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Original Research Article

Heated humidified high flow nasal cannula versus nasal continuous positive airway pressure for respiratory support in extremely low birth weight preterm infants after extubation: a single centre randomized controlled trial

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ABSTRACT

Background: The objective of the study was to assess the indications, frequency of usage, clinical efficacy, and safety of heated humidified high-flow nasal cannula (HHHFNC) and nasal continuous positive airway pressure (NCPAP) in extremely low birth weight preterm infants (ELBWI) after extubation.
Methods: Hospital based prospective randomized control study involving ELBWI with respiratory distress admitted in NICU. In this study, all selected preterm infants were placed on one of the non-invasive respiratory supports (HHHFNC or NCPAP), after a period of positive pressure ventilation (post-extubation). Reintubation rate within 72 hours after initial extubation, duration of invasive ventilation, duration of non-invasive respiratory support, duration of supplemental oxygen, and time to reach full feeds were the primary outcome measures. Duration of total enteral feeding, average weight gain rate, duration of hospitalization, and complications including nasal injury, IVH, BPD, NEC, ROP, and PDA, were the secondary outcomes.
Results: A sample size of 46 ELBWI were included. HHHFNC effectively reduced the incidence of nasal injury and NEC ($p<0.05$) along with the decreased duration of supplementary oxygen. Additionally, HHHFNC achieved a significant advance in time to reach full enteral feeding; increased the average weight gain before discharge; reduced the duration of hospitalization ($p<0.05$).
Conclusions: HHHFNC was effective in preventing extubation failure in mechanically ventilated preterm ELBWI compared to NCPAP. HHHFNC shortens the duration of supplemental oxygen and significantly reduces the incidence of nasal injury and necrotizing enterocolitis; moreover, it can also reduce the duration of hospitalization and its cost.

Keywords: Extremely low birth weight infant, Non-invasive respiratory support extubation, Preterm, HHHFNC, NCPAP

INTRODUCTION

Respiratory distress in the newborn is one of the commonest problems requiring admission in newborn nursery care and it contributes to 30-40% of admissions in the NICU.[1] Respiratory distress syndrome (RDS) is the single most important cause of morbidity and mortality in preterm infants. Respiratory distress occurs in 2.2% of all newborns and in almost 60% of the infants below 1000 grams.[2] In babies born at 28-32 weeks, RDS occurs in up to 50% of live births. According to the National neonatal perinatal database (NNPD) data (2002-03), 5.8% of the live born infants had respiratory morbidities.[3] In most of the neonatal intensive care units (NICUs),

invasive mechanical ventilation (IMV) is widely used. A retrospective study of infants of ≤1000 grams and ≤28 weeks demonstrated a seventeen fold increase in the risk of any BPD in infants ventilated for >7 days, compared to those extubated on days 1 to 3, with a 62% incidence of moderate or severe BPD in the babies extubated for the first time beyond 7 days of age.[4]

Based on data from the NICHD Neonatal Research Network, Walsh et al showed that each week of additional invasive mechanical ventilation (IMV) was associated with a significant increase in the likelihood of neurodevelopmental impairment.[5] Additionally, the endotracheal tube acts as a foreign body, to a portal of entry for pathogens, increasing the risk of ventilator associated pneumonia and late onset sepsis.[6] Clearly, both unnecessarily prolonged invasive ventilatory support and early extubation are not indicated.

Moreover, early extubation leads to extubation failure, which results in more local damage and worsening in the infant's respiratory condition. Non-invasive respiratory support after extubation helps in preventing apnoea, increased work of breathing and chances of re-intubation. Nasal continuous positive airway pressure is the most prevalent and widely accepted non-invasive respiratory support in clinical practice to prevent extubation failure in preterm infants.[7,8] It improves the residual lung capacity, prevents the collapse of alveoli, and recruits them, thereby preventing apnoea.

However, complications like nasal injury and NEC caused by nasal continuous positive airway pressure (NCPAP) shows great concern on neonate outcome.[9] Humidified high flow nasal cannula is another non-invasive respiratory support for the prevention of extubation failure in preterm infants, as its use may be associated with reduced work of breathing, increased efficiency of ventilation, and decreased chances of reintubation in preterm infants.[10] The increasing use of heated humidified high flow nasal cannula (HHHFNC) is due to its greater comfort of use, better patient compliance, and it is as effective as NCPAP. It also prevents complications like nasal trauma and nasal deformities when compared to NCPAP.[11] Hence, this study was performed to assess whether HHHFNC is as effective and safe as NCPAP in providing non-invasive respiratory support in extremely low birth weight preterm infants (ELBWI), post-extubation.

METHODS

This study was conducted in a neonatal intensive tertiary care unit in OMNIRK hospital, Visakhapatnam, Andhra Pradesh, India, over a period of 1 year from August 2019 to July 2020 including neonates admitted in NICU with respiratory distress. Study design employed was hospital based prospective randomized control study involving neonates with respiratory distress admitted in NICU. Study duration was for 1 year.

Inclusion criteria

Inclusion criteria in the current study were neonates with less than 32 weeks of gestational age, birth weight <1000 grams, preterm neonates who were diagnosed with RDS, requiring invasive mechanical ventilation during the first 96 hours of life and post-extubation changed to non-invasive respiratory support and preterm neonate families who gave informed consent.

Exclusion criteria

Exclusion criteria in the current study were nasopharyngeal pathology (choanal atresia, cleft lip, and palate), congenital diaphragmatic hernia, congenital dysplasia of lung, tracheoesophageal fistula, and other antenatally detected life-threatening congenital heart diseases and neonates who failed to complete the treatment.

After taking informed consent, a total of 46 ELBWI were enrolled in the study by simple random sampling. Selected preterm neonates were randomly assigned to either NCPAP or HHHFNC by simple randomization using computer generated random numbers. The study was double blinded; a fixed and standard protocol for initiation of IMV, identification of extubation failure, and weaning of non-invasive respiratory support was used.

Intubation criteria

Infants can be intubated if they have the following conditions; Silverman Anderson score (SAS) >6, severe apnea (>5 episodes within 24 hours, or >1 requiring positive pressure ventilation); pH <7, P_aCO_2 >65 mmHg, and hemodynamic instability needing inotropic support for ≥4 hours.

Extubation criteria

Conventional ventilation mode; PIP 12-14, PEEP <5, oxygen concentration FiO_2 ≤40%, respiratory rate 30-40/min; HFOV mode; mean airway pressure (MAP) of 6-8 cm H_20, FiO_2 ≤40%, and the amplitude of 12-16; having spontaneous breaths and hemodynamically stable.

HHHFNC therapy was administered using RT330 infant oxygen therapy breathing circuit and MR850 humidifier (Fisher and Paykel junior kit) using short binasal prongs. 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). It is initiated at a flow rate of 3 l/min with Fio_2 titrated between 21%-40%, up to a maximum of 60% to maintain saturation between 90-95%. Flow titrated by increasing 1 l/min up to 6 l/min if the infant shows signs of respiratory distress.

NCPAP was delivered by bubble CPAP system (BC 151, Fisher and Paykel Healthcare, Inc.) with an MR850 humidifier using short binasal prongs as the interface

(Hudson RCI infant nasal prong CPAP cannula system). NCPAP was generated with the use of an underwater bubble system. CPAP initiated at 4-6 cm H_2O, flow rates of 5-7 l/min, and FiO_2 of <40%. To maintain a saturation of 90-95% flow was titrated, CPAP up to 7 cm H_20 and up to maximum FiO_2 60%. A maximum of 8 L/min of flow was allowed to ensure adequate bubbling in the water chamber.

Criteria for weaning of non-invasive respiratory support were as follows: the absence of respiratory distress (SAS: 0-1, minimal or retractions), respiratory rate <60/min, a saturation of >90%, minimal or no need for vasopressor support, normal blood gas, an improving X-ray chest, and hemodynamically stable. The parameters of the HHHFNC group were a stepwise reduction of flow to 1 L/min and FiO_2 to 21%; the parameters of the NCPAP group were a stepwise reduction of FiO_2 by 5% until 21% and CPAP to 4 cm H_2O.

Non-invasive respiratory support failure (HHHFNC or NCPAP) was indicated by the following: if the infant is still hypoxic with SPO_2 <88% in spite of FiO_2 >60%, flow rate >6 L/min for HHHFNC group and CPAP >7 cm H_2O for NCPAP group; severe apnoea, recurrent apnoea or any episode of apnoea requiring positive pressure ventilation; SAS >6 in spite of higher settings; pH <7.2, P_aO_2 <50 mmHg P_aCO_2 >60 mmHg on an arterial blood gas with metabolic acidosis not responding to treatment and requiring inotropic support. In any of the above cases, neonate was kept on invasive mechanical ventilation.

Outcome measures

Baseline characteristics were recorded, including gestational age (weeks), birth weight (grams), sex, Apgar scores, duration of initial feeding (day), mother's age (years), mode of delivery, births (single/multiple), and antenatal use of corticosteroids.

Primary outcome measures included the rate of reintubation within 7 days after initial extubation, duration of invasive ventilation, duration of non-invasive respiratory support, and duration of oxygen supplementation.

Secondary outcome measures included the duration of total enteral feeding (day), average weight gain rate (grams/day), and duration of hospitalization (day). Complications included nasal injury, necrotizing enterocolitis, bronchopulmonary dysplasia, intracerebral hemorrhage, retinopathy of prematurity & patent ductus arteriosus.

Data analysis

The collected data was compiled using MS Excel 2007 and statistical data was represented using means±standard deviations (SDs) and analyzed by Chi-square test or Fisher's exact test for association, with the comparison of means, using Student's t-test or the Mann-Whitney U-test. All data were analyzed using SPSS version 25.0 (SPSS, Chicago, IL, USA). Statistical significance was considered at $p<0.05$.

RESULTS

The study was conducted in a neonatal intensive tertiary care unit in OMNIRK hospital, Visakhapatnam. A total of 46 ELBWI <32 weeks of gestation were enrolled in the study over a period of one year from 1 August to 31 July. Among 46 ELBWI, post-extubation, 24 ELBWI were kept on HHHFNC and 22 ELBWI were kept on NCPAP mode of non-invasive respiratory support. Figure 1 shows flow of subject through the study.

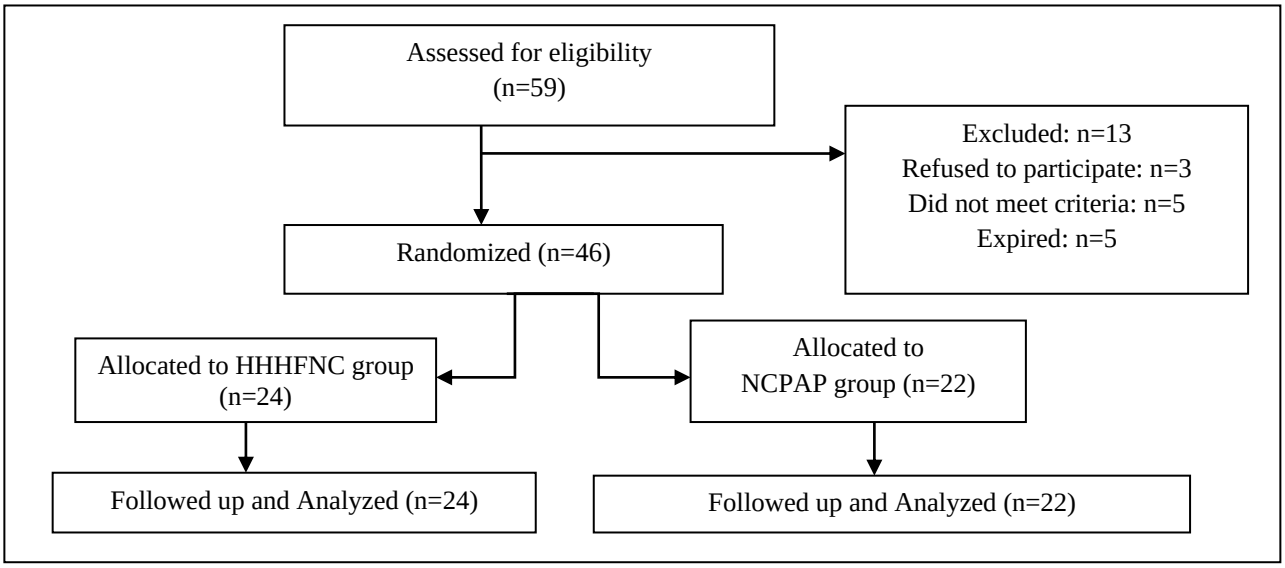

Figure 1: Flow of patients through the trial.

Table 1: Distribution of Baseline characteristics between study groups.

Variables		Groups N (%)		Total (n=46)	P value
		HHHHFNC (n=24)	NCPAP (n=22)		
Gestational age (weeks)	Mean±SD	27.8±2.9	28.5±3.4	28.8±3.2	0.594[b]
	Range	25.2–32.0	25.1–31.5	25.1-32.0	
Birth weight (g)	Mean±SD	816±34.6	798±32.2	818±33.48	0.075[b]
	Range	740–990	720–970	720-990	
Sex	Male	15 (62.5)	15 (68.18)	30 (65.21)	0.686[a]
	Female	9 (37.5)	7 (31.82)	16 (34.78)	
APGAR scores		5.31±0.7	5.49±0.4	5.4±0.6	0.299[b]
Duration of initial feeding	Days	3.25±1.36	3.46±1.23	3.48±1.31	0.796[b]
Mother age (years)		33.5±5.4	34.8±4.7	34.3±5.1	0.391[b]
Mode of delivery	Spontaneous	7 (29.17)	6 (27.27)	13 (28.26)	0.887[a]
	C-section	17 (70.83)	16 (72.72)	33 (71.73)	
Birth number	Single	19 (79.17)	18 (81.81)	37 (80.43)	0.821[a]
	Multiple	5 (20.83)	4 (18.18)	9 (19.56)	
Small for gestational age	No	20 (83.33)	19 (86.36)	39 (84.78)	0.775[a]
	Yes	4 (16.66)	3 (13.63)	7 (15.21)	
Antenatal use of corticosteroids	No	5 (20.83)	5 (22.72)	10 (21.73)	0.876[a]
	Yes	19 (79.17)	17 (77.27)	36 (78.26)	
Extubation age (weeks)	Mean±SD	27.3±2.4	26.8±2.1	27.5±2.3	0.461
	Range	25.5–33.0	25.4–32.5	25.4-33.0	0.594[b]

[a]Chi-square test or Fisher exact test, [b]Student's t- test or Mann-Whitney U-test

Table 2: Comparison of primary outcomes between the study groups.

Variables		Groups N (%)		Statistical test	
		HHHHFNC (n=24) Mean±SD	NCPAP (n=22) Mean±SD	U value	P value
Rate of reintubation within 72 hours	Yes	6 (25.0)	6 (27.27)	0.031	0.861
	No	18 (75.0)	16 (72.72)		
Duration of invasive ventilation	Days	19.7 (11.4-24.9)	18.1 (8.7-23.7)	0.102	0.597[a]
Duration of non-invasive respiratory Support	Days	12.6 (6.1-19.5)	11.2 (4.7-18.9)	0.586	0.391[a]
Duration of oxygen supplementation	Days	29.4 (24.4-41.4)	32.4 (25.4-44.5)	1.783	0.010[a]

[a]Student's t- test or Mann-Whitney U-test

Table 3: Comparison of secondary outcomes between the study groups.

Variables		Groups N (%)		Total (n=46)	P value
		HHHHFNC (n=24) Mean±SD	NCPAP (n=22) Mean±SD		
Duration of enteral feeding	Day	30.23±9.48	36.56±10.65	10.06±3.63	0.039[a]
Average weight gain rate	g/day	16.07±3.10	13.74±4.21	14.62±3.82	0.028[a]
Duration of hospitalization	Day	73.45±18.84	79.24±19.75	79.52±14.95	0.036[a]

[a]Student's t- test or Mann-Whitney U-test.

Table 4: Comparison of complications between the study groups.

Variables		Groups N (%)		Statistical analysis			
		HHHHFNC (n=24) N (%)	NCPAP (n=22) N (%)	X^2	OR	95% CI	P value
Intracerebral hemorrhage (ICH)	Yes	4 (16.66)	4 (18.18)	0.018	0.900	0.196-4.136	0.892
	No	20 (83.33)	18 (81.81)				
Retinopathy of prematurity (ROP)	Yes	9 (37.50)	9 (40.90)	0.056	0.866	0.265-2.836	0.813
	No	15 (62.50)	13 (59.09)				
Patent ductus arteriosus (PDA)	Yes	8 (33.33)	8 (36.36)	0.046	0.875	0.260-2.947	0.829
	No	16 (66.67)	14 (63.63)				
Bronchopulmonary dysplasia (BPD)	Yes	8 (33.33)	7 (31.81)	0.012	1.071	0.312-3.684	0.913
	No	16 (66.67)	15 (68.18)				
Necrotizing enterocolitis (NEC)	Yes	3 (12.50)	8 (36.36)	3.930	0.250	0.056-1.109	0.047
	No	21 (87.50)	14 (63.63)				
Nasal injury	Yes	2 (8.33)	8 (36.36)	5.585	0.159	0.029-0.861	0.018
	No	22 (91.66)	14 (63.63)				

CI, confidence interval; OR, odds ratio; x^2, chi-square test

Baseline characteristics

None of the infants in the two study groups were lost to follow-up. As shown in Table 1, the baseline characteristics of infants were not statistically different between the two groups. Among the 46 infants, the majority of preterm neonates were males (30/46, 65.21%), and the mean gestational age of all neonates was 27.3±3.10 weeks (range 25.1-32.0 weeks).

Primary outcomes

Duration of oxygen supplementation in the HHHFNC group was significantly reduced compared to the NCPAP group in our study, which was statistically significant ($p<0.05$). There were no significant differences in total duration of invasive ventilation, duration of non-invasive respiratory support, and rate of reintubation within 72 hours ($p>0.05$, Table 2).

Secondary outcomes

Duration to reach full enteral feeds (31.24±11.30 vs. 34.21±14.09 days) in the HHHFNC group is earlier compared to NCPAP in our study which was statistically significant ($p<0.05$). Average weight gain before discharge (16.07±3.10 vs. 13.74±4.21; grams/day) was increased, the duration of hospitalization (73.45±18.84 vs. 79.24±19.75 days) was less (Table 3).

Complications

Incidence of nasal injury (8.33 vs. 36.36%) and NEC (12.5 vs. 36.36%) in the HHHFNC group was lower compared to the NCPAP group in our study which was statistically significant ($p<0.05$). There were no significant differences in the incidence of BPD, ROP, ICH, PVL, and PDA between the two groups ($p>0.05$, Table 4).

DISCUSSION

NCPAP is the most prevalent and widely accepted non-invasive respiratory support for post-extubation.[12] NCPAP results in progressive recruitment of alveoli, inflates collapsed alveoli and reduces intrapulmonary shunt. It increases the final residual capacity (FRC) and in turn gaseous exchange. It reduces inspiratory resistance by dilating the airways. This permits a larger tidal volume for a given pressure, so reducing the work of breathing. It regularizes and slows the respiratory rate. It increases the mean airway pressure and improves ventilation perfusion mismatch. In contrast, the physiologic mechanism of HHHFNC by which it is effective to include: flushing the upper airway dead space of CO2, allowing for better alveolar gas exchange; providing a flow adequate to support inspiration, thereby reducing inspiratory work of breathing (WOB); effects of drying/cooling are improved by eliminating lung and airway mechanics; decreasing the metabolic cost of gas conditioning, and dispensing end distending pressure.[13]

Two large RCTs have evaluated HHFNC in neonates. Manley et al. randomized 303 infants of less than 32 weeks to either NCPAP (7cm H2O) or HHFNC (5 to 6 l/min) after extubation. In this noninferiority study, the efficacy of the HHFNC was similar to that of NCPAP, though the result was close to the chosen margin of noninferiority.[14] Yoder et al studied 432 infants from to 42 weeks and found similar efficacy and safety of HHFNC compared to NCPAP, using either device post-extubation or as initial support.[15]

A meta-analysis of randomized controlled trials published

in 2019 showed that for non-invasive respiratory support after extubation, NCPAP group showed lower rates of reintubation than the HHHFNC group (relative risk 1.23, 95% confidence interval 1.01-1.50). The incidence of nasal trauma and pneumothorax in the HFNC group was lower than those in the NCPAP group which was statistically significant ($p<0.0001$ and $p=0.03$).[16] Because of the pressure produced by the dense dressing of the head and face with the NCPAP, it is easy to cause the nasal compression, nasal skin damage, and septal deformities. Nasal congestion can irritate the nostrils leading to the pooling of secretions in the nasal cavity, thereby increasing the chances of getting nasal and systemic infections, especially for ELBWI.[17]

In another systematic review and meta-analysis article published in 2020, Junior et al. also showed the non-inferiority of HHHFNC in relation to NCPAP after the extubation of preterm newborns in terms of therapeutic failure. Besides, the incidence of nasal trauma was lower in the HHHFNC group compared to the NCPAP group which was statistically significant ($p<0.0001$).[18] HHHFNC is a simple device, more easily acceptable non-invasive respiratory support which gets rid of the pressure on the head and face, thus reducing head deformation and nasal injury compared to NCPAP.[19]

In addition to the less weight of the apparatus, HHHFNC has a relatively higher humidification rate of oxygen. If not, there will be more amount of high flow dry and cold air will enter the nasal cavity of the neonate, causing damage to the nasal mucosa, which will increase the chances of getting the infection.

There is an improvement in the work of breathing and compliance of lung in ELBWI which were comparable to the NCPAP 6 cm H2O when the HHHFNC flow reached 3-6 L/min, found by Saslow et al.[20] Sreenan et al found that similar end-expiratory pleural pressures could be maintained between a standard oxygen delivery NC (1 to 2.5 L/min) and NCPAP in a group of 40 premature infants with no differences in desaturations, bradycardia, and apnea.[21] However, this pressure is likely to be highly variable because of leak and the relationship between airway and cannula size. Lampland observed similar end-expiratory pleural pressures between HHFNC (2 to 6 L/min) and NCPAP at 6 cm H2O in premature neonates.[22] This makes it suitable for HHHFNC to replace NCPAP as non-invasive respiratory support post-extubation in ELBWI. Recent studies have indicated that with a flow rate of 4-6 L/min and a suitable size nasal cannula, with a diameter of ~50-75% of that of the infant's nares would be safer for ELBWI preterm.[23]

A meta-analysis also presented that there are no differences in mortality or pulmonary air leakage between the two (HHHFNC and NCPAP) non-invasive respiratory supports. Osman et al found that preterm neonates in the HHHFNC group had significantly less pain and improved tolerance when scored compared to the NCPAP group.[24] This study confirmed that the use of HHHFNC for non-invasive respiratory support post-extubation was significantly shorter than that of the NCPAP, and the rate of reintubation was less than that of the NCPAP group which was statistically significant. These findings are consistent with that of Woodhead et al indicating HHHFNC can reduce work of breathing and the need for reintubation.[25]

Abdominal distension (CPAP belly) and NEC are also important factors in the NCPAP group that can cause the failure of non-invasive respiratory support in preterm infants leading to invasive mechanical ventilation.[26] Incidence of NEC in the NCPAP group compared to the HHHFNC group was higher in our study which was statistically significant ($p<0.05$), which resulted in a longer duration to reach full enteral feeds in the NCPAP group than in the HHHFNC group in our statistically significant study ($p<0.05$).

ELBWI should start with minimal enteral nutrition (MEN) with breast milk as early as possible and the time to reach full enteral feeding can promote the secretion of gastrointestinal hormones and intestinal movement, which are essential for the balance of enteral nutrition and protein/energy.[27] Therefore, HHHFNC is favorable to healthy infant weight gain than NCPAP, which can improve the quality of life.

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

HHHFNC reduced the duration of hospitalization and their costs which were significantly smaller in the HHHFNC group when compared to the NCPAP group was confirmed by this study. The initial duration of feeding in the HHHFNC group was earlier than that in the NCPAP group. The daily weight gain rate was faster and the duration to attain full feeds was earlier in the HHHFNC group than in the NCPAP group. This study also indicated that the incidence of complications such as duration of invasive ventilation and BPD, ROP, PDA, PVL, and intracranial hemorrhage which were not statistically significant ($p>0.05$).

A possible limitation of the above study is that HHHFNC cannot directly measure the actual pressure that is generated of the given flow parameters and whether the thickness of the nasal catheter used directly affects the clinical outcome of the preterm infants.

CONCLUSION

HHHFNC can significantly reduce the rate of reintubation, decreases the duration of non-invasive respiratory support, and significantly reduce the incidence of complications such as nasal injury and NEC compared with that of NCPAP. Incidence of BPD, ROP, PDA, PVL, or intracranial hemorrhage in infants is similar in both groups. Moreover, HHHFNC reduces the duration of hospitalization and its cost, and can greatly reduce the medical burden on low and middle income families. However, HHHFNC can be considered as a safe, efficacious, and more easily acceptable mode of non-invasive respiratory support when compared to NCPAP in ELBWI after extubation. To further explore its safety and efficacy, large-sample multi-centric randomized controlled clinical trials on the mechanism of action of HHHFNC are needed.

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