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Original Research Article

# A COMPARATIVE STUDY OF EFFICACY AND SAFETY BETWEEN HEATED HUMIDIFIED HIGH-FLOW NASAL CANNULA AND NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE IN WEANING OF LOW-BIRTH-WEIGHT PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME AFTER EXTUBATION IN A TERTIARY CARE CENTRE

**K. Sumithra[1], K. Selvaraju[1], V. Mohanraj[2], A. Prabhuraj[1]**

[1]Assistant Professor, Department of Paediatrics, Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamilnadu, India
[2]Postgraduate, Department of Paediatrics, Government Mohan Kumaramangalam Medical College and Hospital, Salem, Tamilnadu, India

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Corresponding Author:
**Dr. A.Prabhuraj,**
Email: rajprabhu1516@gmail.com

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## Abstract

**Background:** Lately, Nasal continuous positive airway pressure (NCPAP) and heated, a humidified high-flow nasal cannula (HHHFNC) have become the backbone of non-invasive respiratory support for preterm infants. The study aimed to compare the clinical efficacy, safety, and outcome of Heated Humidified High Flow Nasal Cannula (HHHFNC) and Nasal Continuous Positive Airway Pressure (NCPAP) in weaning of Low-Birth-Weight Preterm Neonates with Respiratory distress syndrome following extubation. **Materials and Methods:** The hospital-based randomised comparative study was conducted from January 2021 to January 2022 with 25 infants in the HHHFNC group and 25 in the NCPAP group. Re-intubation within 72 hours after initial extubation, total invasive ventilation time, non-invasive ventilation time, and total oxygen inhalation time were taken as primary outcome measures. Duration of enteral feeding, duration of hospitalisation, and complications, including nasal injury, Retinopathy of prematurity (ROP), Bronchopulmonary dysplasia (BPD), Intraventricular haemorrhage (IVH), Necrotising enterocolitis (NEC), Patent ductus arteriosus (PDA), Ventilator-associated pneumonia (VAP), air leak syndrome, sepsis, and epistaxis were considered secondary outcome measures. **Result:** No significant difference in gender, birth weight, gestational age, mode of delivery, corticosteroid given, and grading of RDS between groups. The HHHFNC and NCPAP both have similar efficacy and insignificant results in terms of the rate of reintubation within 72 hours after initial extubation, duration of invasive ventilation, duration of non-invasive respiratory support, duration of enteral feeding, duration of hospitalisation, and complications ($p > 0.05$). **Conclusion:** HHHFNC is equally effective as NCPAP in preventing extubation failure in mechanically ventilated preterm LBW infants with RDS.

## INTRODUCTION

Lately, Nasal continuous positive airway pressure (NCPAP) and heated, humidified high-flow nasal cannula (HHHFNC) has become the backbone of non-invasive respiratory support for preterm infants.[1,2] HHHFNC has gained more popularity as an alternative form of non-invasive respiratory support for newborn infants. On the other hand, NCPAP relies on the principle of continuous expanding pressure.[3-6] HHHFNC is a less invasive form of non-invasive support that will prevent the complications of NCPAP (nasal injury) and low-flow, a non-humidified nasal cannula (thickened secretions, nasal bleeding).[6,7] The HHHFNC approach is widely used in the neonatal intensive care unit (NICU) for various kinds of clinical conditions such as weaning from NCPAP,[8] following extubation,[2,3,9] reducing premature apnea,[10] and as the main therapy for respiratory distress syndrome (RDS).[11] HHHFNC is simple to use, reduces the risk of nasal injuries, and improves feeding with better infant tolerance than NCPAP.[9]

Although there is an increased demand for HHHFNC, large randomised clinical trials (RCTs) are lacking to assess the efficacy between NCPAP


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and HHHFNC in preterm neonates with respiratory distress syndrome (RDS). NCPAP and HHHFNC are currently considered the gold standard for early respiratory management.[1,2] The current study aims to compare the clinical efficacy, safety, and outcome of HHHFNC and NCPAP in weaning of Low-Birth-Weight Preterm Neonates with Respiratory distress syndrome following extubation.

## MATERIALS AND METHODS

The hospital-based randomised comparative study was conducted on 50 preterm low-birth-weight infants in the Neonatal intensive care unit from January 2021 to January 2022. Oral informed consent was obtained from the parents of the preterm infants studied, and the ethics committee clearance was obtained in an institutional ethical committee meeting.

**Inclusion Criteria**

Neonates born with gestational age between 30-36 weeks, birth weight between 1000-2000gm, and preterm neonates diagnosed with RDS requiring mechanical ventilation during the first 72 hours of life and post-extubation were weaned to non-invasive respiratory support were included.

**Exclusion Criteria**

Nasopharyngeal pathology like choanal atresia, cleft lip, cleft palate, congenital diaphragmatic hernia, Tracheoesophageal fistula, Congenital dysplasia of the lung, antenatally diagnosed life-threatening congenital heart diseases, and neonates who failed to complete the treatment were excluded.

All selected preterm neonates were placed alternatively by simple randomisation on one of the non-invasive respiratory support (HHHFNC or NCPAP) after a period of positive pressure ventilation (Post-extubation). Neonates were divided into two groups: The HHHFNC group and the NCPAP group, and each group enrolled 25 preterm low birth weight (1000gm-2000gm) neonates with gestational age (GA) 30-36 weeks with respiratory distress syndrome. Both groups fulfilled the same inclusion and exclusion criteria.

The study was double-blinded; a fixed and standard protocol for initiating invasive mechanical ventilation, identifying extubation failure, and weaning of non-invasive respiratory support was used.

**Intubation Criteria:** Neonates can be intubated if neonates have the following conditions; Silverman Anderson score (SAS) >6, severe apnea (>5 episodes within 24 hours, or >1 requiring positive pressure ventilation); pH 65 mmHg, and hemodynamic instability needing inotropic support for ≥4 hours

**Extubation Criteria:** Neonates can be weaned from conventional ventilation mode if the baby maintains minimal ventilator settings like PIP 12-14, Neonates can be weaned from conventional ventilation mode if baby maintains minimal ventilator settings like PIP 12-14, PEEP <5, oxygen concentration FiO2 requirement ≤40%, respiratory rate 30- 40/min and having spontaneous breaths and hemodynamically stable. HHHFNC therapy was administered using an 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 FiO2 titrated between 21%-40% and 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. The CPAP initiated at 4-6 cm H2O, flow rates of 5-7 L/min, and FiO2 of <40%. The flow was titrated, PEEP up to 7 cm H2O and up to maximum FiO2 60% to maintain a 90-95% saturation. An 8 L/min flow was administered to ensure adequate bubbling in the water chamber.

Criteria for weaning of non-invasive respiratory support: The absence of respiratory distress (SAS: 0-1, minimal or no retractions), respiratory rate 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 FiO2 to 21%; the parameters of the NCPAP group were a stepwise reduction of FiO2 by 5% until 21% and PEEP to 4 cm H2O.

Non-invasive respiratory support failure (HHHFNC or NCPAP): If the infant is still hypoxic with SPO2 60%, flow rate >6 L/min for HHHFNC group and PEEP >7 cm H2O for NCPAP group; severe apnoea or recurrent apnoea or any episode of apnoea requiring positive pressure ventilation; SAS >6 despite higher settings; requiring inotropic support. The neonate was kept on invasive mechanical ventilation in the above cases.

Outcome measures: Baseline characteristics were recorded, including gestational age (weeks), birth weight (grams), sex, APGAR scores, mode of delivery, antenatal use of corticosteroids, RDS grading in CXR, and surfactant administration. Primary outcome measures included the reintubation rate within 72 hours 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) and duration of hospitalisation (day). Complications included nasal injury, air leak syndrome, necrotising enterocolitis, bronchopulmonary dysplasia, intracranial haemorrhage, retinopathy of prematurity, patent ductus arteriosus, ventilator-associated pneumonia, epistaxis, and sepsis.


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**Data Analysis:** The collected data was compiled using MS Excel 2007, and statistical data was represented using means ± standard deviations (SDs) and analysed 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 analysed using SPSS version 25.0 (SPSS, Chicago, IL, USA). Statistical significance was considered at $p<0.05$.

## RESULTS

Among 50 cases, 27 were male (54%), and 23 were female (46%), and the p-value is 0.777. Among 50 cases, 29 had birth weights between 1000 to 1500gm, constituting 58%, and 21 had birth weights between 1500-2000gm, constituting 42%; the p-value is 0.390. Among 50 cases, 14 were GA between 30-32 weeks constituting 28%; 18 were GA between 32-34 weeks, constituting 36%; and 18 were GA between 34-36 weeks, constituting 36%; the p-value is 0.776. Among 50 cases, nine were delivered by assisted vaginal delivery, constituting 18%; 16 were delivered by LSCS, constituting 32%; and 25 were delivered by normal vaginal delivery, constituting 50%; the p-value is 0.151. In the mode of delivery and weaning in 50 cases, 33 were administered corticosteroids, constituting 66%, and 17 were not administered corticosteroids, constituting 34%; the p-value is 0.136. 2% constituted grade 1 RDS, 28% constituted grade 2 RDS, 42% constituted grade 3 RDS, and 28% constituted grade 4 RDS, and the p-value is 0.721 [Table 1].

APGAR score at 1 min and weaning is shown in Table. 7, 42 had an APGAR at 1 minute of 7 or greater, accounting for 84%, 7 had an APGAR at 1 minute of 4 to 6, accounting for 14%, and 1 had an APGAR at 1 minute, accounting for 2%, with a p-value of 0.303.

At 5min, 47 had an APGAR at 5 minutes of 7 or greater, accounting for 94%, 2 had an APGAR at 5 minutes of 4 to 6, accounting for 4%, and 1 had an APGAR at 5 minutes, accounting for 2%, with a p-value of 0.600 [Table 2].

Forty-four had surfactant given, 88%, and six had surfactant not given, 12%, and the p-value is 0.384. $FiO_2$ requirement among 50 cases, 46% required $FiO_2$ <40% and 54% required $FiO_2$ > 40%, and the p-value is 0.395. 52% needed < 48 hours of invasive ventilation, and 48% needed >48 hours of invasive ventilation, and the p-value is 0.571.

Among 50 cases, 18% needed <48 hours of non-invasive ventilation, and 82% needed >48 hours of invasive ventilation, and the p-value is 0.269. In the HHHFNC group, 16% of patients were reintubated within 72 hours; in the NCPAP group, 18% were reintubated within 72 hours; the p-value is 0.713. In the HHHFNC group, 3 cases (12%) were expired, and in the NCPAP group, 3 cases (12%) were expired; the p-value is 0.999 [Table 3].

HHHFNC has been associated with a lower incidence of air-leak syndrome and ventilator-associated pneumonia when compared with NCPAP [Table 4].

Oxygenation duration is higher in the NCPAP group when compared with the HHHFNC group, and the p-value is 0.036. The median and IQR for the HHHFNC group's duration of hospitalisation are 18 and (13, 27). The median and IQR for the NCPAP group are 22 and (16, 28), with a p-value of 0.393.

The median and IQR for the HHHFNC group's duration of enteral feeding are 15 and (9,22), respectively. In contrast, the median and IQR for the NCPAP group are 15 and (10.5,19), respectively, with a p-value of 0.999 [Table 5].

**Table 1: Demographic data of the study**

| | | After extubation weaned to | | P-value |
|---|---|---|---|---|
| | | HHHFNC | NCPAP | |
| Gender | Boy | 14 (56%) | 13 (52%) | 0.777 |
| | Girl | 11 (44%) | 12 (48%) | |
| Birth weight of the baby | 1000-1500gm | 13 (52%) | 16 (64%) | 0.39 |
| | 1500-2000gm | 12 (48%) | 9 (36%) | |
| Gestational age of baby | 30-32weeks | 6 (24%) | 8 (32%) | 0.776 |
| | 32-34weeks | 9 (36%) | 9 (36%) | |
| | 34-36weeks | 10 (40%) | 8 (32%) | |
| Mode of delivery | Avd | 2 (8%) | 7 (28%) | 0.151 |
| | Lscs | 8 (32%) | 8 (32%) | |
| | Nvd | 15 (60%) | 10 (40%) | |
| Is an corticosteroid given | Yes | 19 (76%) | 14 (56%) | 0.136 |
| | No | 6 (24%) | 11 (44%) | |
| Grading of rds in cxr | Grade 1 | 0 (0%) | 1 (4%) | 0.721 |
| | Grade 2 | 8 (32%) | 6 (24%) | |
| | Grade 3 | 10 (40%) | 11 (44%) | |
| | Grade 4 | 7 (28%) | 7 (28%) | |

**Table 2: APGAR score at and weaning**

| APGAR score | | After extubation weaned to | | P-value |
|---|---|---|---|---|
| | | HHHFNC | NCPAP | |
| AT 1min | <4 | 1 (4%) | 0 (0%) | 0.304 |
| | 4 to 6 | 2 (8%) | 5 (20%) | |
| | 7 OR >7 | 22 (88%) | 20 (80%) | |
| AT 5min | <4 | 0 (0%) | 1 (4%) | 0.6 |


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| | | | | |
|---|---|---|---|---|
| | 4 TO 6 | 1 (4%) | 1 (4%) | |
| | 7 OR >7 | 24 (96%) | 23 (92%) | |

**Table 3: Various findings, outcomes and weaning**

| | | After extubation weaned to | | P-value |
|---|---|---|---|---|
| | | HHHFNC | NCPAP | |
| Is surfactant given? | YES | 23 (92%) | 21 (84%) | 0.384 |
| | NO | 2 (8%) | 4 (16%) | |
| $FiO_2$ requirement | <40% | 13 (52%) | 10 (40%) | 0.395 |
| | >40% | 12 (48%) | 15 (60%) | |
| Duration of invasive ventilation | <48HRS | 12 (48%) | 14 (56%) | 0.571 |
| | >48HRS | 13 (52%) | 11 (44%) | |
| Duration of non-invasive ventilation | <48HRS | 6 (24%) | 3 (12%) | 0.269 |
| | >48HRS | 19 (76%) | 22 (88%) | |
| Is the baby reintubated within 72 hours after initial extubation? | YES | 4 (16%) | 5 (20%) | 0.713 |
| | NO | 21 (84%) | 20 (80%) | |
| Outcome | IMPROVED | 22 (88%) | 22 (88%) | 0.999 |
| | EXPIRED | 3 (12%) | 3 (12%) | |

**Table 4: Complications and weaning**

| Complications | After extubating weaned to | | Outcome | |
|---|---|---|---|---|
| | HHHFNC | NCPAP | EXPIRED | IMPROVED |
| AIR LEAK SYNDROME | 0 (0%) | 3 (12%) | 1 (17%) | 2 (5%) |
| EPISTAXIS | 2 (8%) | 0 (0%) | 0 (0%) | 2 (5%) |
| NEC | 0 (0%) | 1 (4%) | 1 (17%) | 0 (0%) |
| NASAL INJURY | 0 (0%) | 6 (24%) | 0 (0%) | 6 (14%) |
| PDA | 1 (4%) | 1 (4%) | 1 (17%) | 1 (2%) |
| ROP | 1 (4%) | 1 (4%) | 0 (0%) | 2 (5%) |
| SEPSIS | 4 (16%) | 3 (12%) | 0 (0%) | 7 (16%) |
| VAP | 1 (4%) | 3 (12%) | 1 (17%) | 3 (7%) |

**Table 5: Duration of oxygenation, hospitalisation and enteral feeding in days**

| After extubation weaned to | Duration of oxygenation | | P-value¥ |
|---|---|---|---|
| | MEDIAN | IQR | |
| HHHFNC | 3 | (2,4) | 0.036 |
| NCPAP | 3.5 | (3,5) | |
| DURATION OF HOSPITALISATION | MEDIAN | IQR | |
| HHHFNC | 18 | (13,27) | 0.393 |
| NCPAP | 22 | (16,28) | |
| DURATION OF ENTERAL FEEDING IN | MEDIAN | IQR | |
| HHHFNC | 15 | (9,22) | 0.999 |
| NCPAP | 15 | (10.5,19) | |

## DISCUSSION

NCPAP is the most widely accepted non-invasive respiratory support for post-extubation in preterm neonates with RDS.[12] NCPAP helps in the progressive recruitment of alveoli, inflates collapsed alveoli, and reduces intrapulmonary shunt, increasing the functional residual capacity (FRC) and gaseous exchange. NCPAP also reduces inspiratory resistance by dilating the airways. The above mechanism causes a larger tidal volume for a given pressure, so it reduces the work of breathing. It normalises and reduces the respiratory rate. CPAP also increases the mean airway pressure and improves ventilation-perfusion mismatch. In contrast, the physiologic mechanism of HHHFNC involves flushing the upper airway dead space of CO2, allowing for good alveolar gaseous exchange and providing a flow adequate to support inspiration, which reduces the inspiratory work of breathing (WOB). The effects of drying and cooling are improved by eliminating the lung and airway mechanics, which also decreases the metabolic cost of gas conditioning, and by dispensing end-distending pressure.[13]

In our study, there was no statistically significant difference between HHHFNC and NCPAP in terms of duration of hospitalisation, reintubation rate within 72 hours, and duration of enteral feeding. So many large RCTs have been evaluated in neonates regarding HHHFNC and NCPAP. Gangu DR et al. found that initiating HHHFNC during weaning from a mechanical ventilator prevents extubation failure in ELBW preterm infants with RDS compared to NCPAP. HHHFNC also shortens the duration of oxygen supplementation, reduces the duration of hospitalisation and its cost, and decreases the incidence of nasal injury and necrotising enterocolitis.[2] Manley et al. In this non-inferiority study, the efficacy of the HHHFNC was the same as that of NCPAP. Still, the incidence of nasal trauma was significantly lower in the high-flow nasal-cannula group than in the NCPAP group (P=0.01), and there were no significant differences in rates of serious adverse events.[14]

Shokouhi et al. found no significant statistical difference between the NCPAP and HFNC groups in


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terms of the primary outcomes like mean duration of respiratory support, mean length of hospital stay, rate of unresponsiveness to treatment, re-intubation, meantime of the first nutrition, mean duration of reaching full feeding, and secondary outcomes like side effects of the nasal cannula (e.g., pneumothorax, intraventricular haemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, and patent ductus arteriosus) and nasal trauma (P=0.05).[15]

Chen et al., a randomised controlled trial done on 94 ELBW infants, showed the results of HHHFNC effectively prevented extubation failure in mechanically ventilated preterm ELBWI w HHHFNC also reduces oxygen consumption time. It significantly reduces the incidence of nasal injury and necrotising enterocolitis. It also reduces the duration of stay and hospitalisation costs. 9 Bhawan Deep Garg et al. found no significant difference between NCPAP and HHHFNC when used post-extubation in VLBW infants.[16] Yoder et al. found that HHHFNC had the same efficacy and safety as NCPAP, using either device as post-extubation or as initial ventilation support in neonates.[17] Esmaeilnia Shirvani et al. compared HHHFNC and NCPAP and found both had the same efficacy in premature infants with RDS. Still, HHHFNC is the less invasive method of ventilation when compared with NCPAP.[18]

According to Jeonghee Shin et al., HHHFNC is not inferior to NCPAP for the initial treatment of preterm infants (30 and 35 weeks of gestation) with respiratory distress and has equal efficacy between the two.4 Xi Lin et al. found that HHHFNC has a higher treatment failure rate when used as primary respiratory support for preterm infants with RDS than NCPAP.[19] Armanian et al. concluded that HHHFNC is not recommended as a primary mode of treatment for preterms with RDS.[20]

In our study, we found that HHHFNC has similar efficacy when compared with NCPAP in terms of duration of hospitalisation, duration of enteral feeding, rate of reintubation within 72 hours, and complications. HHHFNC is associated with decreased duration of oxygenation and a lower incidence of nasal injury when compared with NCPAP.

## CONCLUSION

The HHHFNC is equally effective as NCPAP in preventing extubation failure in preterm neonates with respiratory distress syndrome after extubation and also has the same efficacy as NCPAP in terms of rate of reintubation within 72 hours after initial extubation, duration of invasive ventilation, duration of non-invasive respiratory support, duration of enteral feeding, and duration of hospitalisation. HHHFNC has been associated with a lower incidence of air-leak syndrome and ventilator-associated pneumonia, a shorter duration of oxygenation, and a lower incidence of nasal injury when compared with NCPAP.

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