjective nature of the nasal trauma diagnosis, which is made by the attending physicians or nurses based on determination of mild erythema to severe ulceration of the nose.

The incidence rates of nasal breakdown and neonatal complications, such as pneumothorax, BPD, IVH, NEC, patent ductus arteriosus, and sepsis, are not different between the HHHFNC and NIPPV groups[31]. The NIPPV set (positive end expiratory pressure, 6 cmH_2O; peak inspiratory pressure, 14–22 cmH_2O; and rate, 12–30 breaths/min), and HHHFNC set (flow rate started at 1 L/min and increased by 0.5–1 L/min according to the infant's weight and respiratory status) were similar to those in other studies. However, nasal trauma did not occur in both groups, which may have been related to the much shorter duration of noninvasive respiratory support than reported in other studies (4.0 days; range, 1.0–15.0 days in HHHFNC group vs. 2.0 days; range, 0.3–6.5 days in NIPPV group).

According to Rønnestad et al.[36], early-onset sepsis diagnosed at 2–7 days postnatally is mainly caused by nosocomial flora and is dominant in preterm infants (less than 28 weeks GA, or birth weight less than 1,000 g) receiving nCPAP. Those authors suggested that the increase in unexplained sepsis in patients receiving nCPAP is related to nasal mucosal breakdown and nasal injury by nCPAP. However, most studies considering safety of HHHFNC have reported that sepsis does not decrease in the HHHFNC group, and that there are no differences in sepsis between HHHFNC and other NIV modes. Further studies on nasal trauma and sepsis are therefore required. A Cochrane meta-analysis reported that HHHFNC is a safe mode of respiratory support after extubation. Significantly less nasal trauma and pneumothorax were reported in the HHHFNC group than those in the nCPAP group[28].

Conclusion

We do not have long-term experience with HHHFNC, the most recently introduced NIV mode for respiratory support in preterm infants, and few randomized controlled trials have investigated the efficacy and safety of HHHFNC. However, use of HHHFNC is increasing rapidly in many NICUs due to technical ease of use without sealing, and attending physicians prefer this mode of support due to its empirical efficacy compared to that of other NIV modes. Some researchers have concluded that the rate of extubation failure was higher[26], the duration of oxygen therapy was longer, and the duration of respiratory support was longer in the HHHFNC group compared to nCPAP group[27]. In addition, no weaning or withdrawal strategy for HHHFNC has been established[37]. HHHFNC may deliver unpredictably high airway-distending pressure to the lungs, which can cause airway trauma or air leakage.

Nasal breakdown and neonatal complications are significantly lower when using a HHHFNC than those of nCPAP or NIPPV. There were no significant differences in the rates of reintubation after extubation between HHHFNC and nCPAP. However, evidence supporting HHHFNC as initial respiratory support, particularly in extremely preterm infants, is unclear. The size of the nasal prongs must be considered according to airway size and

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body weight to allow air leakage between the prongs and nares. In summary, although evidence supporting the use of HHHFNC as a respiratory support after extubation is strong, data from studies in extremely preterm infants is still limited. A large randomized controlled trial is therefore needed before considering HHHFNC as an NIV standard, particularly in extremely preterm infants.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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