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Original Article

Comparison of the Heated Humidified High-flow Nasal Cannula with Nasal Continuous Positive Airway Pressure as Primary Respiratory Support for Preterm Neonates: A Prospective Observational Study

Tisha Ann Skariah[1*], Laveena Dias[2], Leslie Edward Lewis[3]

1. Department of Respiratory Therapy, School of Allied Health Science, Manipal Academy of Higher Education, Manipal, Karnataka, India
2. Hamad Medical Corporation, Qatar
3. Department of Pediatrics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

ABSTRACT

Background: Heated humidified high-flow nasal cannula (HHHFNC) is gaining popularity in the management of respiratory distress in preterm neonates. However, it is not known whether it takes precedence over the gold standard nasal continuous positive airway pressure (NCPAP) in this age group as a primary mode of non-invasive ventilation (NIV). There is limited evidence addressing this issue in the literature. Therefore, this study aimed to focus on the effect of HHHFNC on preterm neonates with respiratory distress, compared to NCPAP as a primary mode of respiratory support.

Methods: A prospective observational study conducted in tertiary level III NICU. The preterm neonates 28-36 weeks with respiratory distress syndrome (onset of distress within ≤4 hours of life with FiO2 ≥0.25 with compatible chest radiograph) were managed with either HHHFNC or nCPAP The need for invasive ventilation within 72 hours of initiation of non-invasive respiratory support was studied. FiO2 and Downe's scores were recorded every 4th hour for the first 48 hours.

Results: In total, 84 neonates were enrolled in this study. Treatment failure for HHHFNC group was 34.4%, whereas it was 32.2% (P=0.34) for NCPAP group which indicated no significant differences. In the late preterm strata, NCPAP group obtained longer duration for NIV (Median: 64 vs 43 hours, respectively; P<0.001); however, there were no differences between the study groups regarding the use of supplemental oxygen. The estimation of the survival time was plotted using the Kaplan-Meier curve (P<0.001). In addition, the two groups were compared through Gehan–Breslow–Wilcoxon test. Moreover, the results revealed differences between the two groups in terms of the hazards ratio for time to success regarding such items as the intervention group, gestational age, birth weight, surfactant therapy, and Downe's score (1.17; CI: 95% [0.7, 1.8]).

Conclusion: Early HHHFNC obtained similar results, compared to NCPAP as a primary mode of NIV for a preterm population with respiratory distress, and it may not be superior to NCPAP.

Keywords: Heated humidified high-flow nasal cannula, Nasal continuous positive airway pressure, Non-invasive ventilation, Preterm neonates

Introduction

Respiratory failure remains a common problem in the neonatal intensive care unit (NICU). Concerns with ventilator-induced lung injury have led to a concerted effort in many NICUs to avoid prolonged ventilator support through the early application of non-invasive ventilation (NIV), most widely use of which is nasal continuous positive pressure (NCPAP) (1, 2). The NIV also contributes to reducing long-term respiratory morbidity in preterm infants. There are a large number of devices available to cater to the increasing demand of NIV for this age group. One of the newest one is heated humidified high flow nasal cannula (HHHFNC) which has gained

* *Corresponding author*: Tisha Ann Skariah, Department of Respiratory Therapy, School of Allied Health Science, MAHE, Manipal, Karnataka, India. Tel: 00919008765696; Email: tisha_skariah@hotmail.com

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popularity due to the ease of administration. Data suggests that HHHFNC is effective in eliminating the dead space (3), reducing the work of breathing, improving lung compliance at higher flow rates (4), and delivering some degree of continuous positive airway pressure (CPAP) (3,5).

Over the years, Sreenan et al. (6) used the term "high-flow nasal cannula" in reporting the nasal cannula with a blood flow of 2.5 l/min. It was suggested that it could be as effective as NCPAP for treating apnea in prematurity and considering delivered pressure via nasal cannula, the flow could be regulated using esophageal pressure measurements. Standard nasal cannula systems routinely use in-adequately warmed and humidified gas, limiting the use of higher flow rates secondary to the risk of mucosal injury and nosocomial infection (7-9). To circumvent these concerns, HHHFNC systems were developed as possible alternatives to NCPAP for non-invasive respiratory support of neonates.

A survey conducted by Ojha S et al. (10) reported that HHHFNC was used in 77% of hospital wards. In addition, the results obtained from this study highlighted that HHHFNC was used mainly as an alternative to, or weaning off, NCPAP after extubation. Early retrospective and observational studies suggested that HHHFNC can be applied safely and effectively as non-invasive respiratory management of premature infants with respiratory dysfunction. The purpose of this prospective observational trial was to investigate whether the HHHFNC was safer and reduced the need for mechanical ventilation, compared to NCPAP in preterm neonates when given as a primary mode of respiratory support.

Methods

This prospective observational study was conducted from February 2015 to July 2016 at a level III tertiary NICU. The study protocol was approved by the Ethics Committee of Kasturba Hospital, Manipal and registered at the Clinical Trial Registry of India (CTRI/2017/09/009910). All preterm neonates (27-36 weeks) with respiratory distress (Downe's score of > 3) within 2 h of life were enrolled in the study.

On the other hand, the preterm neonates with congenital cyanotic heart disease, major congenital malformations, and air leak syndromes were excluded from the study. Once the neonate was admitted to the NICU and met the inclusion criteria, they were either administered with NCPAP or HHHFNC as the primary NIV mode for treating respiratory distress. The allocation was made using quasi-experimental allocation. Neonates who required surfactant were administered by INSURE technique and then allotted to NIV mode. Methylxanthines (i.e., caffeine or aminophylline) were administered as per NICU protocol. The primary outcome was the "failure" of noninvasive respiratory support which necessitated intubation and mechanical ventilation within 72 h of initiation of either therapies or change in treatment modality.

The criteria for "failure" was any one of the following: 1) $PaCO_2$>60mmHg with pH<7.2, 2) Apnea's lack of response to tactile stimulation requiring bag and mask ventilation, 3) The presence of ≥6 apneic episodes requiring stimulation within 6 consecutive h, and 4) The presence of episodes of desaturation (SpO_2<85%) not responding to maximum settings.

The secondary observed outcomes included the duration of respiratory support, NICU stay, and days to reach full feed, as well as complications, such as retinopathy of prematurity (ROP) according to the International Committee for Classification of ROP, periventricular leukomalacia, severe intraventricular hemorrhage (IVH; grade ≥3 according to Papile grading), necrotizing enterocolitis based on Modified Bell's Staging Criteria, and feed intolerance.

Neonates who failed NCPAP were treated with unsynchronized nasal intermittent positive pressure ventilation (NIPPV) or intubated according to the NICU protocol. On the other hand, the newborns who failed HHHFNC were switched over to either NCPAP or NIPPV, or intubated according to the severity of distress.

The NCPAP was provided with a ventilator (Drager baby log 8000, Germany) or underwater bubble system (Fischer and Paykel, New Zealand) using a nasal mask as an interface with initial settings of positive end-expiratory pressure of 5 cm H_2O.

In addition, the HHHFNC was delivered by Airvo (Fischer and Paykel, New Zealand) or RT350 humidifier (Fischer and Paykel, New Zealand) using nasal cannula with the initial setting of 8l/min. The flow rate was weaned to a minimum of 2 l/min before discontinuing support. The FiO_2 was adjusted to maintain the target oxygen saturation as per center protocol.

Furthermore, statistical analysis was performed in SPSS software (version 16.0), and the student t-test was employed to compare continuous measures between groups. Following that,

non-parametric continuous outcomes were compared using Man Whitney U test; moreover, survival analysis was performed utilizing Cox's proportional hazards model and Kaplan Meier Analysis. P-value less than 0.05 was considered statistically significant.

Results

During the study period, a total of 210 preterm neonates were admitted to the NICU. Out of which 126 were excluded due to the aforementioned exclusion criteria. Eventually, a total of 84 neonates were eligible to participate in the study. According to Figure 1, 43 and 41 neonates received HHHFNC and NCPAP as the primary mode of NIV, respectively. The baseline characteristics were compared between the groups, and there were no significant differences between the two groups in this regard (Table 1).

According to the primary results, there were no differences between the two groups as well as within the age subgroups regarding the failure rates. On the other hand, the neonates remained in the NCPAP mode significantly longer than neonates in HHHFNC at 33-36 weeks of gestation (Median: 64 vs 43 hours, respectively, P<0.001). However, there were no differences between the study groups regarding the use of supplemental oxygen, as well as other clinical outcomes and complications (Table 2).

Cox's proportional hazards model was used for survival-time outcomes regarding factors, such as the intervention group, gestational age, birth weight, surfactant therapy, and Downe's score (Table 3). It can be seen that the successful outcome was 1.17 times more likely to occur in the HHHFNC than in the NCPAP group. Similarly, regarding the gestational age, the success rate was 0.40 times less likely to occur in the lower gestational age strata (27-32weeks), compared to higher gestational age strata (33-36 weeks).

Birth weight as a confounding factor was analyzed and the success was more as the birth weight increased indicating a higher success rate

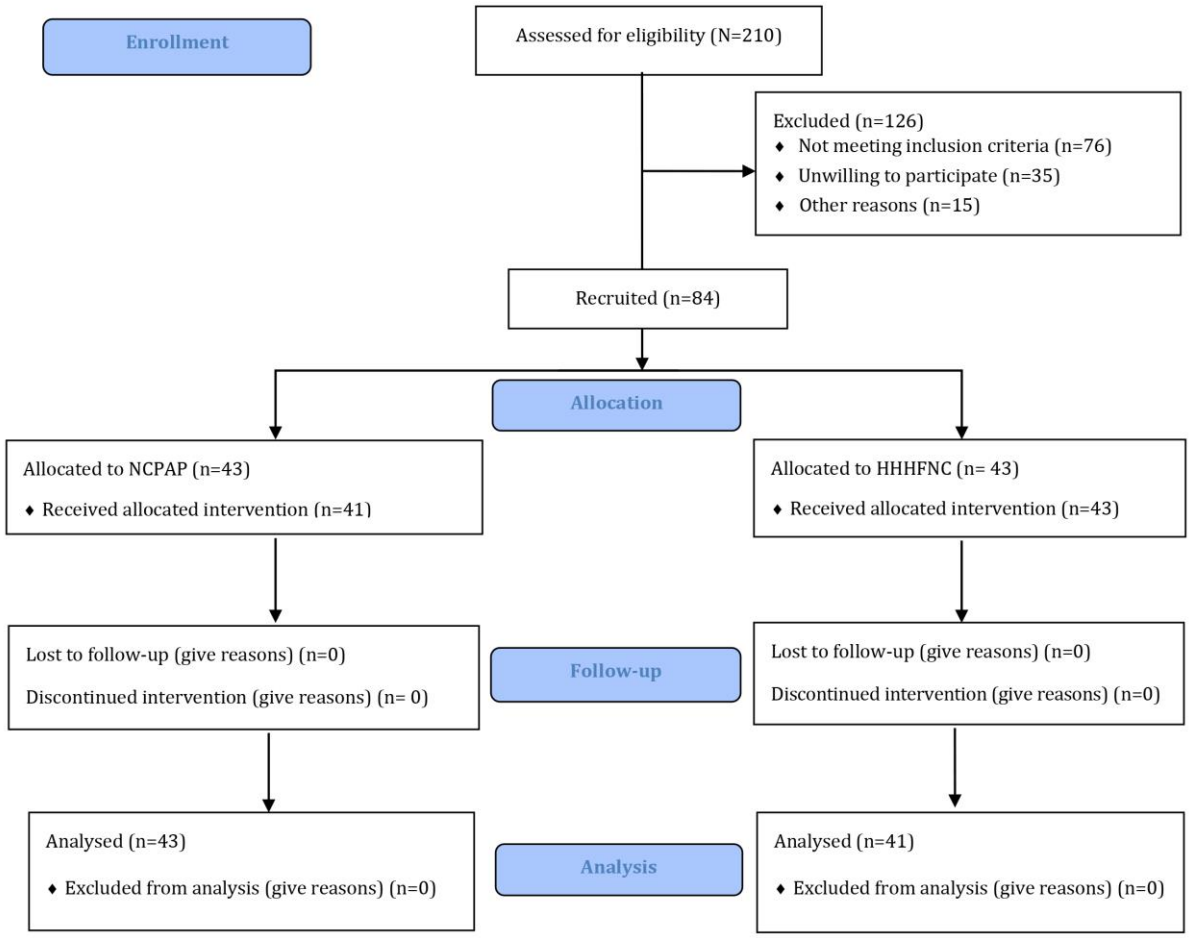

Figure 1. Flow Diagram of the study

Table 1. Baseline demographic and clinical characteristics of the infants

Baseline characteristics	27-32 weeks		33-36 weeks	
	*HHHFNC (n=15)	**NCPAP (n=22)	HHHFNC (n=26)	NCPAP (n=21)
Birth Weight (g) (mean±SD)	1413±311.41	1342±318.14	2396±512.08	1898±463.37
Gender Male/Female	9/6	9/13	17/9	12/9
Gestational age (weeks) (mean±SD)	30.8±1.45	30.7±1.31	34.7±1.00	33.72±1.7
Mode of delivery: Lower section cesarean section	15	22	20	21
Packed cell volume (mean±SD)	48.6±7.76	47.44±4.52	45.65±6.41	49±7.72
Antenatal Steroid (%)	9/15 (45.5)	21/22(30.2)	11/26 (63.6)	6/11 (54.5)
Methylxanthines				
Caffeine (%)	10/15(50)	9/22 (45)	8/26(25)	10/21(31.2)
Aminophylline (%)	5/15 (27.8)	13/22 (72.2)	5/26 (18.5)	8/21(29.6)
Surfactant therapy				
INSURE technique (%)	4/15 (10.8)	9/22 (24.3)	1/25 (2.1)	0
Antibiotics (%)	915 (24.3)	18/22 (48.6)	11/26 (23.4)	7/21 (14.9)

*HHHFNC: Heated humidified high-flow nasal cannula
**NCPAP: Nasal continuous positive airway pressure

Table 2. Outcome measures

Outcome	28-32 weeks		P-value	33-36 weeks		P-value
	*HHHFNC (n=15)	**NCPAP (n=22)		HHHFNC (n=26)	NCPAP (n=21)	
Failure (%)	4/15 (26.7)	5/22(22.7)	0.223	2/26(7.7)	2/21(9.5)	0.127
Duration of non-invasive ventilation (h) Median Interquartile range	74 (44, 68)	87 (49,96)	0.81	43 (27, 59)	64 (55,72)	<0.001
Feed intolerance (%)	2/15 (5.4)	1/22 (2.7)	3.36	1/26 (2.1)	2/21 (4.3)	0.429
Necrotizing enterocolitis (%)	1/15(2.7)	Nil	0.220	1/26(2.7)	0	0.364
Air leak (%)	0	1/22(2.7)	0.403	0	0	-
Intraventricular hemorrhage (%)	3/15 (8.3)	1/22 (2.8)	0.151	1/26(2.1)	0	0.364
Retinopathy of prematurity (%)	2/15 (5.4)	3/22 (8.3)	0.979	1/26 (2.1)	0	0.261

*HHHFNC: Heated humidified high-flow nasal cannula
**NCPAP: Nasal continuous positive airway pressure

Table 3. Cox's proportional hazards model for survival-time outcomes

Parameters	Variable (n)	Success (%)	Relative risk
Group	HHHFNC(41)	36(85.4)	1.17
	NCPAP(43)	35(83.7)	1
Gestational age	28-32(37)	37(75.7)	0.40
	33-36(47)	47(91.5)	1
Birth weight (g)	<1000(6)	5(60.0)	0.304
	1000-2000(26)	25(76.9)	0.305
	2000-3000(27)	28(85.2)	0.479
	>3000(25)	26(96.0)	1
Surfactant therapy	Received(14)	14(85.7)	1
	Not received(70)	70(78.6)	0.68
Downe's score	DS<4(77)	77(88)	1
	DS>5(7)	7(57)	0.915

with late preterm or term neonates. In addition, the successful outcome was 0.68 times less likely to occur in neonates who received no surfactant therapy. Moreover, the neonates who obtained Downe's score of more than 5 were less likely to succeed.

Kaplan-Meier survival analysis was performed for each stratum (i.e., 27-32 and 33-36 weeks of gestation). It can be seen that the time to discontinue NIV support is more in NCPAP than HHHFNC group.

Discussion

According to the results obtained from the need for invasive ventilation, no difference was observed between the two modalities of NIV in this study. This implies that HHHFNC and NCPAP are on par with each other when considered as primary modes of NIV in preterm neonates with respiratory distress. This result is in line with

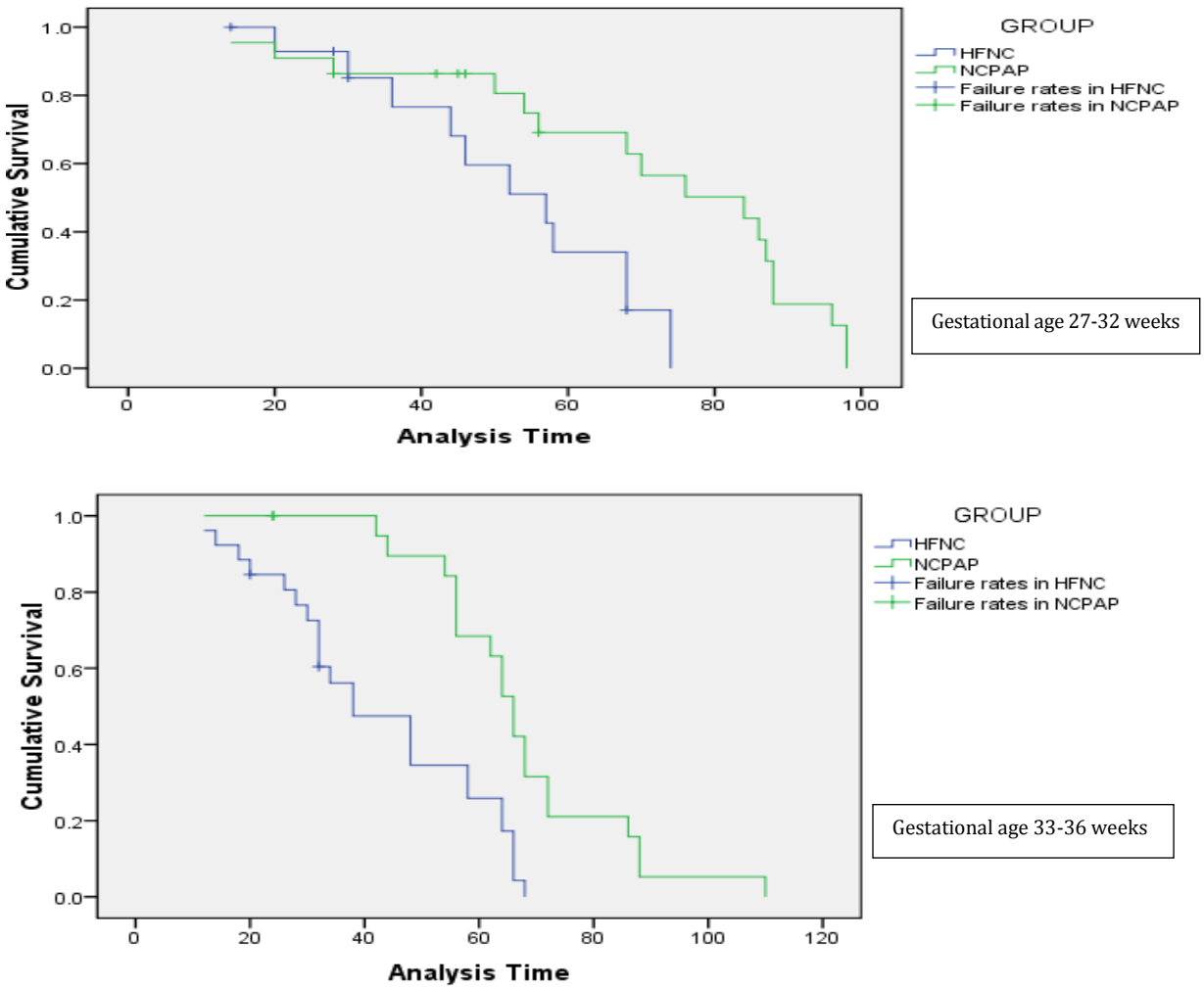

Figure 2. Kaplan-Meier Estimate

the findings obtained from a randomized controlled trial conducted by Bradley A. Yoder et al. (11). They found that HHHFNC appeared to have similar efficacy and safety, compared to NCPAP.

The most common reason for treatment failure in this study was persisting or worsening respiratory distress on the initial mode of NIV. Of the 7 neonates that failed NCPAP, 3 ones were managed with NIPPV and the rest were intubated within 72 h of the primary mode of ventilation. The neonates who failed HHHFNC were switched over to NCPAP initially, out of which 2 ones got intubated due to impending respiratory failure, 1 neonate was scaled up with NIPPV, and the remaining 3 newborns recovered with NCPAP.

The results of a trial performed by Roberts et al. on high flow nasal cannula as primary support in the treatment of early respiratory distress (HIPSTER) showed a higher rate of treatment failure in CPAP with high flow treatment as primary support in preterm infants with respiratory distress (12). The secondary analysis of HIPSTER conducted by Manley et al. (13) proposed a "30-30 rule", in which HHFNC was more likely to be successful if the infants were born ≥30 weeks and received FiO2 ≤ 0.30 early (<2 h of age). However, NCPAP remains to be superior to HHFNC in preventing respiratory failure in this study. In addition, another study done by Manley et al. (14) showed apnea as the main reason for failure and the neonates were treated using NIPPV, NCPAP, or invasive ventilation depending on the degree of distress.

Nevertheless, this trend was not observed when it was employed as a post-extubation NIV mode. The studies done by Campbell and Wilkinson (15, 16) suggested that HHHFNC probably should not be used as an equivalent form of NCPAP in preterm infants. They reported that

HHHFNC was associated with an increase in the number of extubation failures and higher levels of oxygen requirement.

In the same line, another study conducted by Kalyan et al. (17) also reported similar results stating that the HHHFNC obtained higher failure rates, compared to NCPAP group (36.7% vs 14.7%, P=0.043). Furthermore, Holleman-Duray et al. (18) showed that HHHFNC was a safe and well-tolerated device for extubated neonates and decreased the duration of invasive respiratory support, especially in preterm infants. In the present study, the duration of NIV was shorter in HHHFNC, compared to that of NCPAP at 33-36 weeks of gestation, which was statistically significant.

The results of a study conducted by Lampland et al. (19) revealed that HHHFNC could produce continuous distending pressure; however, a pressure-limiting valve within an HHHFNC system appeared to be necessary to limit the potential for delivery of very high distending pressures to the lungs of premature.

Spence et al. (5) mentioned the range of flow rate used in HHHFNC, and they concluded that HHHFNC pressure increased with increasing flow rate. However, in the present study, there was no measurement regarding the pressure at any point in the airway, and no neonates were treated with HHHFNC which developed air leak syndrome during the course. Since all studies face limitations, the long term outcomes of the interventions and the cross over bias between the intervention groups can be regarded as the limitations in this study. It is suggested that future studies perform more randomized clinical trials, preferably multicenter ones which include developing countries to optimize the use of HHHFNC as a primary mode of NIV in preterm neonates.

Conclusion

It can be concluded that HHHFNC does not decrease the need for invasive mechanical ventilation, compared to NCPAP in the first 72 h of support. However, it appears to have similar clinical efficacy and safety as a primary mode of NIV. The results revealed that the total duration of NIV support was shorter in the HHHFNC group. Additional large randomized trials are required to confirm the use of HHHFNC and generate a protocol to follow across all gestational ages.

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Conflicts of interests

There is no conflict of interest regarding the publication of the study.

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