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Heated, Humidified High-Flow Nasal Cannula vs Nasal Continuous Positive Airway Pressure for Respiratory Distress Syndrome of Prematurity
A Randomized Clinical Noninferiority Trial

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IMPORTANCE Heated, humidified high-flow nasal cannula (HHHFNC) has gained increasing popularity as respiratory support for newborn infants thanks to ease of use and improved patient comfort. However, its role as primary therapy for respiratory distress syndrome (RDS) of prematurity needs to be further elucidated by large, randomized clinical trials.

OBJECTIVE To determine whether HHHFNC provides respiratory support noninferior to nasal continuous positive airway pressure (nCPAP) or bilevel nCPAP (BiPAP) as a primary approach to RDS in infants older than 28 weeks' gestational age (GA).

DESIGN, SETTING, AND PARTICIPANTS An unblinded, monocentric, randomized clinical noninferiority trial at a tertiary neonatal intensive care unit. Inborn infants at 29 weeks 0 days to 36 weeks 6 days of GA were eligible if presenting with mild to moderate RDS requiring noninvasive respiratory support. Criteria for starting noninvasive respiratory support were a Silverman score of 5 or higher or a fraction of inspired oxygen higher than 0.3 for a target saturation of peripheral oxygen of 88% to 93%. Infants were ineligible if they had major congenital anomalies or severe RDS requiring early intubation. Infants were enrolled between January 5, 2012, and June 28, 2014.

INTERVENTIONS Randomization to either HHHFNC at 4 to 6 L/min or nCPAP/BiPAP at 4 to 6 cm H_2O.

MAIN OUTCOMES AND MEASURES Need for mechanical ventilation within 72 hours from the beginning of respiratory support. The absolute risk difference in the primary outcome and its 95% confidence interval were calculated to determine noninferiority (noninferiority margin, 10%). An intention-to-treat analysis was performed.

RESULTS A total of 316 infants were enrolled in the study: 158 in the HHHFNC group (mean [SD] GA, 33.1 [1.9] weeks; 52.5% female) and 158 in the nCPAP/BiPAP group (mean [SD] GA, 33.0 [2.1] weeks; 47.5% female). The use of HHHFNC was noninferior to nCPAP with regard to the primary outcome: failure occurred in 10.8% vs 9.5% of infants, respectively (95% CI of risk difference, −6.0% to 8.6% [within the noninferiority margin]; $P = .71$). Significant between-group differences in secondary outcomes were not found between the HHHFNC and nCPAP/BiPAP groups, including duration of respiratory support (median [interquartile range], 4.0 [2.0 to 6.0] vs 4.0 [2.0 to 7.0] days; 95% CI of difference in medians, −1.0 to 0.5; $P = .45$), need for surfactant (44.3% vs 46.2%; 95% CI of risk difference, −9.8 to 13.5; $P = .73$), air leaks (1.9% vs 2.5%; 95% CI of risk difference, −3.3 to 4.5; $P = .70$), and bronchopulmonary dysplasia (4.4% vs 5.1%; 95% CI of risk difference, −3.9 to 7.2; $P = .79$).

CONCLUSIONS AND RELEVANCE In this study, HHHFNC showed efficacy and safety similar to those of nCPAP/BiPAP when applied as a primary approach to mild to moderate RDS in preterm infants older than 28 weeks' GA.

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Owing to its potential of reducing lung injury associated with mechanical ventilation, the use of noninvasive respiratory support, particularly nasal continuous positive airway pressure (nCPAP), has become a common strategy for early respiratory management of preterm infants.[1,2] In recent years, heated, humidified high-flow nasal cannula (HHHFNC) has increased in popularity in high-resource countries as an alternative form of noninvasive respiratory support for newborn infants.[3-5] In contrast to nCPAP, for which the rationale is essentially based on the provision of a continuous distending pressure, multiple mechanisms have been suggested to explain HHHFNC functioning, such as washout of the nasopharyngeal dead space, optimal gas conditioning, and provision of a variable distending pressure.[6-9] The HHHFNC approach has been applied in the neonatal intensive care unit (NICU) in a variety of clinical situations: weaning from nCPAP,[10] preventing apnea of prematurity,[11] following extubation,[3,4,12-14] and as primary therapy for respiratory distress syndrome (RDS).[15] Compared with nCPAP, HHHFNC offers ease of use,[16] reduced risk of nasal injuries,[17] better infant tolerance with improved feeding, and bonding.[18,19]

Despite its increasing popularity, only a few large randomized clinical trials (RCTs) have been conducted to assess the efficacy and safety of HHHFNC in newborn infants.[15,20,21] They mostly were performed to evaluate the use of HHHFNC following extubation in infants younger than 32 weeks' gestational age (GA).[15,20,21] Two studies investigated the role of HHHFNC as initial treatment for RDS. Yoder et al[15] compared HHHFNC vs nCPAP either following extubation or as a primary approach to RDS in infants born between 28 and 42 weeks' GA. Kugelman et al[22] designed a pilot study of HHHFNC as a primary approach to RDS in infants born earlier than 35 weeks' GA and having a birth weight greater than 1000 g, with a limited number of patients enrolled.

As nCPAP is currently considered the gold standard for early respiratory management[2,23] and considering the benefits associated with HHHFNC compared with nCPAP,[16-19] the objective of our study was to evaluate whether HHHFNC provides respiratory support noninferior to nCPAP or bilevel nCPAP (BiPAP) when applied exclusively as a primary approach to mild to moderate RDS in preterm infants older than 28 weeks' GA.

Key Points

Question Does heated, humidified high-flow nasal cannula provide respiratory support noninferior to nasal continuous positive airway pressure (nCPAP) or bilevel nCPAP (BiPAP) as a primary approach to mild to moderate respiratory distress syndrome in infants older than 28 weeks' gestational age?

Findings In this randomized clinical noninferiority trial of 316 infants, the use of heated, humidified high-flow nasal cannula was noninferior to nCPAP/BiPAP with regard to the primary outcome: failure, defined as need for mechanical ventilation within 72 hours, occurred in 10.8% vs 9.5% of infants, respectively.

Meaning In this study, HHHFNC showed efficacy and safety similar to those of nCPAP/BiPAP when applied in infants older than 28 weeks' gestational age.

Methods

Study Design and Patients

A prospective, monocentric, unblinded, randomized clinical noninferiority trial was performed. The trial protocol can be found in the Supplement. Infants were eligible for the study if they matched the following inclusion criteria: (1) GA of 29 weeks 0 days (29^{+0} weeks) to 36 weeks 6 days (36^{+6} weeks); (2) mild to moderate RDS requiring noninvasive respiratory support, characterized by a Silverman score of 5 or higher or a fraction of inspired oxygen (FIO_2) greater than 0.3 for target saturation of peripheral oxygen (SpO_2) 88% to 93%; and (3) parental consent obtained. Patients were ineligible if they presented with the following: (1) severe RDS requiring early intubation according to the American Academy of Pediatrics guidelines for neonatal resuscitation[24]; (2) major congenital anomalies that might affect respiratory outcomes; or (3) severe intraventricular hemorrhage. The ethical committee of the Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano approved the study. Parents provided written informed consent before patient enrollment.

Randomization

Block randomization was applied, with a block size of 4. Infants were stratified according to GA: 29^{+0} to 32^{+6} weeks, 33^{+0} to 34^{+6} weeks, and 35^{+0} to 36^{+6} weeks. Infants born from multiple gestations were assigned by individual randomization. A sequentially numbered, sealed, opaque envelope of the appropriate GA stratum was opened by clinicians if all the criteria for enrollment were matched.

Study Intervention

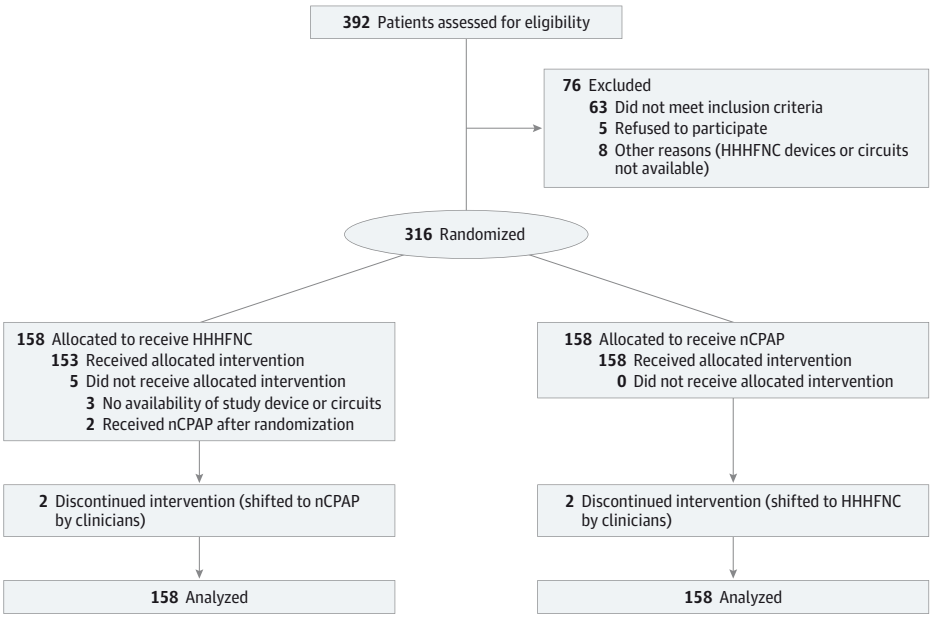
All the infants enrolled had chest radiography performed before starting respiratory support. The infants assigned to HHHFNC were supported by Vapotherm-Precision Flow. Nasal cannula size was chosen, according to manufacturer suggestions, so that the prongs occupied approximately 50% of the nares. The HHHFNC flow was started at 4 to 6 L/min and increased to a maximum of 6 L/min if the FIO_2 was increased greater than 0.1 of the starting value or for intensification of respiratory distress as assessed by Silverman score.

Nasal CPAP was provided by SiPAP (Viasys Healthcare). The starting pressure was set at 4 to 6 cm H_2O and the pressure was increased up to 6 cm H_2O according to the same criteria for altering HHHFNC flow. Moreover, in the nCPAP group, infants were shifted to BiPAP in the case of more than 4 episodes of apnea per hour or more than 2 episodes per hour requiring positive pressure ventilation or if deemed by clinicians because of increased work of breathing. The BiPAP was set with a starting rate of 30 breaths/min, inspiratory time of 0.7 to 1 second, and a mean airway pressure of 6 to 8 cm H_2O.

Surfactant (Curosurf; 200 mg/kg) was administered in the case of increased FIO_2 greater than 0.35 to a target SpO_2 of 86% to 93%, by the INSURE (intubation, surfactant, extubation) technique.[25,26]

Criteria for intubation and mechanical ventilation were the following: (1) persistent FIO_2 greater than 0.40 to a target SpO_2

Figure 1. The CONSORT Flow Diagram



HHHFNC indicates heated, humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure.

of 86% to 93% after surfactant administration; (2) severe apnea (>4 apnea episodes per hour or >2 apnea episodes per hour requiring positive pressure ventilation); and (3) persistent $PaCO_2$ greater than 70 mm Hg and pH lower than 7.20 despite application of noninvasive respiratory support. Extubation criteria were the following: (1) FIO_2 less than 0.30 to target SpO_2; (2) $PaCO_2$ less than 65 mm Hg and pH higher than 7.25; and (3) adequate spontaneous breathing drive.

Weaning was started by decreasing the HHHFNC flow by 1 L/min or nCPAP pressure by 1 cm H_2O if infants presented with an FIO_2 less than 0.30 to target SpO_2 and minimal or no signs of respiratory effort. The respiratory support was discontinued according to the study protocol for flow of 2 L/min or less or pressure of 2 cm H_2O or less.

Primary and Secondary Outcomes

The primary noninferiority outcome was the respiratory support failure determined by the need for mechanical ventilation within 72 hours from the beginning of the study mode. Secondary outcomes were established a priori. Respiratory outcomes included days receiving respiratory support, days receiving noninvasive respiratory support, and days receiving supplemental oxygen; days receiving caffeine treatment; need for surfactant; rate of air leaks; and rate of bronchopulmonary dysplasia (BPD).[27] Other secondary outcomes were rate of sepsis (confirmed by positive results on blood culture), necrotizing enterocolitis, patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, death, and the combined outcome including all the previous outcomes plus rates of air leaks and BPD. Secondary outcomes also included the number of days when full enteral feeding was achieved (≥120 mL/kg per day), body weight at discharge, exclusive breastfeeding at discharge, and length of hospitalization. Data were collected until discharge to home.

Statistical Analysis

According to a retrospective analysis for the 2-year period of 2009 through 2010, the risk of failure while receiving nCPAP/BiPAP in our center for infants older than 28 weeks' GA was 15%. The sample size was computed considering a noninferiority margin for HHHFNC of 10% above the failure rate of nCPAP/BiPAP, $P = .05$, and a power of 80%. We determined that 316 patients were required to assess noninferiority for HHHFNC with a 1-tailed 95% confidence interval (equivalent to a 2-tailed 90% confidence interval). The 95% confidence interval of the risk difference or difference in medians (Hodges-Lehmann median difference)[28] was calculated for all the outcomes using SAS/STAT version 9.2 statistical software (SAS Institute, Inc). Dichotomous outcomes were compared by χ^2 tests. Continuous outcomes were compared by using Wilcoxon 2-sample test.

A posteriori, a logistic model was applied to detect factors possibly affecting the probability of failure. The covariates included in the logistic model were respiratory support modes, GA strata, sex, birth weight less than 1500 g, high-risk pregnancy (including clinically diagnosed chorioamnionitis, rupture of membranes >18 hours, preeclampsia, and placental abruption), antenatal steroids, and multiple gestations.

Results

A total of 316 infants were enrolled between January 5, 2012, and June 28, 2014: 158 in the HHHFNC group (mean [SD] GA, 33.1 [1.9] weeks; 52.5% female) and 158 in the nCPAP/BiPAP group (mean [SD] GA, 33.0 [2.1] weeks; 47.5% female). Data analysis was performed on an intention-to-treat basis. Seven infants in the HHHFNC group and 2 in the nCPAP/BiPAP group did not receive or had a discontinuation of the allocated treatment because of unavailability of the study devices or circuits or being

shifted to the other support mode after correct randomization (**Figure 1**). There was only 1 death, in the nCPAP/BiPAP group, due to late-onset sepsis by *Streptococcus agalactiae*. There was no parental consent withdrawal throughout the study. Outcomes were available for all the patients until discharge home.

The 2 groups were homogeneous for baseline characteristics at randomization (**Table 1**). By GA strata, 144 infants were enrolled in the stratum of 29^{+0} to 32^{+6} weeks' GA, 106 in the stratum of 33^{+0} to 34^{+6} weeks' GA, and 66 in the stratum of 35^{+0} to 36^{+6} weeks' GA.

Table 1. Baseline Characteristics of the Study Population[a]

Characteristic	HHHFNC (n = 158)	nCPAP/BiPAP (n = 158)
Gestational age, wk		
Mean (SD)	33.1 (1.9)	33.0 (2.1)
No. (%)[b]		
29^{+0} to 32^{+6}	71 (44.9)	73 (46.2)
33^{+0} to 34^{+6}	53 (33.5)	53 (33.5)
35^{+0} to 36^{+6}	34 (21.5)	32 (20.2)
Birth weight		
Mean (SD), g	1968 (581)	1908 (528)
<1500 g, No. (%)	43 (27.2)	50 (31.6)
Small for gestational age, No. (%)	12 (7.5)	15 (9.4)
Female, No. (%)	83 (52.5)	75 (47.5)
Multiple birth, No. (%)	76 (48.1)	90 (57.0)
Antenatal steroids, No. (%)	105 (66.5)	109 (69.0)
High-risk pregnancy, No. (%)[c]	50 (31.6)	44 (27.8)
Cesarean delivery, No. (%)	141 (89.2)	147 (93.0)
Neonatal resuscitation, No. (%)	89 (56.3)	99 (62.7)
Apgar score at 5 min, median (IQR)	9 (8-9)	9 (8-9)
pH before enrollment, mean (SD)[d]	7.21 (0.06)	7.21 (0.07)
P_{CO_2} before enrollment, mean (SD), mm Hg[d]	58.1 (10.9)	59.0 (11.1)
F_{IO_2} before enrollment, median (IQR)	0.25 (0.21-0.30)	0.23 (0.21-0.30)
Silverman score before enrollment, median (IQR)	6 (5-6)	5.5 (5-6)

Abbreviations: BiPAP, bilevel nasal continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; HHHFNC, heated, humidified high-flow nasal cannula; IQR, interquartile range; nCPAP, nasal continuous positive airway pressure; P_{CO_2}, partial pressure of carbon dioxide.

[a] $P > .05$ for all the comparisons.

[b] Gestational age is presented as weeks^{+days}.

[c] Includes clinically diagnosed chorioamnionitis, prolonged premature rupture of membranes greater than 18 hours, preeclampsia, and placental abruption.

[d] Blood gas result from capillary or venous blood sample.

The use of HHHFNC was noninferior to nCPAP/BiPAP with regard to the primary outcome. Failure of the noninvasive respiratory support within 72 hours from the beginning of the study occurred in 17 of the 158 infants in the HHHFNC group (10.8%) and 15 of the 158 infants in the nCPAP/BiPAP group (9.5%) (95% CI of risk difference, −6.0% to 8.6%; $P = .71$) (**Table 2**). The upper 95% confidence limit (8.6%) was below the noninferiority margin of 10%, and the lower 95% confidence limit (−6.0%) was below 0% (**Figure 2**). The use of HHHFNC was also noninferior to nCPAP/BiPAP when applying a per-protocol analysis (Figure 2). There were no significant differences in failure rates between the 2 modes in any of the GA strata (Table 2). The application of a logistic model also confirmed no association between respiratory support mode and failure or with any other covariates (GA strata, sex, birth weight <1500 g, high-risk pregnancy, antenatal steroids, and multiple gestations).

The median postnatal age at the start of mechanical ventilation for infants in the HHHFNC group with failure was 27 hours (interquartile range [IQR], 8.0-36.0 hours) vs 7 hours (IQR, 3.0-19.0 hours) for the infants in the nCPAP/BiPAP group with failure (95% CI of difference in medians, −24.5 to 0.0; $P = .06$) (Table 2), as 3 infants in the HHHFNC group were intubated when they presented with clinical signs of volvulus. After surgery, mechanical ventilation was discontinued when the extubation criteria were matched. The median duration of mechanical ventilation was similar between the HHHFNC and nCPAP/BiPAP groups (median [IQR], 3.2 [1.2-5.0] vs 3.0 [1.2-6.0] days, respectively; 95% CI of difference in medians, −1.25 to 2.25; $P = .72$) (Table 2).

There were no significant differences between the 2 groups for any of the secondary respiratory outcomes (**Table 3**). According to the study protocol, 84 infants in the nCPAP group (53.2%) were treated at some point with BiPAP. The HHHFNC and nCPAP/BiPAP groups were similar in overall duration of respiratory support (median [IQR], 4.0 [2.0 to 6.0] vs 4.0 [2.0 to 7.0] days; 95% CI of difference in medians, −1.0 to 0.5; $P = .45$), days of noninvasive respiratory support (median [IQR], 3.5 [2.0 to 6.0] vs 3.5 [2.0 to 7.0] days; 95% CI of difference in medians, −1.0 to 0.5; $P = .48$), days of oxygen supplementation (median [IQR], 0.0 [0.0 to 1.0] vs 0.0 [0.0 to 0.8]; 95% CI of difference in medians, 0.0 to 0.0; $P = .43$), need for surfactant (44.3% vs 46.2%; 95% CI of risk difference, −9.8 to 13.5; $P = .73$), and duration of caffeine treatment (median [IQR], 12.0 [6.0 to 22.0] vs 15.0 [7.0 to 24.0] days; 95% CI of difference in

Table 2. Primary Outcome Results

Outcome	HHHFNC (n = 158)	nCPAP/BiPAP (n = 158)	95% CI of Risk Difference or Difference in Medians	*P* Value[a]
Mechanical ventilation within 72 h, No. (%)	17 (10.8)	15 (9.5)	−6.0 to 8.6	.71
Gestational age[b]				
29^{+0} to 32^{+6}	10 (14.1)	8 (10.9)		.70
33^{+0} to 34^{+6}	2 (3.8)	4 (7.5)		.67
35^{+0} to 36^{+6}	5 (14.7)	3 (9.4)		.76
Age at start of mechanical ventilation, median (IQR), h	27.0 (8.0-36.0)	7.0 (3.0-19.0)	−24.5 to 0.0	.06
Duration of mechanical ventilation, median (IQR), d	3.2 (1.2 to 5.0)	3.0 (1.2 to 6.0)	−1.25 to 2.25	.72

Abbreviations: BiPAP, bilevel nasal continuous positive airway pressure; HHHFNC, heated, humidified high-flow nasal cannula; IQR, interquartile range; nCPAP, nasal continuous positive airway pressure.

[a] Dichotomous outcomes were compared by χ^2 test; continuous outcomes were compared by Wilcoxon 2-sample test.

[b] Gestational age is presented as weeks^{+days}.

medians, −1.0 to 4.0; *P* = .25). Interestingly, the rate of air leaks was similarly low for both modes (1.9% vs 2.5%; 95% CI of risk difference, −3.3 to 4.5; *P* = .70). Finally, we did not find a significant between-group difference in the rate of BPD (4.4% vs 5.1%; 95% CI of risk difference, −3.9 to 7.2; *P* = .79) (Table 3).

Any acute adverse events besides air leaks and long-term complications of prematurity were strictly monitored after study entry. The 2 groups did not show significant difference for any of them (Table 3). One infant in the nCPAP/BiPAP group died of septic shock by *S agalactiae*. The overall rate of sepsis was similar between the 2 groups. The combined outcome of "any adverse event" was not significantly different between the 2 groups.

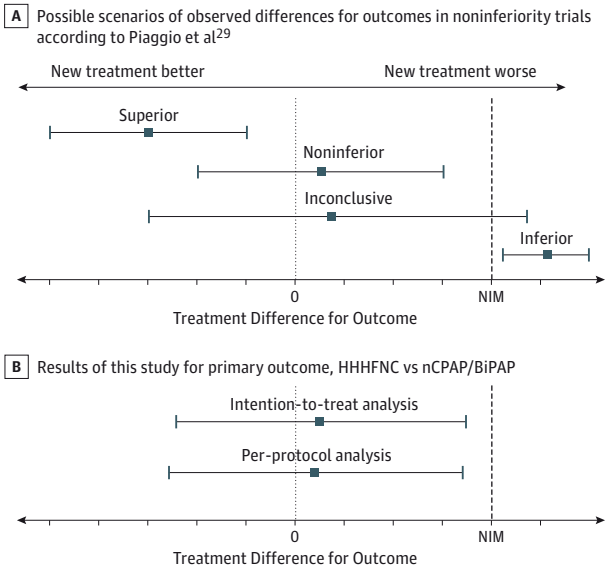
Finally, no statistically significant differences were found in duration of hospitalization, full enteral feeding, weight, or exclusive breastfeeding at discharge (Table 3).

The application of the logistic model to the secondary outcomes did not show significant association with either of the 2 study modes.

Discussion

The main finding of the study was that HHHFNC showed similar efficacy as standard nCPAP or BiPAP when applied as the primary approach to mild to moderate RDS in preterm infants between 29^{+0} and 36^{+6} weeks' GA in respect to the primary outcome of the need for mechanical ventilation within 72 hours from the beginning of respiratory support. Also, no difference was found

Figure 2. Possible Scenarios of Results for a Noninferiority Trial and Results of This Study



A, Possible scenarios of results for a noninferiority trial according to Piaggio et al.[29] B, Results of this study concerning the primary outcome according to both intention-to-treat analysis and per-protocol analysis. BiPAP indicates bilevel nasal continuous positive airway pressure; nCPAP, nasal continuous positive airway pressure; NIM, noninferiority margin; and error bars, 95% confidence interval of the risk difference.

Table 3. Secondary Outcome Results

Outcome	HHHFNC (n = 158)	nCPAP/BiPAP (n = 158)	95% CI of Difference in Medians or Risk Difference	*P* Value[a]
Duration received, median (IQR), d				
Respiratory support	4.0 (2.0 to 6.0)	4.0 (2.0 to 7.0)	−1.0 to 0.5	.45
Noninvasive respiratory support	3.5 (2.0 to 6.0)	3.5 (2.0 to 7.0)	−1.0 to 0.5	.48
Oxygen supplementation	0.0 (0.0 to 1.0)	0.0 (0.0 to 0.8)	0.0 to 0.0	.43
Caffeine treatment	12.0 (6.0 to 22.0)	15.0 (7.0 to 24.0)	−1.0 to 4.0	.25
Surfactant, No. (%)				
Administration	70 (44.3)	73 (46.2)	−9.8 to 13.5	.73
Multiple doses	7 (4.4)	8 (5.1)	−4.6 to 6.0	.85
Adverse event, No. (%)				
Air leaks	3 (1.9)	4 (2.5)	−3.3 to 4.5	.70
BPD	7 (4.4)	8 (5.1)	−3.9 to 7.2	.79
Confirmed sepsis	10 (6.3)	13 (8.2)	−4.4 to 8.2	.51
Confirmed NEC	1 (0.6)	2 (1.3)	−2.1 to 3.5	.56
IVH	6 (3.8)	4 (2.5)	−3.2 to 5.8	.52
PDA	8 (5.1)	9 (5.7)	−5.0 to 6.2	.80
ROP	1 (0.6)	0	−1.2 to 2.4	.32
Death	0	1 (0.6)	−1.2 to 2.4	.32
Any[b]	28 (17.7)	28 (17.7)	−9.0 to 9.0	>.99
Full enteral feeding, median (IQR), d	9.0 (6.0 to 15.0)	10.0 (6.0 to 16.0)	−1.0 to 1.0	.53
Exclusive breastfeeding at discharge, No. (%)	49 (31.0)	43 (27.2)	−6.3 to 12.8	.46
Hospitalization, median (IQR), d	20.0 (11.0 to 35.0)	23.0 (12.0 to 36.0)	−4.0 to 2.0	.41
Weight at discharge, median (IQR), g	2250 (2030 to 2485)	2287 (2065 to 2535)	−100.0 to 50.0	.47

Abbreviations: BiPAP, bilevel nasal continuous positive airway pressure; BPD, bronchopulmonary dysplasia; HHHFNC, heated, humidified high-flow nasal cannula; IQR, interquartile range; IVH, intraventricular hemorrhage; nCPAP, noninferior to CPAP; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

[a] Dichotomous outcomes were compared by χ^2 test; continuous outcomes were compared by Wilcoxon 2-sample test.

[b] Includes confirmed sepsis, confirmed NEC, IVH, PDA, ROP, BPD, air leaks, and death.

in respiratory support failure in any GA stratum. Additionally, there was no difference between the groups in any of the respiratory and extrarespiratory secondary outcomes explored.

To our knowledge, this study was the first large RCT comparing HHHFNC with nCPAP/BiPAP in preterm infants exclusively as primary therapy for RDS. Previous large RCTs by Collins et al[20] and Manley et al[21] showed similar efficacy between HHHFNC and nCPAP after extubation in preterm infants younger than 32 weeks' GA. However, the findings of these studies could not be translated to the acute phase of RDS, when lung derecruitment and the trend to alveolar collapse still play an important role in the pathogenesis of respiratory failure. Yoder et al[15] conducted a large RCT on HHHFNC vs nCPAP in infants between 28 and 42 weeks' GA, either as primary therapy or following extubation. Despite the high number of infants enrolled, the heterogeneity in stages of respiratory failure and treatment (before and after extubation) of the study population may have limited the interpretation of the results. Kugelman et al[22] published a pilot study on HHHFNC vs nasal intermittent positive pressure ventilation as primary treatment of RDS. They observed no difference between the 2 modes; however, the study was underpowered to assess the primary outcome. Despite the differing study design, in agreement with the previous RCTs, we found that HHHFNC has efficacy and safety similar to those of nCPAP/BiPAP when applied exclusively as primary treatment to mild to moderate RDS in preterm infants older than 28 weeks' GA.

The median age at the start of mechanical ventilation for infants in the HHHFNC group with failure was older than for infants in the nCPAP/BiPAP group with failure, although the difference was not statistically significant (P = .06) (Table 2). This result was due to 3 infants having been intubated following the study protocol when they presented with clinical signs of volvulus. They were not excluded because they also showed pulmonary disease of varying degrees, as assessed by chest radiography, need for surfactant, and duration of oxygen and pressure support required.

Concerns about the generation of inadvertently elevated pressure might have previously limited the use of HHHFNC in the NICU.[30] The pressure generated by HHHFNC depends on multiple factors, including the flow rate, the amount of leak around the cannula, and infant weight.[7] The pressure generated in HHHFNC has been measured in many studies, revealing highly heterogeneous data.[7,8,11,31,32] Differences might be due to varying methods of measurement, but they may also reflect important intrapatient, interpatient, and within-center variability. The pressure generated in HHHFNC was not measured during this study, but we can presume from previous research[7,9,31] that both nCPAP and BiPAP at the settings applied in the study should have provided, on average, a higher distending pressure than HHHFNC up to 6 L/min. Nonetheless, because of the concerns about safety related to the generated pressure, when the study was conceived, there was a decision to limit the flow rate in HHHFNC to 6 L/min. Despite this limitation in maximum allowable flow rate, the 2 groups showed similar results. In agreement with previous studies,[15,20-22] we found a similarly low rate of air leaks. According to our results, the pressure generated in HHHFNC up to 6 L/min seems to be safe and to not affect the efficacy of the respiratory support compared with nCPAP/BiPAP at the settings applied in the study.

Among the secondary outcomes, no difference was found in the rate of BPD. However, the following should be acknowledged: (1) the actual definition of the disease itself might present some limitations in describing the complexity of BPD physiopathology and phenotypes; (2) the age of the study population is not the most susceptible to developing BPD; and (3) the study was not specifically designed to assess this outcome. In contrast with the study by Yoder et al,[15] we found no difference in the duration of the respiratory support between the 2 modes. Because there is still no consensus on how to wean from HHHFNC, this outcome might have been affected more than others by local practice and availability of devices. Long-term follow-up of lung function and respiratory morbidities would probably add more useful information on the compared long-term effects of the 2 respiratory modes.

Finally, some authors reported sporadic cases of infections causing concerns about the use of HHHFNC in the NICU.[33,34] In agreement with the previous large RCTs on HHHFNC, we did not observe any difference in the rate of sepsis when compared with nCPAP/BiPAP. Additionally, no differences were found in terms of incidence of prematurity-associated complications or their combined outcome, suggesting comparable safety between the study modes for these age groups.

This study had some limitations. It was a monocentric rather than multicentric RCT. For obvious reasons, the study groups could not be blinded.

The study was conducted in an nCPAP-oriented NICU, meaning that the caregivers were more comfortable with the nCPAP/BiPAP technique than with HHHFNC. When the study was started, HHHFNC had been used for only a few months in our unit, having had, by contrast, a long experience with nCPAP/BiPAP management. This might explain the higher number of drop-offs in the HHHFNC group. However, the vast majority of drop-offs occurred in the first months of enrollment, suggesting that the lack of experience and confidence with the novel technique might have played a role.

Unlike some previous studies,[12,13] we did not use a specific scale to evaluate nasal trauma. Regardless, the rate of nasal injury associated with nCPAP/BiPAP in our NICU has been extremely low in the last few years and no macroscopic trauma was detected in either group throughout the study.

Finally, Klingenberg et al[19] found no difference in patient comfort using HHHFNC vs nCPAP, even if parents preferred HHHFNC. We did not systematically measure the degree of patient comfort, but we did not find any indirect benefit of using HHHFNC on duration of hospitalization, time to reach full enteral feeding, or exclusive breastfeeding at discharge.

Conclusions

The use of HHHFNC showed efficacy and safety similar to those of standard nCPAP or BiPAP when applied exclusively as the primary approach to mild to moderate RDS in preterm infants between 29^{+0} and 36^{+6} weeks' GA. Randomized clinical trials should be conducted to verify our findings concerning the use of

HHHFNC in preterm infants with RDS in a wider context. In addition, further studies are needed to investigate the role of HHHFNC in managing RDS in infants with younger GA and lower weight. Because a consensus on how to administer HHHFNC is missing, future research should address how to optimize this technique in preterm infants in diverse pathophysiological contexts.

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