Original Article

Heated Humidified High-Flow Nasal Cannula versus Nasal Continuous Positive Airways Pressure for Respiratory Support in Preterm Neonates – A Noninferiority Trial at a Tertiary Care Center

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Abstract

Background: In the neonatal period, respiratory failure remains a difficult challenge and is associated with high morbidity and mortality. Humidified high-flow nasal cannula (HHFNC) is being used as an alternative form of respiratory support for preterm infants with respiratory distress syndrome, apnea, and chronic lung disease. **Objective:** The objective was to assess the indications, frequency of usage, efficacy, and safety of heated HHFNC (HHHFNC) as compared to nasal continuous positive airway pressure (NCPAP) in providing respiratory support in preterm neonates after a period of positive pressure ventilation. (postextubation). **Materials and Methods:** This study was conducted in a Level II b neonatal intensive tertiary care unit in North Karnataka, India. In this study, all preterm neonates less than 37 weeks of gestation were placed on one of the respiratory supports (HHHFNC or NCPAP), immediately following extubation from mechanical ventilation. The primary outcome measures assessed were death, days on mechanical ventilation, need for reintubation (failure), air leak, nasal injury, and bronchopulmonary dysplasia (BPD). **Results:** There were no significant differences in major clinical outcomes including death, BPD, ventilator-days, necrotizing enterocolitis, severe intraventricular hemorrhage, retinopathy of prematurity, or time to full feeds. Failure of assigned mode of respiratory support was seen in 12% of infants on HHHFNC compared to 16% on NCPAP (P = 0.48). No significant difference in other outcome measures was seen between the groups. No nasal injury was observed in the HHHFNC group against 10% in the NCPAP group (P = 0.55). **Conclusion:** There was no statistically significant difference within the primary and secondary outcomes. At 5% level of significance, HHHFNC was found to be noninferior compared to NCPAP with 3.5% difference in the rates of failure of assigned mode of respiratory support. Hence, HHHFNC can be considered to be a safe, efficacious, and more easily acceptable mode of respiratory support as compared to NCPAP in preterm neonates after a period of positive pressure ventilation.

Keywords: *High-flow nasal cannula, nasal continuous positive airways pressure, neonate, post extubation, respiratory distress or disease*

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Introduction

In the neonatal period, respiratory failure is a difficult challenge and is associated with high morbidity and mortality. In neonates, respiratory support can be provided either through invasive or noninvasive ventilation. Noninvasive ventilation includes

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supplemental oxygen via a head box or by nasal cannula; continuous positive airway pressure (CPAP) via nasal prongs or mask; and heated humidified high-flow nasal cannula (HHHFNC).[1,2]

Nasal CPAP (NCPAP) improves the residual lung capacity, prevents atelectasis of alveoli, and recruits them, thereby reducing apnea. NCPAP applied postextubation reduces the rates of extubation failure.[3-5]

In contrast, "high-flow" nasal cannula (HFNC) delivers oxygen or blended oxygen and air at higher flow rates (>2 L/min). Gas given via HFNC is routinely heated and humidified, as with CPAP. High gas flows that is between 2 and 8 l/min in preterm neonates may provide low levels of positive end-expiratory pressure (PEEP).[6,7]

NCPAP is a recognized mode of respiratory support for preterm neonates. Recently, the practice of HHHFNC usage has become an increasingly popular alternative to NCPAP for noninvasive support of preterm neonates after extubation.

The increasing use of HHHFNC is, in part, due to its greater comfort of use, better patient compliance, and similar effectiveness to NCPAP. In addition, there are decreased incidences of nasal trauma and nares distortion compared to NCPAP.[8]

Hence, this study was performed to assess whether HHHFNC is as effective and safe as NCPAP in providing respiratory support in preterm neonates (postextubation).

Aims and objectives

1. The aims and objectives were to assess the efficacy of HHHFNC as compared to NCPAP in providing respiratory support in preterm neonate's post extubation
2. To assess the safety of HHHFNC as compared to NCPAP in providing respiratory support in preterm neonate's post extubation.

Materials and Methods

This study was conducted in a Level II b neonatal intensive tertiary care unit in North Karnataka. In this study, all preterm neonates less than 37 weeks of gestation were placed on one of the respiratory supports (HHHFNC or NCPAP), immediately following extubation from mechanical ventilation based on clinicians' discretion and unit protocol.

Inclusion criteria

Preterm neonates <37 weeks of gestation who required ventilation during the first 96 h of life and postextubation being placed on either HHHFNC or NCPAP were included in the study.

Exclusion criteria

- Antenatally detected life-threatening congenital heart diseases
- Babies who were subsequently discharged against medical advice.

Treatment failure was defined by

- A FiO_2 of 20% or more above the baseline value prior to extubation to achieve a peripheral oxygen saturation of more than 90%
- FiO_2 >60% to achieve a PO_2 >50 mmHg on an arterial blood gas
- A pH <7.2 on an arterial blood gas with pCO_2 >60 mmHg
- More than one apnoeic episode requiring positive pressure ventilation within 24 h postextubation and,
- Need for reintubation and ventilation within 72 h of extubation as determined by the treating clinician.

Neonates in the HHHFNC group received flows via the Fischer and Paykel junior kit (RT330, Maurice Paykel Place, East Tamaki Auckland, New Zealand.).

Neonates were fitted with nasal prongs that occluded more than 50% of the nares. The starting flow rates were based on the weight (2 L/kg). The staring FiO_2 was usually 21%–40% and then adjusted to maintain target oxygen saturation.

Neonates in the NCPAP group received PEEP via the binasal midline prongs (Fischer and Paykel Healthcare). NCPAP was generated with the use of an underwater bubble system. The starting PEEP was 4–6 cmH_2O, flow rates of 5–8 L/min, and FiO_2 of 21%–40%.

Outcomes

Primary outcomes

- Failure of assigned mode of respiratory support (treatment failure criteria mentioned above)
- Chronic lung disease
- Death of the neonate prior to discharge.

Secondary outcomes

- Retinopathy of prematurity (ROP)
- Intraventricular hemorrhage (IVH)
- Nosocomial sepsis (blood culture or cerebrospinal fluid positive. Sample taken post extubation)
- Severe necrotizing enterocolitis (NEC) (Stage II or more according to Bells criteria)
- Nasal trauma (erythema or erosion of the nasal septum or nasal mucosa)
- Air leak syndromes (pneumothorax, pneumomediastinum and pulmonary interstitial emphysema)
- Patent ductus arteriosus (PDA)
- Duration of respiratory support (days/hours)

- Duration of supplementary oxygen
- Duration of hospitalization (days)
- Number of days to attain full feeds that is 120 ml/kg/day
- Weight gain prior to discharge (grams).

Data were represented using mean ± standard deviation and analyzed by Chi-square test for association, with comparison of means using *t*-test, ANOVA, and diagrammatic presentation.

Results

The study was performed in a Level II B neonatal intensive care unit (NICU) in a tertiary care hospital in North Karnataka. A total of 106 neonates less than 37 weeks of gestation were enrolled in the study. All of these neonates had required invasive ventilation within the first 96 hours of life. Among 106 neonates, post extubation, 54 babies were put on NCPAP, whereas 52 were put on HHHFNC mode of respiratory support. There were no differences noted in the baseline characteristics between the comparison groups such as mean gestation, birth weight, and gender distribution [Table 1 and Figure 1].

Primary outcomes

Failure of assigned mode of respiratory support

Failure of the assigned modality of respiratory support post extubation (as defined by the criteria mentioned above) was seen in five babies in the HHHFNC group and three babies in the NCPAP group.

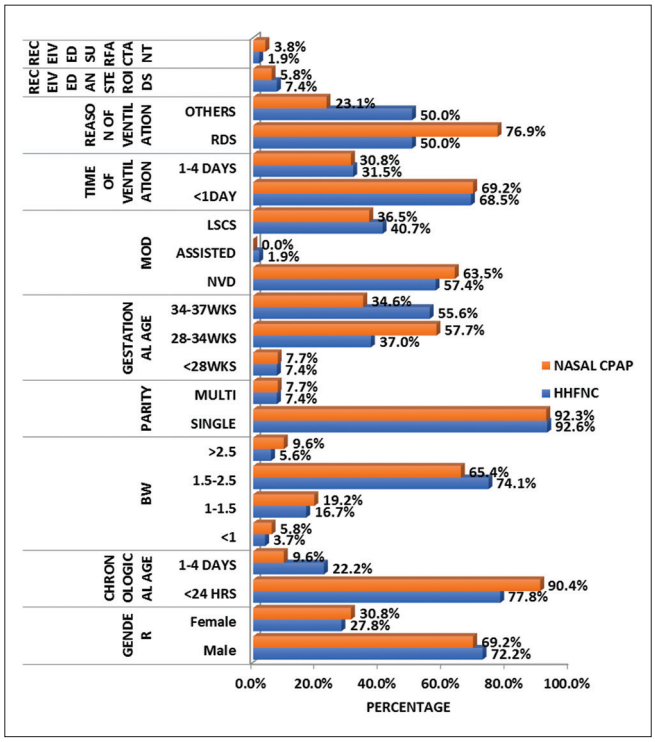

Figure 1: Distribution of baseline parameters

This difference was not statistically significant [Table 2 and Figure 2].

Chronic lung disease

Chronic lung disease was seen in three babies in the HHHFNC group and two babies in the NCPAP group. This difference was not statistically significant [Table 3 and Figure 3].

Death of the baby prior to discharge

Death of the baby prior to discharge was seen in three babies put on HHHFNC post extubation and two babies on NCPAP. This difference was statistically not significant [Table 4 and Figure 4].

Secondary outcomes

There were no significant differences in secondary outcomes including ROP, IVH, nosocomial infection, PDA, air leaks, days on respiratory support, days on supplemental oxygen, duration of hospital stay, and weight gain (kg). Outcomes such as NEC, nasal trauma, and days to reach full feeds show statistically significant difference between the HHHFNC and NCPAP groups [Table 5].

Discussion

The use of HHHFNC has increased significantly in recent years in NICUs all over the world. This is mainly because of the ease of application and better patient tolerance. Also, it has got added advantages such as minimal nasal trauma and less interference with feeding or kangaroo mother care as compared to NCPAP. Despite its wide acceptance clinically, there is sparse data regarding its efficacy and safety in preterm neonates' post extubation. Clinical outcomes associated with the use of HHHFNC are being considered to be at least similar to those of NCPAP usage by some neonatologists. On the basis of our prespecified definition of noninferiority, the use of HHHFNC was found to be noninferior to NCPAP as a means of respiratory support in preterm neonates after a period of positive pressure ventilation.

Earlier randomized controlled trials (RCTs) (comparing NCPAP and HHHFNC or different high-flow devices)

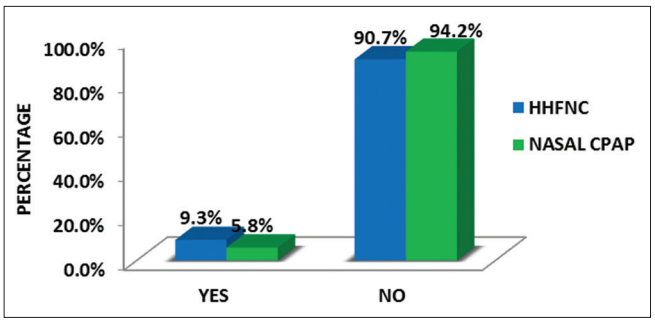

Figure 2: Failure of assigned means of respiratory support between the study groups

between 2006 and 2010 had relatively small study samples and low flow rates compared to the current practice.[3,9,10]

In 2013, the publication of three large RCTs added to the evidence for the use of HHHFNC.

The first by Collins *et al*.[11] included 132 neonates <32 weeks of gestation, who were randomized to either HHHFNC or NCPAP after extubation. The rates of extubation failure did not differ significantly (22% in the

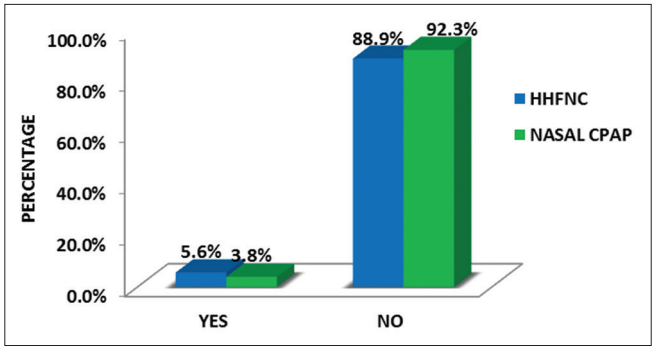

Figure 3: Distribution of chronic lung disease between the study groups

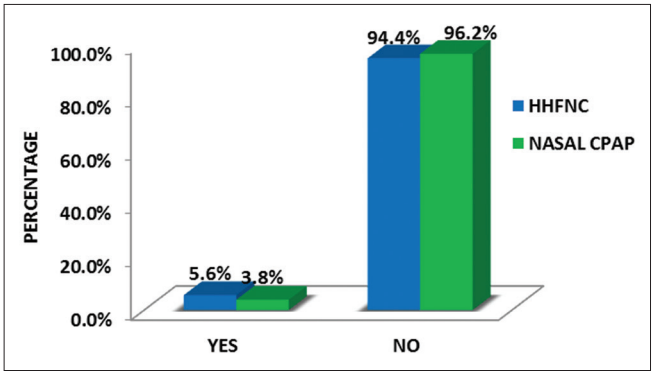

Figure 4: Death prior to discharge between the study groups

Table 1: Distribution of Baseline Characteristics of Study Groups.

BASELINE PARAMATERS		HHHFNC (*n*=54)		NCPAP (*n*=52)		*p*
		N	%	*N*	%	
GENDER	Male	39	72.2%	36	69.2%	0.735
	Female	15	27.8%	16	30.8%	
CHRONOLOGICAL AGE	<24 HRS	42	77.8%	47	90.4%	0.077
	1-4 DAYS	12	22.2%	5	9.6%	
BIRTH WEIGHT	<1	2	3.7%	3	5.8%	0.753
	1-1.5	9	16.7%	10	19.2%	
	1.5-2.5	40	74.1%	34	65.4%	
	>2.5	3	5.6%	5	9.6%	
PARITY	SINGLE	50	92.6%	48	92.3%	0.956
	MULTI	4	7.4%	4	7.7%	
GESTATIONAL AGE	<28WKS	4	7.4%	4	7.7%	0.081
	28-34WKS	20	37.0%	30	57.7%	
	34-37WKS	30	55.6%	18	34.6%	
MODE OF DELIVERY	NVD	31	57.4%	33	63.5%	0.537
	ASSISTED	1	1.9%	0	0.0%	
	LSCS	22	40.7%	19	36.5%	
TIME OF VENTILATION	<1DAY	37	68.5%	36	69.2%	0.937
	1-4 DAYS	17	31.5%	16	30.8%	
REASON OF VENTILATION	RDS	27	50.0%	40	76.9%	0.004*
	OTHERS	27	50.0%	12	23.1%	
RECEIVED AN STEROIDS		4	7.4%	3	5.8%	0.734
RECEIVED SURFACTANT		1	1.9%	2	3.8%	0.536
Total		54	100.0%	52	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Table 2: Failure of Assigned Means of Respiratory Support Between Study Groups

FAILURE OF ASSIGNED MEANS OF RESPIRATORY SUPPORT	HHHFNC (*n*=54)		NCPAP (*n*=52)		*p*
	N	%	*N*	%	
YES	5	9.3%	3	5.8%	
NO	49	90.7%	49	94.2%	0.496
Total	54	100.0%	52	100.0%	

Note: * significant at 5% level of significance (p<0.05)

HHHFNC group and 34% in the NCPAP group). Also, the rates of reintubation were not statistically significant (17% in the HHHFNC group and 24% in the NCPAP group).

A similar study by Manley *et al*.[8] compared HHHFNC and NCPAP using a noninferiority design. Three hundred and three preterm neonates were included in the study. Treatment failure as defined by prespecified criteria occurred in 34.2% of neonates in the HHHFNC group and 25.8% of neonates in the NCPAP group. Reintubation was required within 7 days of extubation in 17.8% of neonates in the HHHFNC group compared to 25.2% in the NCPAP group.

The third RCT by Yoder *et al*.[12] included neonates between 28 and 42 weeks of gestational age. A total of 291 babies were randomized to HHHFNC or NCPAP after extubation, and the primary outcome of need for reintubation within 72 h (11.6% in HHHFNC and 6.5% in NCPAP group) did not differ significantly between the two groups.

A Cochrane review updated in 2016[13] observed six studies, including 934 neonates who were randomized to either HHHFNC or NCPAP as postextubation means of respiratory support. A meta-analysis demonstrated no additional risk of treatment failure in the HHHFNC group. It also suggested that in neonates from 28 to 32 weeks of gestation, HHHFNC (with the availability of rescue CPAP) may be an appropriate modality of respiratory support after extubation.

Our study was done at a tertiary care center in the district of Vijayapura in Karnataka. A total of 106 neonates below 37 weeks of gestation were included in the study. After a period of positive pressure ventilation, they were placed on either HHHFNC or NCPAP. Fifty-four babies were placed on HHHFNC, while 52 babies received NCPAP. The primary characteristics were similar in both the study groups. The primary outcomes of the study were failure of assigned mode of respiratory support, chronic lung disease, and death during respiratory support.

Failure of the assigned means of respiratory support was seen in five babies in the HHHFNC group and three babies in the NCPAP group. This difference was statistically not significant. Similar results were obtained in the study by Yoder *et al.* and Manley *et al*.

Chronic lung disease was defined as requirement of supplemental oxygen at 36 weeks of post gestational age for neonates born at <32 weeks of gestation or 28 days of age for neonates born at 32 weeks of gestation or later.

In our study, 5.6% of neonates on HHHFNC developed chronic lung disease (CLD), whereas 3.7% of neonates on NCPAP developed CLD. This difference was not statistically significant. The findings were similar to the study conducted by Manley *et al.* and Yoder *et al.,* in which the difference in the incidence of chronic lung disease in both the study groups was not statistically significant.

Death of the neonate prior to discharge was seen in three babies from the HHHFNC group and two babies in the NCPAP group. This difference was statistically not significant. This finding was similar to that observed in the study conducted by Manley *et al*. [Table 6].

Table 3: Distribution of Chronic Lung Disease Between Study Groups

Chronic Lung Disease	HHHFNC (*n*=54)		NCPAP (*n*=52)		*p*
	N	%	*N*	%	
YES	3	5.6%	2	3.8%	0.834
NO	48	88.9%	48	92.3%	
N/A	3	5.6%	2	3.8%	
Total	54	100.0%	52	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Table 4: Death Prior To Discharge Between Study Groups

DEATH PRIOR TO DISCHARGE	HHHFNC (*n*=54)		NCPAP (*n*=52)		*p*
	N	%	*N*	%	
YES	3	5.6%	2	3.8%	0.678
NO	51	94.4%	50	96.2%	
Total	54	100.0%	52	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Table 5: Secondary Outcomes of The Study Groups.

Secondary Outcomes	HHHFNC (*n*=54)	NCPAP (*n*=52)	*P*
Retinopathy of Prematurity	2(3.7%)	2(3.8%)	0.917
Intraventricular Hemorrhage	2(3.7%)	2(3.8%)	0.969
Nosocomial Infection	8(14.8%)	8(15.4%)	0.935
Necrotizing Enterocolitis	1(1.9%)	13(25%)	<0.001*
Nasal Trauma	1(1.9%)	30(57.7%)	<0.001*
PDA	00	00	-
Air Leaks	00	00	-
Days on Respiratory Support	3.31±1.49	2.92±1.41	0.549
Days on Supplemental Oxygen	3.16±4.15	3.86±4.17	0.398
Duration 0f Hospital Stay	20.54±9.81	22.00±12.59	0.505
Days to Reach Full Feeds	14.20±5.91	16.40±3.27	0.047*
Weight Gain (Kg)	-0.01±0.16	-0.06±0.17	0.112

Note: * significant at 5% level of significance (p<0.05)

Table 6: Comparison of the Outcomes with Other Studies.

Outcome	Our study			Manley *et al.*		
	HHHFNC	CPAP	*p*	HHHFNC	CPAP	*p*
Failure of respiratory support	5 (9.2%)	3 (5.7%)	0.581	52 (34.2%)	39 (25.8%)	0.68
Chronic lung disease	3 (5.6%)	2 (3.7%)	0.834	47 (30.9%)	52 (34.4%)	0.57
Death prior to discharge	3 (5.6%)	2 (3.7%)	0.678	5 (3.3%)	6 (4.0%)	0.45
Retinopathy of prematurity	3 (5.6%)	2 (3.7%)	0.448	8 (5.3%)	8 (5.3%)	0.99
Intraventricular haemorrhage	2 (3.7%)	2 (3.7%)	0.996	3 (2%)	8 (5.3%)	0.12
Nosocomial infection	8 (14.8%)	8 (14.8%)	0.935	26 (17.1%)	30 (19.9%)	0.54
Necrotising enterocolitis	1 (1.9%)	13(24.1%)	<0.001*	3 (2%)	7 (4.6%)	0.20
Nasal trauma	1 (1.9%)	30 (55.6%)	<0.001*	29(19.1%)	80 (53%)	**<0.001***
Air leaks	0	0		0	1 (0.7%)	0.32
Patent Ductus Arteriosus	0	0		64(42.1%)	64(42.4%)	0.96
Days on respiratory support	3.31	2.92	0.549	34	38	0.44
Days on oxygen	3.16	3.86	0.398	38	49	0.15
Duration of hospital stay	20.54	22.0	0.545	79	84	0.38
Days to reach full feeds.	14.20	16.40	<0.047*	NA	NA	NA.

*_significant at 5% level of significance (p<0.5)

Secondary outcomes of the study were ROP, NEC, IVH, nasal trauma, nosocomial infection, air leaks, and opening up of PDA.

Most of the parameters showed no statistically significant difference between the HHHFNC and NCPAP groups except nasal trauma and incidence of NEC which were more in the NCPAP group.

The incidence of ROP, IVH, air leaks, nosocomial infection, and PDA was comparable between the two groups in our study. These findings were similar to the observations by Manley *et al*.

The incidence of NEC was more in the NCPAP group as compared to the HHHFNC group in our study, and this difference was statistically significant.

The incidence of nasal trauma was more in the NCPAP group as compared to the HHHFNC group, and this difference was statistically significant in our study. These findings were similar to the observations by Manley *et al*.

The number of days on respiratory support, number of days on oxygen, and duration of hospital stay were comparable between the NCPAP and HHHFNC groups. These findings were similar to those in the study by Manley *et al*. However, in our study, the duration required to reach full feeds was longer in the NCPAP group as compared to the HHHFNC group, with the difference being statistically significant. This finding did not correlate with that of Manley's study.

At 5% level of significance, HHHFNC was found to be noninferior compared to NCPAP with 3.5% difference in the rates of failure of assigned mode of respiratory support. In fact, it had added advantages such as minimal nasal trauma, less incidence of NEC, and lesser number of days required to reach full feeds.

Although this study is limited by small sample size, the lack of randomization of the samples into the HHHFNC group or NCPAP group, data presented here indicate that HHFNC is better tolerated and an effective alternative respiratory support mode to NCPAP in the preterm infant population.

Conclusion

There was no statistically significant difference in the primary and secondary outcomes. It was observed that babies on HHHFNC had lesser incidence of nasal trauma, NEC, and lesser number of days required to reach full feeds. Hence, it can be said that HHHFNC was not inferior compared to NCPAP as a postextubation mode of respiratory support. At 5% level of significance, HHHFNC was found to be noninferior compared to NCPAP with 3.5% difference in the rates of failure of assigned mode of respiratory support. Hence, HHHFNC can be considered to be a safe, efficacious, and more easily acceptable mode of respiratory support as compared to NCPAP in preterm neonates after a period of positive pressure ventilation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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