

Heated, Humidified High-Flow Nasal Cannula Versus Nasal CPAP for Respiratory Support in Neonates



WHAT'S KNOWN ON THIS SUBJECT: Heated, humidified high-flow nasal cannula (HHFNC) is a noninvasive mode of respiratory support that is commonly used in the majority of US NICUs. No large randomized trial has evaluated safety or efficacy of HHFNC.



WHAT THIS STUDY ADDS: This large randomized controlled trial suggests that HHFNC is as effective as nCPAP for noninvasive respiratory support and can be safely applied to a wide range of neonates.

abstract

BACKGROUND AND OBJECTIVE: Heated, humidified high-flow nasal cannula (HHFNC) is commonly used as a noninvasive mode of respiratory support in the NICU. The safety and efficacy of HHFNC have not been compared with other modes of noninvasive support in large randomized trials. The objective was to assess the efficacy and safety of HHFNC compared with nasal continuous positive airway pressure (nCPAP) for noninvasive respiratory support in the NICU.

METHODS: Randomized, controlled, unblinded noncrossover trial in 432 infants ranging from 28 to 42 weeks' gestational age with planned nCPAP support, as either primary therapy or postextubation. The primary outcome was defined as a need for intubation within 72 hours of applied noninvasive therapy.

RESULTS: There was no difference in early failure for HHFNC (23/212 [10.8%]) versus nCPAP (18/220 [8.2%]; $P = .344$), subsequent need for any intubation (32/212 [15.1%] vs 25/220 [11.4%]; $P = .252$), or in any of several adverse outcomes analyzed, including air leak. HHFNC infants remained on the study mode significantly longer than nCPAP infants (median: 4 vs 2 days, respectively; $P < .01$), but there were no differences between study groups for days on supplemental oxygen (median: 10 vs 8 days), bronchopulmonary dysplasia (20% vs 16%), or discharge from the hospital on oxygen (19% vs 18%).

CONCLUSIONS: Among infants ≥ 28 weeks' gestational age, HHFNC appears to have similar efficacy and safety to nCPAP when applied immediately postextubation or early as initial noninvasive support for respiratory dysfunction. *Pediatrics* 2013;131:e1482–e1490

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KEY WORDS

high-flow nasal cannula, CPAP, respiratory support, NICU

ABBREVIATIONS

BPD—bronchopulmonary dysplasia

F_IO₂—fraction of inspired oxygen

HHFNC—heated, humidified high-flow nasal cannula

lpm—liters per minute

NC—nasal cannula

nCPAP—nasal continuous positive airway pressure

Dr Yoder initiated the study design and implementation, participated in patient enrollment, and led data analysis and manuscript writing; Drs Stoddard and King participated in the study design and patient enrollment and contributed to manuscript writing and revisions; Drs Dirnberger and Li contributed to patient enrollment, manuscript writing, and revisions; and Dr Abbasi contributed to patient enrollment, data analysis, and manuscript writing and revisions.

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Respiratory failure remains a common problem in the NICU. Concerns with ventilator-induced lung injury have led to a concerted effort in many NICUs to avoid prolonged ventilator support through early application of noninvasive modes of respiratory support, most often nasal continuous positive airway pressure (nCPAP).^{1,2} CPAP systems are not always easily applied or well tolerated in the neonatal population. Difficulties with the application of nCPAP include complicated fixation techniques, positional problems, nasal trauma, and apparent agitation.^{3,4}

The use of increased nasal cannula (NC) flow to deliver positive airway pressure was initially described by Locke et al⁵ in 1991 in 13 preterm infants. They reported the potential to deliver positive pressure with NC flows up to 2 L per minute (lpm), given a large NC diameter (3 mm). They cautioned about indiscriminate use of higher flow rates via NC due to potential for unregulated pressure delivery. Ten years later Sreenan et al⁶ used the term “high-flow nasal cannula” in reporting that NC flows up to 2.5 lpm could be as effective as nCPAP for treating apnea of prematurity, and that delivered pressure via NC flow could be regulated by using esophageal pressure measurements. Standard NC systems routinely use inadequately warmed and humidified gas, limiting use of higher flow rates secondary to the risk of mucosal injury and nosocomial infection.^{7–9} To circumvent these concerns, heated, humidified high-flow nasal cannula (HHHFNC) systems were developed as possible alternatives to nCPAP for noninvasive respiratory support of neonates.

Over the past decade, HHHFNC use has become widespread across academic and nonacademic NICUs in the United States, as well as globally (R.H. Clark, personal communication, 2012; refs 10 and 11). The introduction of HHHFNC into clinical practice has not been

accompanied by apparent changes in neonatal outcome, but this has not been systematically studied in a randomized controlled approach. Early retrospective and observational studies suggested that HHHFNC can be applied safely and effectively as noninvasive respiratory management of premature infants with respiratory dysfunction.^{8,12–14} Despite increasing popularity, caution has been voiced due to concerns regarding both efficacy and safety of HHHFNC in comparison with other noninvasive modes.^{15–17}

The purpose of this randomized controlled trial was to test the null hypothesis that there is no difference between HHHFNC and nCPAP in preventing extubation failure when applied as noninvasive respiratory support modes for neonates with respiratory dysfunction.

METHODS

This was a prospective, randomized, unblinded controlled trial that was approved by the institutional review board of the University of Utah and by the institutional review board at each participating site (University Hospital, Primary Children’s Medical Center, and Intermountain Medical Center, Salt Lake City, UT; Utah Valley Regional Medical Center, Provo, UT; McKay Dee Regional Medical Center, Ogden, UT; Hebei Provincial Children’s Hospital, Shijiazhuang, China; Wilford Hall Medical Center, Lackland Air Force Base, TX; University of Pennsylvania Hospital, Philadelphia, PA). Informed parental consent was obtained before any study involvement. This study was registered at clinicaltrials.gov (NCT00609882).

Study Population

Infants were eligible for study inclusion if they met the following criteria: (1) birth weight ≥ 1000 g and gestational age ≥ 28 weeks and (2) at the time of randomization there was an intention

to manage the infant with either noninvasive (no endotracheal tube) respiratory support from birth initiated in the first 24 hours of life or noninvasive respiratory support at any age after a period of mechanical ventilation with an endotracheal tube. Infants were excluded from study participation for the following reasons: (1) birth weight < 1000 g, (2) gestational age < 28 weeks, (3) presence of active air leak syndrome, (4) concurrent participation in a study that prohibited HHHFNC, (5) abnormalities of upper and lower airways (Pierre-Robin, Treacher-Collins, Goldenhar, choanal atresia, cleft lip/palate), or (6) serious abdominal, cardiac, or respiratory malformations including tracheal esophageal fistula, intestinal atresia, omphalocele, gastroschisis, or diaphragmatic hernia.

Randomization

Infants were randomly assigned at each study site via opaque sealed envelopes in blocks of 10 by study site by using random-number generation. Randomization was stratified by the following: birth weight 1000 to 1999 g or ≥ 2000 g and age at randomization of ≤ 7 days or > 7 days of age.

Study Devices

No specific device for nCPAP or HHHFNC has shown superiority over another²; therefore, we did not dictate a particular approach for nCPAP or HHHFNC. nCPAP was provided by various interfaces including bubble, Infant Flow nCPAP System (in CPAP mode only, not for SiPAP; CareFusion, Yorba Linda, CA), and ventilator. Devices used for HHHFNC included Comfort Flo (Hudson RCI, Research Triangle, NC), Fisher and Paykel Healthcare (Irvine, CA), and Vapotherm (Stevensville, MD). Vapotherm devices (6 devices, 2000i) were provided on loan for use at 3 of the study sites.

Study Procedure

Management of HHHFNC

Nasal cannulas were applied per manufacturer suggestions with recommendations that the prong outer diameter occupy ~50% of the nares internal diameter. Free egress of flow around the cannula was routinely auscultated by respiratory therapy and nursing staff. Fraction of inspired oxygen (FiO₂) was initiated at the same value if the infant was on another mode of noninvasive support, but 5% to 10% higher if the infant was being extubated. Initial flow rate for HHHFNC (in lpm) was determined by the current infant weight as follows: (1) 1000 to 1999 g = 3 lpm, (2) 2000 to 2999 g = 4 lpm, and (3) ≥3000 g = 5 lpm. Flow rate could be increased within each weight category by a maximum of 3 lpm above the starting flow rate. We recommended increasing the flow rate in 1-lpm increments if (1) FiO₂ increased by >10% above the starting FiO₂, (2) pCO₂ increased by >10 mm Hg above the baseline value, (3) increased distress or retractions were noted, or (4) decreased lung expansion was noted on chest radiograph. We recommended decreasing the flow rate by 0.5- to 1.0-lpm increments if all of the following were sustained for at least a 4-hour period: (1) FiO₂ <30% and oxygen saturation within ordered parameters, (2) pCO₂ was maintained within ordered parameters, (3) no signs of significant distress were noted, and (4) lung expansion was deemed adequate, if chest radiograph was obtained (chest radiographs and blood gas measurements were obtained only as clinically indicated per the attending clinician).

Management of nCPAP

The recommended starting pressure for nCPAP was 5 to 6 cm H₂O or a value equivalent to the positive end-expiratory pressure level on ventilator support. nCPAP pressure could be

increased to a maximum of 8 cm H₂O on the basis of the same criteria used for escalating the HHHFNC flow rate. nCPAP support was weaned by using the same weaning criteria as for weaning from HHHFNC.

Discontinuation of Study Support

Transition to standard NC or oxygen hood therapy was recommended when the HHHFNC flow rate was weaned to <2 lpm or when nCPAP was weaned to 4 to 5 cm H₂O and the infant remained stable based on the above criteria, including an FiO₂ <30%.

Recommended Blood Gas and Oxygen Saturation Values

Oxygenation and ventilation goals were established by each site on the basis of internal protocols. Recommended saturation goals ranged from 85% to 98% depending on gestational age, retinopathy of prematurity risk, and presence of pulmonary hypertension. Recommended values for pCO₂ were 40 to 65 mm Hg for arterial blood gases and 45 to 0 mm Hg for capillary blood gases.

Primary Outcome

The primary outcome was defined by failure of the study support mode as determined by intubation within the first 72 hours of study support. Similar guidelines for intubation were used at each study site (Table 1). Crossover between HHHFNC and nCPAP was not permitted for the first 72 hours of study support. Infants "failing" either during intervention during the first 72 hours of support were required to be intubated. After the initial 72 hours of study support, or after failure requiring intubation, any mode of noninvasive respiratory support was allowed at the discretion of attending provider.

Secondary Outcomes

Data were collected until hospital discharge on all enrolled infants. Numerous

TABLE 1 Recommended Guidelines for Intubation From Optimized Noninvasive Respiratory Support with nCPAP or HHHFNC Support

Guidelines
Apnea despite 30 seconds of PPV
Heart rate <100 beats per minute and not increasing despite 30 seconds of PPV
FiO ₂ >0.6 to maintain SpO ₂ ≥88%
Frequent or severe apnea and bradycardia
More than 1 apnea event per 12-hour period requiring PPV
Persistent marked/severe retractions
Suspected airway obstruction (despite adequate suctioning)
Cardiovascular collapse (heart rate <60 beats per minute or shock)
Severe metabolic acidosis (arterial base deficit > -10)
Severe respiratory acidosis (arterial pCO ₂ >65 torr)

PPV, positive pressure ventilation; SpO₂, pulse oxygen saturation.

secondary outcomes were established a priori including the following: (1) total ventilator days, days of noninvasive support (nCPAP and/or HHHFNC), and oxygen use up to the time of discharge; (2) need for delayed intubation (beyond 72 hours of study support); (3) frequency of adverse events including significant apnea, pulmonary air leaks, feeding intolerance, abdominal distention, necrotizing enterocolitis, intestinal perforation, and late-onset nosocomial infection; (4) assessment of nasal mucosal injury and respiratory effort determined at specified intervals by using scoring systems previously reported by Woodhead et al⁸; (5) overall infant comfort (assessed by a bedside nurse and respiratory therapist at 24-hour intervals (by using a 3-point Likert scale); (6) the incidence of BPD (based on an oxygen reduction test)¹⁸; and (7) discharge from the hospital on oxygen. We also evaluated the impact of HHHFNC and nCPAP on time to establish full oral enteral feedings (≥120 mL/kg per day).

Statistical Methods

The risk of early failure of noninvasive respiratory support in this population

of infants was determined to be ~15% on the basis of a 2-year (2005–2006) retrospective review of NICU admissions at the University of Utah. We determined a 50% reduction in risk to be clinically significant. To reliably detect this difference between the 2 study groups with an α (type I error) of .05 (2-tailed) and a power of 80% ($\beta = .20$), we determined that a sample size of 190 infants per group was needed. We assumed a 10% loss from withdrawal or late exclusion and thus sought to enroll 210 infants in each study group.

The primary outcome was analyzed by χ^2 as an intention-to-treat analysis. χ^2 or Fisher's exact test were used for all other categorical comparisons. Student's *t* test was used for analysis of normally distributed continuous data. Mann-Whitney *U* test was applied for ordinal data or continuous data that were not normally distributed. Two-sided *P* values <0.05 were considered statistically significant, and no adjustments were made for multiple comparisons. Statistical analysis was performed by using SPSS (version 19; IBM, Armonk, NY).

Before study initiation we planned a single interim analysis to be performed after 50% accrual of study enrollment. Analysis was conducted by an external data safety monitoring committee by using predefined criteria for recommending either continuation or cessation of the trial.

RESULTS

A total of 432 infants from 8 level III NICUs were enrolled between December 2007 and April 2012. As shown in Fig 1, 220 infants were randomly assigned to nCPAP and 212 to HHHFNC. Outcomes were available for all study infants, including 1 infant in the nCPAP group whose parents withdrew consent for study participation after early nCPAP failure but allowed continued data collection until discharge from the

hospital. There were 5 deaths: 1 in the HHHFNC group (38 weeks, died at 48 days with severe pulmonary hypertension) and 4 in the nCPAP group (29 weeks at 12 days from acute encephalopathy, 31 weeks at 4 days from acute herpes simplex encephalitis, 34 weeks at 25 days from severe pulmonary hypertension, and 36 weeks at 100 days from severe pulmonary hypertension). Demographic characteristics were similar between the 2 groups at time of randomization (Table 2). More than 90% of the infants were <7 days of age at initial randomization with respiratory distress syndrome being the most common diagnosis.

There was no significant difference between nCPAP and HHHFNC in the primary outcome rate for failure of study mode and intubation within the first 72 hours of therapy (Table 3). Subgroup comparisons, including gestational age <32 weeks, mechanical ventilation at time of randomization, and study entry before 7 days of age, also revealed no differences in early respiratory failure by study mode. Adjustment for gestation, birth weight, ventilator support, surfactant therapy, and primary diagnosis did not alter the failure to identify a significant difference between the 2 study modes for early intubation (odds ratio: 1.67;

95% confidence interval: 0.79–3.52). All but 1 of 41 infants with early failure were intubated within 36 hours of study entry (median: 11 hours [25%] to 4–20 hours [75%]). Reasons for early failure and intubation were similar between both study modes and were as follows: increasing respiratory distress nCPAP ($n = 15$ [83%]) and HHHFNC ($n = 19$ [83%]; $P = .951$), increased FiO₂ nCPAP ($n = 9$ [50%]) and HHHFNC ($n = 9$ [39%]; $P = .539$), and severe apnea nCPAP ($n = 2$ [11%]) and HHHFNC ($n = 5$ [22%]; $P = .438$) (note: total numbers exceeded 41 because 18 infants had >1 reason cited for early failure and intubation). There was also no difference between centers for rates of early failure.

Although we found no difference in ventilator days, infants managed with nCPAP had fewer days of any positive pressure support (ventilator, nCPAP, or HHHFNC) as well as shorter duration of study mode support than infants managed by HHHFNC (median: 2 fewer days; Table 4 and Fig 2). By 7 days after study entry significantly more infants remained on HHHFNC ($n = 49$ [23%]) compared with nCPAP ($n = 20$ [9%]; $P < .001$). Despite the longer time on any positive pressure support for HHHFNC study infants, there was no difference in time to wean to room air. Diagnosis

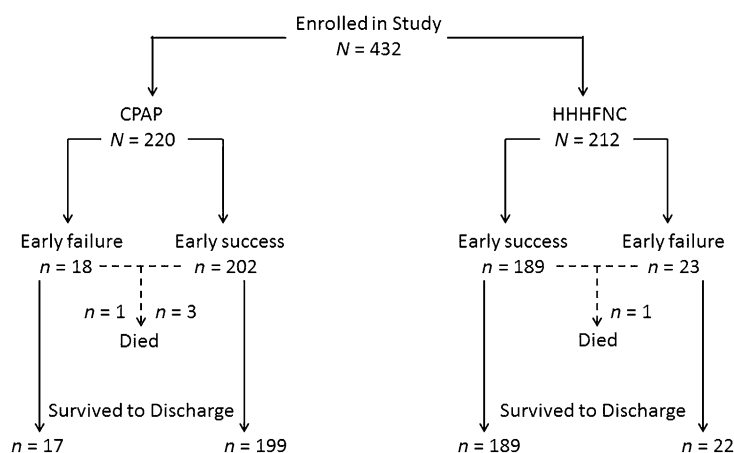


FIGURE 1
Study flowchart for infants by randomization mode.

of bronchopulmonary dysplasia (BPD) at 36 weeks' gestational age for infants born at <32 weeks' gestation was similar between study groups, as was the proportion of infants discharged from the hospital on oxygen (Table 4). After study entry, several potential adverse outcomes were closely monitored. As shown in Table 5, the overall adverse event rate was similar

between infants randomly assigned to nCPAP compared with HHHFNC. Importantly, the rate of any form of air leak occurring on study mode support was quite low and not different between groups. There were also no differences in the occurrence of increased apnea or sepsis, frequency of delayed intubation, or time to full oral feedings between study groups. The

only difference in measured adverse outcomes was a small but statistically significant higher rate for any nasal trauma during nCPAP support (Table 5). We compared infants successfully managed by either study mode with those with early study failure to determine if there were identifiable characteristics that might help to predict early failure. We did not find any differences in prestudy characteristics (Table 6). Specifically, gestational age, birth weight, surfactant therapy, prestudy respiratory support mode, respiratory support pressure, and FiO_2 were similar for infants experiencing early failure compared with those successfully managed by either nCPAP or HHHFNC.

Rates for early failure were not significantly different between devices ($P = .521$): Fisher and Paykel (16 of 143; 11%), VapoTherm (4 of 52; 8%), and Hudson Comfort-Flo (3 of 17; 18%). Likert scale assessments from the bedside nurse and respiratory therapist related to ease of care and patient comfort revealed no differences between the 2 study modes.

TABLE 2 Demographic Characteristics of Infants Randomly Assigned to nCPAP or HHHFNC

	nCPAP (n = 220)	HHHFNC (n = 212)
Gestational age, mean \pm SD, wk	33.2 \pm 3.2	33.5 \pm 3.6
<32 wk, n (%)	75 (34)	75 (35)
Birth weight, mean \pm SD, g	2108 \pm 782	2201 \pm 816
<2000 g, n (%)	111 (50)	100 (47)
Male, n (%)	137 (62)	137 (65)
Antenatal steroids, n (%)	71 (32)	80 (38)
Respiratory distress syndrome, n (%)	162 (74)	156 (74)
Study start age, median (25%–75%), h	20 (7–54)	24 (8–62)
Start age <7 d, n (%)	201 (91)	194 (92)
Prestudy support mode, n (%)		
Ventilator	145 (66)	146 (69)
nCPAP	46 (21)	39 (18)
Other (NC, hood O_2 , room air)	29 (13)	27 (13)
Prestudy surfactant, n (%)	129 (59)	142 (67)
Prestudy nitric oxide, n (%)	18 (8)	13 (6)
Prestudy caffeine, n (%)	66 (30)	58 (27)

$P > .05$ for all comparisons.

TABLE 3 Early Respiratory Failure in Infants Managed With nCPAP and in Those Managed With HHHFNC

	nCPAP (n = 220)	HHHFNC (n = 212)	OR (95% CI) ^a
Early failure, all	18 (8.2)	23 (10.8)	1.37 (0.71–2.61)
<32 weeks' gestational age	5/75 (6.7)	3/75 (4.0)	0.58 (0.13–2.53)
Prestudy ventilator	9/145 (6.2)	17/146 (11.6)	1.89 (0.86–4.63)
Start age <7 d	16/201 (8.0)	23/194 (11.9)	1.56 (0.80–3.04)

Data are shown as n (%). Data in rows 3–5 are also shown as number of failures/number of infants (%). CI, confidence interval; OR, odds ratio.

^a Unadjusted.

TABLE 4 Respiratory Support Outcomes Among Infants Randomly Assigned to nCPAP Compared With HHHFNC

	nCPAP (n = 216)	HHHFNC (n = 211)	P
Days on study mode	2 (1–4)	4 (2–7)	<.001
Delayed use of other study mode, n (%)	31 (14)	19 (9)	.096
Days ventilated	2 (1–4)	2 (1–5)	.476
Days any positive pressure support	4 (2–8)	6 (3–11)	<.001
Days supplemental O_2	8 (5–24)	10 (5–27)	.357
BPD, ^a n (%)	12/73 (16)	15/75 (20)	.575
Home oxygen, n (%)	38 (18)	40 (19)	.698
Age at discharge	25 (13–47)	25 (14–49)	.756

Data are shown as medians (25%–75%) unless otherwise indicated.

^a Only surviving infants <32 weeks' gestational age at birth.

DISCUSSION

In this multicenter randomized trial involving neonates ≥ 28 weeks' gestational age undergoing planned non-invasive respiratory support, we found no significant difference between HHHFNC and nCPAP with regard to the primary outcome of intubation within the initial 72 hours of support. In addition, we found no differences between infants randomly assigned to nCPAP compared with HHHFNC for several respiratory outcomes, including duration of oxygen supplementation, diagnosis of BPD, or discharge from the hospital on oxygen. Despite concerns over unregulated/unmonitored pressure delivery during HHHFNC support, we found no differences in the occurrence rate for any form of air

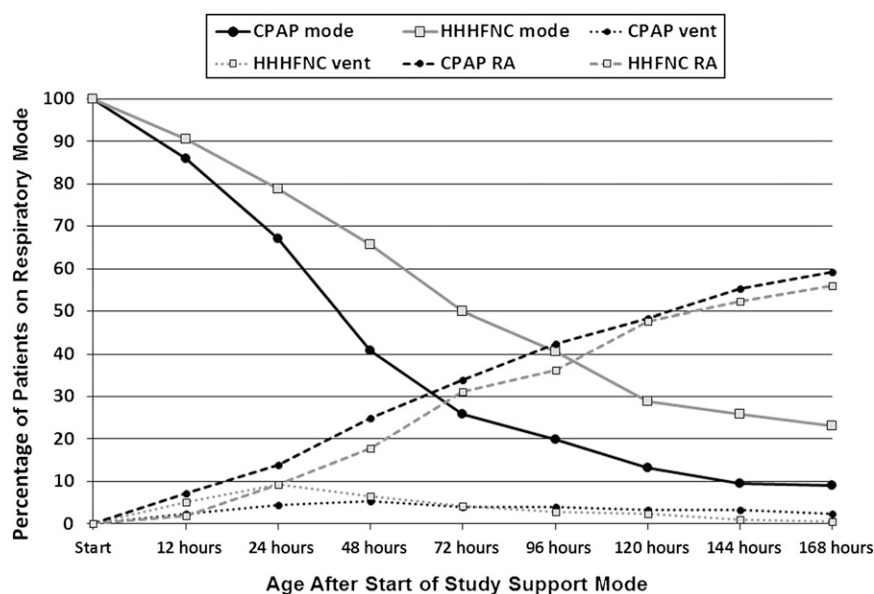


FIGURE 2

Infants randomly assigned to nCPAP (black line) had significantly shorter duration of study support mode compared with infants randomly assigned to HHHFNC (gray line); $P < .01$. There were no significant differences between study groups for duration of ventilator support (dotted lines) or time to wean to room air (dashed lines) in the 7 days after study entry. RA, room air.

TABLE 5 Occurrence Rates for Secondary Outcomes in the nCPAP Compared With the HHHFNC Study Group

	nCPAP (n = 220)	HHHFNC (n = 212)
Any adverse event	46 (21)	52 (25)
Air leak	5 (2)	1 (<1)
Increased apnea	15 (7)	23 (11)
Confirmed sepsis	7 (3)	7 (3)
Confirmed NEC	4 (2)	2 (1)
Reintubation, any	25 (11)	32 (15)
<72 hours	18 (8)	23 (11)
<7 days	21 (10)	23 (11)
No nasal trauma	180 (84)	187 (91)*
Abdominal distention	17 (8)	21 (10)
Days to full oral feedings, median (25%–75%)	17 (8–35)	18 (8–41)
Death	4 (2)	1 (<1)

Data are shown as n (%) unless otherwise indicated. * $P = .047$. NEC, necrotizing enterocolitis.

leak. The outcome results from this relatively large randomized trial indicate that the use of HHHFNC, as described in this report, appears to be as effective and as safe as nCPAP in this population of infants.

The actual approach to “high-flow” nasal cannula must be carefully considered in evaluating all studies. Some investigators have described “high-flow” in the presence of flow limited to 1 to 2 lpm and in the absence of a well-heated, humidified gas source for flow.

Flow limitation has been based on earlier studies from Locke et al⁵ and Sreenan et al⁶ suggesting the potential for high, unregulated positive airway pressure. Over the past decade, systems have been designed to allow much higher flow rates (2–8 lpm for neonates and up to 50 lpm in adults) accompanied by optimal heating (37°C) and humidification (100%) of the delivered gas. We, and others, have defined this system of NC therapy as heated, humidified high-flow nasal cannula or

HHHFNC.¹⁹ Recent studies have reported much lower airway pressures using HHHFNC, both indirectly via pharyngeal or esophageal pressure measurement and, in an animal model of neonatal respiratory distress, directly via intra-tracheal pressure monitor.^{20–23} The importance of the NC interface in the potential delivery of airway pressure should not be minimized. In recent neonatal studies, external NC diameters were typically limited to <3 mm. This size appears to be a critical dimension for neonatal HHHFNC, because Locke et al⁵ demonstrated that high airway pressures were measurable with a cannula diameter of 3 mm but not when the cannula was 2 mm in diameter. All infants in our study were managed with NC having an external diameter of <3 mm, with 95% measuring <2.0 mm.

Several retrospective and observational studies have been published suggesting that HHHFNC may be effective and safe in managing preterm infants with respiratory dysfunction.^{8,12–14} It is important to differentiate findings from these reports from those of other investigations in which high-flow nasal cannula has been applied with the use of inadequately heated/humidified gas at significantly lower flow rates. Abdel-Hady et al²⁴ reported that weaning from nCPAP to high-flow NC limited to 2 lpm was associated with longer duration of oxygen and respiratory support compared with infants maintained on nCPAP until weaned directly to room air. In their study, not only was NC flow rate limited but the gas conditioning may have been inadequate. Campbell et al²⁵ reported in 40 infants that “HF-CPAP” [high-flow CPAP], administered via standard NC, was less effective at preventing reintubation than nCPAP. There were limitations in NC flow rate (range: 1.4–1.7 lpm) and gas conditioning similar to those in the Abdel-Hady et al study, and “HF-CPAP”

TABLE 6 Comparison of Prerandomization Variables Between Study Infants Successfully Managed With Those With Early Support Mode Failure (Intubation)

	Treatment Success (<i>n</i> = 391)	Treatment Failure (<i>n</i> = 41)
Gestational age, mean ± SD, wk	33.3 ± 3.4	33.8 ± 3.1
Birth weight, mean ± SD, g	2148 ± 815	2227 ± 662
Antenatal steroids, <i>n</i> (%)	142 (36)	9 (22)
Prestudy surfactant, <i>n</i> (%)	244 (62)	27 (66)
RDS, <i>n</i> (%)	283 (72)	35 (85)
Study start age, median (25%–75%), h	21 (8–60)	27 (8–76)
Prestudy support mode, <i>n</i> (%)		
Ventilator	265 (68)	26 (63)
nCPAP	74 (19)	11 (27)
Other	52 (13)	4 (10)
Prestudy PAW, mean ± SD, cm H ₂ O	7.9 ± 2.1	7.7 ± 2.1
Prestudy FiO ₂ , mean ± SD	0.26 ± 0.10	0.27 ± 0.07

P > .05 for all comparisons. PAW, mean airway pressure; RDS, respiratory distress syndrome.

pressures were assumed rather than measured. The importance of adequate gas conditioning to upper and lower airway function is well described and includes reduced metabolic work, maintained ciliary function, prevention of airway desiccation and squamous epithelial cell injury, reduced inspiratory work of breathing, and improved lung mechanics.^{7,19,26–28}

With the inclusion of HHHFNC as a mode of “positive pressure” support, we found a slight but significant increase in days of any positive pressure support among infants randomly assigned to HHHFNC. This increase was associated with an extended use of HHHFNC in that study group. The reasons for this are unclear. We were not able to identify differences between groups in bedside nurse or respiratory therapist assessment of patient comfort, device humidification, or ease of use. This result is in contrast to recent pediatric and adult studies reporting improved patient comfort with HHHFNC compared with nCPAP.^{29,30} Although we did not find a measureable difference in nursing/respiratory therapist assessment, a potential “preference” by care providers may still have existed and contributed to the median 2-day increased time infants in the HHHFNC study group were managed on the study mode. Despite the difference in duration of positive pressure support

we did not observe sustained long-term effects between infants managed on nCPAP compared with HHHFNC based on similar duration of oxygen support, BPD rates among preterm infants, length of hospitalization, and home oxygen use.

Similar to the study by Miller and Dowd¹³ we did not identify any difference in preventing early intubation between the different HHHFNC devices used. However, numbers were small and the power to detect any difference was limited.

There are several limitations to our study. First, the study groups could not be blinded. Given that more infants in the nCPAP group were switched to HHHFNC after the initial 72-hour study window, it is possible that HHHFNC may have been preferred by the bedside providers. In addition, in some centers it became more difficult over time to get permission to approach parents about study participation due to clinical provider preference for 1 mode of support over the other (more often HHHFNC than nCPAP); given limited study resources we were unable to track this additional source of potential study bias. Thus, some degree of bias cannot be completely ruled out. We did not measure pressure at any point in the airway. Other studies have measured these pressures in similar or smaller infant populations by using

flow rates comparable to those we used.^{21–23} Given the large number of infants enrolled and the multiple centers participating, we determined that measurement efforts would be problematic. We did restrict enrollment to infants ≥28 weeks’ gestational age. This restriction was due to the presence of competing studies initiated at several centers before the HHHFNC/nCPAP trial that involved infants <28 weeks and/or <1000 g, and in which the use of HHHFNC was specifically proscribed. Other large randomized trials will be needed to investigate the efficacy and safety of HHHFNC use in this population. Because the majority of infants had a primary diagnosis of respiratory distress syndrome, we cannot necessarily infer that the apparent effectiveness and safety of HHHFNC compared with nCPAP will be found for all types of neonatal respiratory diseases. Finally, we did not limit participation to only those infants being extubated from mechanical ventilator support. Approximately one-third of the study population was randomly assigned before any mechanical ventilation, and the majority were already on early CPAP support. Given the significant trend over the past decade to use noninvasive modes of respiratory support to prevent intubation and mechanical ventilation, we decided that it would be important to include any infants deemed candidates for nCPAP as appropriate study participants. We found similar early failure rates regardless of prestudy respiratory support mode, suggesting this was a reasonable assumption.

By the study design, we planned to achieve 80% power to detect a 50% risk reduction in early intubation between nCPAP and HHHFNC by assuming a pooled outcome rate of 15% and 420 subjects. The actual pooled primary outcome rate observed was 9.5% in the study based on a total of 432 study

patients. On the basis of the actual n and observed outcome rates, we obtained 80% power to detect a 60% relative risk reduction. Assuming the observed rates for early intubation remain the same (8.2% vs 10.8%), a total of 3000 infants would need to be randomly assigned to the 2 study groups to demonstrate statistical significance with a power of 80% and a P value <0.05 .

CONCLUSIONS

For the conditions represented in this population of infants ≥ 28 weeks' gestational age, HHHFNC appears to have similar clinical efficacy and safety to nCPAP as a mode of noninvasive respiratory support. This finding was evident whether HHHFNC was used as the initial mode of support or when

primarily applied at the time of extubation. Additional large randomized trials are needed to evaluate the use of HHHFNC among smaller preterm infants as well as to compare different devices for and approaches to administering HHHFNC.

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