

Comparative Study of Weaning Strategies from Nasal CPAP in Preterm Neonates: Direct Weaning Versus Via HHHFNC

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OPEN ACCESS

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Received: 21-06-2025

Accepted: 09-07-2025

Available Online: 02-08-2025



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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a leading cause of morbidity and mortality in preterm neonates due to surfactant deficiency and immature lung development. Non-invasive respiratory support, particularly nasal continuous positive airway pressure (nCPAP), is standard for management. This study aimed to compare the efficacy and safety of direct weaning from nCPAP versus transition to HHHFNC in preterm neonates <32 weeks gestation with RDS.

Methods: In this prospective randomized controlled trial conducted at the NICU of RNT Medical College, Udaipur, 148 preterm neonates were randomized into two groups: Group A (nCPAP weaning) and Group B (HHFNC weaning). Primary outcome was successful weaning from non-invasive ventilation. Secondary outcomes included weaning failure rates, duration of respiratory support, hospital stay, complications, and mortality. Biochemical parameters were also assessed.

Results: The HHHFNC group showed significantly higher weaning success (78.4% vs. 52.7%, $p=0.003$), lower weaning failure post-discontinuation (18.9% vs. 40.5%, $p=0.004$), and fewer complications (12.2% vs. 31.1%, $p=0.005$), especially nasal trauma. Mortality was significantly lower in the HHHFNC group (4.1% vs. 13.5%, $p=0.042$). There were no significant differences in biochemical markers between groups. The restricted mean time to clinical outcome supported the non-inferiority of HHHFNC to nCPAP.

Conclusions: HHHFNC is a safe, effective, and superior alternative to direct nCPAP weaning in preterm neonates with RDS. It offers higher weaning success, fewer complications, and reduced mortality, supporting its integration into standard neonatal respiratory care protocols.

Keywords: Preterm neonates, respiratory distress syndrome, nasal CPAP, HHHFNC, weaning, neonatal respiratory support, randomized controlled trial, non-invasive ventilation, neonatal intensive care, neonatal outcomes.

INTRODUCTION

Respiratory distress syndrome (RDS) remains a significant cause of morbidity and mortality in preterm neonates, primarily due to surfactant deficiency and immature lung development^{1,2}. Affecting a substantial proportion of infants born before 32 weeks' gestation, RDS often necessitates respiratory support to ensure adequate oxygenation and ventilation.³ The long-term consequences of severe RDS can include chronic lung disease and neurodevelopmental impairments, underscoring the critical need for effective and safe respiratory management strategies in this vulnerable population.⁴ Nasal continuous positive airway pressure (nCPAP) has emerged as a cornerstone in the non-invasive respiratory support of preterm neonates with RDS.⁵ By providing a constant distending pressure, nCPAP helps to maintain lung volume, prevent alveolar collapse, and improve gas exchange, thereby reducing the need for invasive mechanical ventilation and its associated complications.^{6,7} The widespread adoption of nCPAP has significantly

improved outcomes for preterm infants, making it an indispensable tool in neonatal intensive care units (NICUs) worldwide.

Despite the proven benefits of nCPAP, the process of weaning infants off respiratory support presents considerable challenges. Inappropriate or premature discontinuation of nCPAP can lead to extubation failure, increased respiratory effort, and the need for re-initiation of support, which may prolong hospital stay and increase the risk of complications.⁸ Various weaning strategies have been explored, including gradual pressure reduction and intermittent nCPAP, yet optimal approaches remain a subject of ongoing research to minimize adverse events and facilitate successful transition to spontaneous breathing.⁹ Heated humidified high-flow nasal cannula (HHFNC) has gained increasing attention as an alternative or adjunctive non-invasive respiratory support modality for preterm neonates.¹⁰ HHFNC delivers warmed and humidified oxygen-air mixtures at high flow rates, offering benefits such as improved mucociliary clearance, reduced work of breathing, and provision of a modest positive airway pressure. Its ease of use and perceived comfort for infants have led to its growing popularity in NICUs, particularly in the post-extubation period or as a step-down therapy from nCPAP.¹¹ Given the ongoing debate regarding optimal weaning practices and the increasing use of HHFNC, this study aims to compare the efficacy and safety of weaning preterm neonates from nCPAP versus transitioning them to HHFNC. By evaluating key outcomes such as successful weaning rates, time to complete weaning, and incidence of complications, this prospective randomized controlled trial seeks to provide evidence-based insights to guide clinical practice and improve respiratory management for preterm infants with RDS.

MATERIALS AND METHODS

This hospital-based prospective randomized controlled trial was conducted in the Neonatal Intensive Care Unit (NICU) of RNT Medical College, Udaipur, from July 2024 to July 2025, following approval from the Institutional Ethics Committee. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment.

Study Population:- The study population comprised preterm neonates with gestational age less than 32 weeks and birth weight below 1.8 kg, admitted within the first 24 hours of life and diagnosed with respiratory distress syndrome (RDS). Eligible neonates were required to be stabilized on bubble nasal continuous positive airway pressure (nCPAP) with a positive end-expiratory pressure (PEEP) ≤ 5 cm H₂O and fraction of inspired oxygen (FiO₂) ≤ 0.30 for a minimum of 24 hours.

Inclusion and Exclusion Criteria:- Neonates fulfilling the following criteria were included: (i) gestational age < 32 weeks, (ii) birth weight < 1.8 kg, (iii) admission within 24 hours of birth, (iv) diagnosis of RDS requiring initial stabilization on nCPAP. Exclusion criteria included the presence of major congenital malformations, significant congenital heart disease, chromosomal abnormalities, severe intraventricular haemorrhage (grade III or IV), and refusal of parental consent.

Sample Size:- sample size was 74 neonates per group, totalling 148 participants.

Randomization and Blinding:- Participants were randomized into two groups using a computer-generated random number table. Group allocation was concealed in sequentially numbered, opaque, sealed envelopes which were opened only after enrolment. Due to the nature of the intervention, blinding of caregivers was not feasible; however, outcome assessors and data analysts were blinded to group allocation.

Intervention Protocol:- All neonates were initially managed with bubble nCPAP using Hudson binasal prongs and humidified air-oxygen mixtures. Once stabilization criteria were met, neonates were randomized into one of the two intervention arms:

- **Group A (CPAP Group):** Infants remained on nCPAP. Pressure was reduced by 1 cm H₂O every 24 hours until a PEEP of 4 cm H₂O was achieved. CPAP was then discontinued if the infant remained clinically stable.
- **Group B (HHFNC Group):** Infants were transitioned to heated humidified high-flow nasal cannula (HHFNC) using Optiflow Junior nasal prongs. Initial flow rates were set at 6–8 L/min depending on weight and reduced by 1 L/min every 12 hours down to 2–3 L/min. HHFNC was discontinued once clinical stability was confirmed.

All neonates received standard supportive care, including caffeine citrate therapy for apnoea prevention and routine airway suctioning every 4–6 hours.

Data Collection and Statistical Analysis :- Demographic, clinical, and biochemical data were recorded using a pre-structured data collection form. Laboratory parameters (random blood sugar, haemoglobin, total leukocyte count, platelet count, serum urea, creatinine, and C-reactive protein) were assessed at baseline, Day 0, and Day 7 post-intervention. Data were entered and analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean \pm standard deviation and compared using Student's t-test. Categorical variables were summarized using frequencies and percentages, and associations were analyzed using the Chi-square test or Fisher's exact test where appropriate. A p-value of <0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

Table 1: Maternal and Neonatal Baseline Characteristics (CPAP vs HHFNC, n = 148)

Characteristic	CPAP Group (n=74)	HHFNC Group (n=74)	p-value
Maternal Age (years)	23.11 \pm 3.54	23.47 \pm 2.56	0.54
Primigravida (%)	36.5%	37.8%	0.84
No Antenatal Complications (%)	60.8%	66.2%	0.86
Vaginal Delivery (%)	73.0%	66.2%	0.37
Gestational Age (weeks)	30.19 \pm 0.85	30.22 \pm 0.87	0.576
Birth Weight (kg)	1.26 \pm 0.21	1.29 \pm 0.21	0.732
Male Sex (%)	51.3%	47.3%	0.129
No Resuscitation Required (%)	56.8%	73.0%	0.118
Silverman Anderson Score	4.96 \pm 1.96	4.69 \pm 1.67	0.478

Table 2: Biochemical Parameters at Baseline, Day 0, and Day 7 (CPAP vs HHFNC)

Parameter	Group	Baseline	Day 0	Day 7	p-value (Day 7)
RBS (mg/dL)	CPAP	88.80 \pm 27.18	87.61 \pm 20.05	112.37 \pm 31.21	0.825
	HHFNC	90.02 \pm 25.45	86.42 \pm 21.16	111.32 \pm 30.61	
Haemoglobin(g/dL)	CPAP	15.80 \pm 1.77	14.79 \pm 1.88	14.09 \pm 1.95	0.871
	HHFNC	15.73 \pm 1.71	14.65 \pm 1.84	14.14 \pm 1.91	
TLC ($\times 10^3/\text{mm}^3$)	CPAP	14.45 \pm 3.87	15.56 \pm 3.28	16.46 \pm 3.38	0.754
	HHFNC	14.68 \pm 3.64	15.28 \pm 3.39	16.28 \pm 3.49	
Platelets ($\times 10^3/\text{mm}^3$)	CPAP	193.04 \pm 65.4	167.49 \pm 54.98	167.21 \pm 89.20	0.944
	HHFNC	189.16 \pm 62.8	165.37 \pm 51.14	168.32 \pm 88.74	
S. Urea (mg/dL)	CPAP	39.14 \pm 9.95	33.74 \pm 11.47	41.90 \pm 11.11	0.728
	HHFNC	38.47 \pm 10.12	34.21 \pm 11.90	41.28 \pm 11.39	
S.Creatinine (mg/dL)	CPAP	0.68 \pm 0.28	0.63 \pm 0.33	0.79 \pm 0.40	0.909
	HHFNC	0.70 \pm 0.26	0.64 \pm 0.30	0.80 \pm 0.40	
CRP (mg/L)	CPAP	3.86 \pm 4.04	11.61 \pm 5.15	15.54 \pm 17.93	0.883
	HHFNC	4.10 \pm 3.98	11.83 \pm 5.02	15.17 \pm 17.96	

Table 3: Weaning Outcomes, Complications, and Clinical Results (CPAP vs HHFNC)

Variable	CPAP (%) or Mean \pm SD	HHFNC (%) or Mean \pm SD	p-value
Weaning Success (%)	52.7	78.4	0.003*
Weaning Failure During Weaning (%)	6.8	2.7	0.049*
Weaning Failure After Weaning (%)	40.5	18.9	0.004*
NIV Duration (days)	8.07 \pm 5.32	9.65 \pm 4.37	0.050*
Oxygen Duration (days)	9.14 \pm 6.17	10.20 \pm 4.83	0.243
Hospital Stay (days)	19.00 \pm 10.99	21.26 \pm 8.63	0.167
Mode of Ventilation After Failure (%)	SIMV: 24.3	SIMV: 9.5	0.009*

	CPAP: 21.6	CPAP: 12.2	
	Nasal Prongs: 1.4	Nasal Prongs: 0.0	
No Support Needed Post-Weaning (%)	52.7	78.4	—
Complications Present (%)	31.1	12.2	0.005*
- Nasal Trauma (%)	9.5	2.7	—
- Respiratory Complications (%)	10.9	0.0	—
- Infectious Complications (%)	5.5	4.1	—
- Neurological/GI/Cardiac (%)	5.4	5.4	—
Discharged (%)	86.5	95.9	0.042*
Mortality (%)	13.5	4.1	0.042*
LAMA (%)	4.1	1.4	—
Restricted Mean Time (days)	13.96	14.39	—

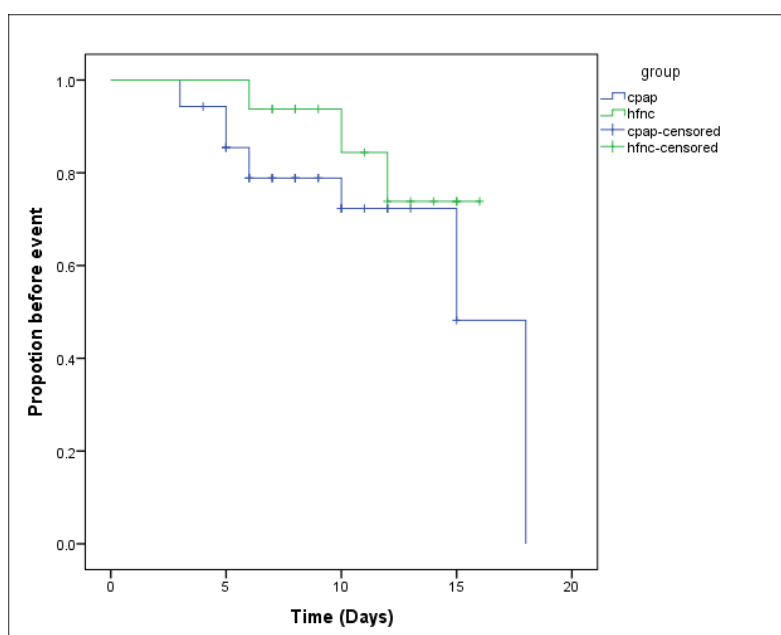


Figure1: Kaplan–Meier Survival Curve Comparing Time to Clinical Outcome Between nCPAP and HHHFNC Groups

Figure 1 shows that restricted mean time to clinical outcome was 13.96 days for nCPAP and 14.39 days for HHHFNC. With a 15% non-inferiority margin, the results confirm that HHHFNC is non-inferior to nCPAP, supporting its use as an effective alternative for neonatal respiratory support.

DISCUSSION

The management of respiratory distress in preterm neonates is a critical aspect of neonatal care, with a focus on effective yet minimally invasive support. The present study was conducted to compare the outcomes of two weaning strategies: direct weaning from nasal continuous positive airway pressure (nCPAP) versus a step-down approach using heated humidified high-flow nasal cannula (HHHFNC) in preterm neonates <32 weeks gestation. Our findings provide compelling evidence that utilizing HHHFNC as a transitional support modality is a safer and more effective strategy. The data from this trial demonstrated significantly higher weaning success, fewer complications, and lower mortality in the HHHFNC group, contributing to a growing body of evidence that supports its use in this context.

A primary outcome of this study was the significantly higher rate of weaning success in the HHHFNC group (78.4%) compared to the CPAP group (52.7%, $p=0.003$). This suggests HHHFNC provides a more stable physiological bridge for immature lungs, enhancing the transition off respiratory support. Our findings are directly corroborated by the CHiPS randomized trial by Clements et al., which also demonstrated a significant reduction in treatment failure among neonates

weaned using HHFNC compared to direct CPAP weaning (24% vs. 47.5%).¹² Further support comes from Tang et al., who observed that infants weaned abruptly without HHFNC were more likely to deteriorate and require re-initiation of support, whereas those transitioned to HHFNC experienced smoother transitions.¹³ Choi et al. also concluded that HHFNC is a safe and practical alternative to CPAP in preterm infants, offering similar efficacy with improved patient comfort.¹⁴

The lower rate of weaning failure in our HHFNC group, both during the weaning period (2.7% vs. 6.8%) and after discontinuation (18.9% vs. 40.5%), aligns with trends noted in a meta-analysis by Balhareth & Razak, which pointed towards lower post-extubation instability with HHFNC.¹⁵ While the evidence in their review was graded as low certainty due to heterogeneity, our results provide stronger, statistically significant support for this benefit. The physiological basis for this stability may lie in the consistent, heated, and humidified flow that reduces airway resistance and metabolic cost of breathing. The literature is not uniformly in favour of HHFNC in all contexts. Manley et al., in a large trial in special care nurseries, reported a higher rate of treatment failure with HHFNC (20.5%) compared to CPAP (10.2%) .¹⁶ It is crucial to note that their study evaluated HHFNC as a *primary* respiratory support, not as a weaning tool, which represents a different clinical application and may explain the discrepancy with our findings. Our study, with its randomized controlled design, mitigates this bias and clearly demonstrates HHFNC's superiority specifically for weaning.

Our study revealed a significantly lower overall complication rate in the HHFNC group (12.2%) compared to the CPAP group (31.1%, $p=0.005$). The most pronounced difference was in the incidence of nasal trauma, a well-documented drawback of the CPAP interface. Our findings are strongly supported by a randomized controlled trial by Soonsawad et al., who also reported significantly less nasal trauma in their HHFNC group versus the CPAP group (20% vs. 42%) .¹⁷ The high incidence of nasal injury with CPAP is further highlighted by Guimarães et al., who reported that up to 65% of very low birth weight infants on prolonged CPAP developed some form of nasal trauma.¹⁸

The Cochrane review by Wilkinson et al. provides robust, high-level evidence, concluding that HHFNC is associated with significantly reduced nasal trauma compared to CPAP when used for post-extubation support.¹⁹ This advantage is further confirmed by Morsy et al., who noted that 90.6% of all nasal trauma cases in their comparative study occurred in the CPAP group,²⁰ and by Mahboob et al., who linked CPAP to a higher incidence of sepsis and nasal mucosal injuries in their 2024 study.²¹ By providing a gentler interface, HHFNC circumvents the pressure points and friction that cause skin breakdown and septal damage, leading to improved patient tolerance, which likely contributes to the higher weaning success we observed.

One of the most clinically significant findings of this study was the markedly lower mortality rate in the HHFNC group (4.1%) compared to the CPAP group (13.5%, $p=0.042$), alongside a higher rate of successful discharge. This suggests that the benefits of HHFNC extend beyond comfort and weaning efficacy to improved survival in this cohort. While large-scale trials have often reported comparable mortality rates, our finding may reflect the cumulative benefit of reduced complications and weaning failures. This aligns with the perspective of comprehensive reviews, such as that by Roehr et al., who emphasize that a key goal of modern non-invasive ventilation is to minimize iatrogenic harm, including air leaks and trauma, to improve long-term respiratory outcomes.²² Furthermore, the successful management of an extremely low birth weight neonate with HHFNC in a resource-limited setting, as reported by Enato et al.²³, demonstrates the modality's potential to improve outcomes even in the most vulnerable populations. It is important to contextualize this finding. A large randomized trial by Shirvani et al. ²⁴ found no significant differences in major outcomes, including mortality, between HHFNC and CPAP groups. Similarly, a trial by Shin et al. established the non-inferiority of HHFNC to CPAP as primary support but did not demonstrate superiority in terms of mortality.²⁵ The study by Mahboob et al. found that while HHFNC users had shorter hospital stays, CPAP was associated with slightly higher survival in *extremely* preterm infants, highlighting the importance of patient selection .²¹ The positive outcome in our study may therefore be specific to the population of preterm infants <32 weeks undergoing a structured weaning protocol, where the reduction of weaning-related stress and injury proves critical.

In our study, there were no statistically significant differences in biochemical markers—including inflammatory and metabolic parameters—between the two groups at baseline, Day 0, or Day 7. This indicates that HHFNC does not impose

greater systemic stress than CPAP and is physiologically well-tolerated. These findings are consistent with results from both Shirvani et al.²⁴ and Mahboob et al.,²¹ who also reported no significant biochemical disturbances attributable to either modality. This biochemical stability, coupled with physiological studies like that of Taiga et al. showing HHFNC can improve thoraco-abdominal synchrony and reduce the work of breathing without causing adverse cardiorespiratory effects underscores its safety.²⁶ The absence of sepsis-related biochemical derangements further supports the finding that HHFNC is not associated with an increased risk of infection.^{27,28}

CONCLUSION

In conclusion, the findings from this randomized controlled trial provide compelling evidence that HHFNC is a safe, effective, and superior alternative to nCPAP for weaning preterm neonates <32 weeks of gestation. HHFNC was associated with significantly higher weaning success, lower rates of weaning failure, and a marked reduction in complications, particularly nasal trauma. Most importantly, these benefits translated into a significant reduction in mortality. Our results, supported by a growing body of literature, advocate for the integration of HHFNC into standard weaning protocols for this vulnerable population. Future research should focus on long-term outcomes, including neurodevelopment, and further optimization of HHFNC protocols.

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