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Comparative efficacy of High-Flow Nasal Cannula (HFNC) versus Continuous Positive Airway Pressure (CPAP) in Preventing Bronchopulmonary Dysplasia (BPD) among Preterm Neonates

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ABSTRACT

Bronchopulmonary dysplasia (BPD) remains a major cause of respiratory morbidity in preterm infants requiring respiratory support. Non-invasive ventilation strategies such as nasal continuous positive airway pressure (CPAP) and high-flow nasal cannula (HFNC) are commonly used, but evidence comparing their effectiveness in preventing BPD remains limited, particularly in low- and middle-income settings. **Objectives:** To compare HFNC and CPAP as primary non-invasive respiratory support in preterm neonates <34 weeks' gestation, with BPD at 36 weeks postmenstrual age as the primary outcome. **Methods:** This cohort study was conducted in a tertiary-care neonatal intensive care unit in Peshawar, Pakistan. Preterm neonates <34 weeks who received HFNC or CPAP as initial respiratory support between April 2024 and March 2025 were included. Multivariable logistic regression was performed to identify predictors of BPD. **Results:** A total of 189 neonates were analyzed (HFNC n=95; CPAP n=94). The incidence of BPD was similar between HFNC and CPAP groups (25.3% vs 27.7%; p=0.709). Mortality and major neonatal complications were also comparable. Respiratory modality was not independently associated with BPD (aOR 1.41; 95% CI 0.69–2.90; p=0.348). Intubation was strongly associated with BPD (aOR 19.30; p=0.005), while complete antenatal steroid exposure was protective (aOR 0.24; p=0.016). **Conclusions:** HFNC and CPAP showed similar outcomes in preterm neonates <34 weeks. However, due to the observational design, further prospective studies are needed to confirm these findings.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a major cause of respiratory morbidity in preterm infants requiring respiratory support and oxygen therapy [1]. Despite advances in neonatal care, it remains associated with prolonged hospitalization, recurrent respiratory admissions, and long-term pulmonary and neurodevelopmental complications [2]. Therefore, contemporary neonatal respiratory strategies increasingly focus on minimizing lung injury by promoting effective gas exchange while reducing volutrauma, barotrauma, and oxygen toxicity [3]. Lung-protective neonatal care largely depends on non-invasive ventilation [4]. Nasal continuous positive airway pressure (CPAP) is the most commonly used first-line respiratory support for preterm neonates

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with respiratory distress syndrome (RDS) and helps reduce the need for invasive ventilation [5]. Current guidelines emphasize early non-invasive support and antenatal steroid exposure to reduce the risk of BPD [6, 7]. Heated humidified high-flow nasal cannula (HFNC) has emerged as an alternative non-invasive respiratory modality because of its ease of application, improved patient comfort, and potentially lower rates of nasal trauma related to the interface [8, 9]. However, HFNC generates variable distending airway pressure that depends on flow rate, cannula size, and mouth position, raising uncertainty about whether it provides respiratory support equivalent to CPAP in very preterm infants or those with more severe respiratory distress [10]. Some studies have suggested that HFNC used early after birth may be associated with similar risks of death or BPD compared with CPAP or nasal intermittent positive pressure ventilation, although higher rates of treatment failure have occasionally been reported [11]. Several systematic reviews and meta-analyses have evaluated HFNC compared with CPAP for non-invasive respiratory support in preterm infants. Overall, these pooled analyses have generally demonstrated minimal or no significant difference in BPD risk between the two modalities, although heterogeneity among studies and variations in clinical practice limit the certainty of the available evidence [12]. In particular, many studies have focused on treatment failure or need for intubation rather than BPD as a primary outcome, and relatively few observational cohort studies have specifically examined BPD development in very preterm infants receiving primary non-invasive respiratory support.

Furthermore, there is limited evidence from low- and middle-income countries where neonatal intensive care unit (NICU) resources, patient characteristics, and clinical practice patterns may differ substantially from those reported in large randomized trials conducted in high-income settings. In Pakistan, locally generated evidence comparing HFNC and CPAP in preterm neonates remains scarce, particularly in infants born before 34 weeks' gestation and in studies evaluating BPD as a primary outcome. Therefore, this study aimed to compare the effectiveness of HFNC versus CPAP as primary non-invasive respiratory support in preterm neonates <34 weeks' gestation admitted to a tertiary-care NICU in Pakistan. The primary outcome was bronchopulmonary dysplasia at 36 weeks postmenstrual age, while secondary outcomes included short-term clinical outcomes and major neonatal complications.

METHODS

This cohort study was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Northwest General Hospital and Research Centre, Peshawar, Pakistan. The study included preterm neonates admitted between April 2024 and March 2025, and clinical data were retrospectively extracted from NICU medical records. Neonates were followed until discharge or 36 weeks postmenstrual age (PMA) to determine the occurrence of bronchopulmonary dysplasia. Ethical approval for the study was obtained from the Institutional Review Board and Ethical Committee of Alliance Healthcare (Pvt.) Ltd (Reference No. IRB&EC/2024-GH/0278; dated 27th March 2024). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki for research involving human participants (World Medical Association, 2013) [13]. As the study involved retrospective review of routinely collected clinical data, the requirement for individual informed consent was waived, and patient confidentiality was strictly maintained through anonymization of all identifiable information. Sample size estimation was performed using the two-proportion comparison formula: $n = (Z\alpha/2 + Z\beta)^2 \times [p1(1-p1) + p2(1-p2)] / (p1 - p2)^2$, where p1 represents the expected incidence of bronchopulmonary dysplasia in the CPAP group, and p2 represents the expected incidence in the HFNC group. Based on previously published neonatal respiratory support studies reporting BPD rates ranging between 20–30% among preterm infants receiving non-invasive ventilation, an expected incidence of 30% in the CPAP group and 15% in the HFNC group [5] was assumed with a 95% confidence level and 80% statistical power. The minimum calculated sample size was approximately 180 neonates. A total of 189 neonates were ultimately included in the final analysis after applying the eligibility criteria. Eligible participants included preterm neonates with gestational age <34 weeks who required non-invasive respiratory support shortly after birth and received either HFNC or CPAP as the initial respiratory modality. Neonates with major congenital anomalies, chromosomal abnormalities, significant congenital heart disease other than patent ductus arteriosus, those requiring immediate invasive ventilation after birth, transfers within 24 hours of admission, or incomplete clinical records were excluded. Respiratory support was provided according to standard NICU clinical protocols. HFNC therapy was delivered using heated and humidified blended oxygen via nasal cannula, typically initiated at flow rates between 4–6 L/min and adjusted according to gestational age, oxygen saturation, and clinical response. CPAP support was delivered through nasal prongs with initial pressures generally ranging between 5–7 cmH_2O, with adjustments based on oxygen requirement, work of breathing, and arterial blood gas findings. Standard neonatal supportive care included thermoregulation, nutritional support, caffeine therapy for

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apnea of prematurity, and surfactant administration when clinically indicated. The choice of respiratory modality (HFNC or CPAP) was determined by treating neonatologists based on clinical judgment and unit practice rather than random allocation. To reduce potential confounding by indication, important clinical variables, including gestational age, birth weight, antenatal steroid exposure, surfactant therapy, baseline FiO_2 requirement, sepsis, and patent ductus arteriosus, were included as covariates in the multivariable regression model. Escalation to invasive mechanical ventilation was considered in cases of treatment failure, including persistent or worsening respiratory distress, sustained oxygen requirement greater than 60%, recurrent apnea despite caffeine therapy, severe respiratory acidosis (pH <7.20 with elevated $PaCO_2$), or hemodynamic instability. Clinical data were collected retrospectively using a structured data extraction form that included maternal characteristics, perinatal factors, neonatal baseline characteristics, respiratory support parameters, early clinical course, complications, and outcomes. Bronchopulmonary dysplasia was defined as oxygen dependence at 36 weeks postmenstrual age according to commonly used clinical definitions in neonatal research. Physiologic oxygen reduction testing and NICHD severity grading were not routinely performed in the study unit. A total of 204 NICU records were initially screened for eligibility. After a detailed review, 15 records were excluded due to incomplete or contradictory clinical documentation, resulting in a final sample of 189 neonates included in the analysis. Data quality was ensured by cross-checking extracted information with both electronic medical records and nursing charts. Double-entry verification was performed to minimize transcription errors.

Statistical analysis was conducted using IBM SPSS Statistics version 26.0. Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation and compared using the independent-samples t-test. In contrast, non-normally distributed variables were presented as median with interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the Chi-square test or Fisher's exact test, as appropriate. Multivariable binary logistic regression analysis was performed to identify independent predictors of bronchopulmonary dysplasia at 36 weeks PMA. Variables considered clinically relevant or demonstrating a p-value <0.200 in univariable analysis were included in the multivariable model. Results were reported as adjusted odds ratios (aOR) with 95% confidence intervals. Model adequacy was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Multicollinearity among predictor variables was assessed using variance inflation factors (VIF). Model discrimination was further assessed using the area under the receiver operating characteristic (ROC) curve and overall classification accuracy. A p-value ≤0.050 was considered statistically significant.

RESULTS

A total of 204 NICU records were screened, of which 15 records were excluded due to incomplete or contradictory documentation, leaving 189 preterm neonates included in the final analysis (HFNC n=95; CPAP n=94). Baseline maternal and neonatal characteristics were largely comparable between the HFNC and CPAP groups. There was no significant difference in maternal age, antenatal care status, PROM, maternal comorbidities, gestational age, birth weight, Apgar scores, sex distribution, or surfactant administration between groups. However, a significantly higher proportion of mothers in the HFNC group received a complete course of antenatal steroids compared with the CPAP group (69.5% vs 54.3%; p=0.036*). Other maternal and neonatal variables were similar between the two groups, suggesting overall baseline comparability (Table 1).

Table 1: Baseline Maternal and Neonatal Characteristics

Variables	HFNC (n=95), Mean ± SD / n (%)	CPAP (n=94), Mean ± SD / n (%)	p-value
Maternal Age (years)	28.52 ± 4.60	29.24 ± 4.78	0.292
Booked Antenatal Care	74 (77.9%)	65 (69.1%)	0.173
Complete Antenatal Steroids	66 (69.5%)	51 (54.3%)	0.036*
PROM	18 (18.9%)	27 (28.7%)	0.115
Hypertension/Preeclampsia	16 (16.8%)	21 (22.3%)	0.341
Maternal Diabetes	11 (11.6%)	15 (16.0%)	0.382
Gestational Age (Weeks)	29.63 ± 2.28	29.18 ± 2.34	0.186
Birth Weight (g)	1273.85 ± 284.09	1199.47 ± 327.99	0.097
Male Sex	52 (54.7%)	46 (48.9%)	0.425
SGA/IUGR	15 (15.8%)	12 (12.8%)	0.553
Surfactant Given	55 (57.9%)	52 (55.3%)	0.721

*Indicates statistically significant difference at p ≤ 0.050

The respiratory support characteristics were similar between the two study groups. There were no significant differences in FiO_2 at initiation, peak FiO_2 within the first 72 hours, duration of non-invasive ventilation, total oxygen therapy duration, or age at initiation of respiratory support. Clinical outcomes were also comparable between the groups. Bronchopulmonary dysplasia at 36 weeks PMA occurred in 24 (25.3%) neonates in the HFNC group and 26 (27.7%) in the CPAP group (p=0.709). Mortality before discharge, NICU length of stay, and discharge weight were also similar between groups (Table 2).

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Table 2: Respiratory Support Characteristics and Clinical Outcomes

Variables	HFNC (n=95)	CPAP (n=94)	p-value
FiO_2 at Initiation, Median (IQR)	0.42 (0.16)	0.44 (0.15)	0.975
Peak FiO_2 within 72 h	0.59 (0.19%)	0.59 (0.25%)	0.553
Total NIV Duration (Days), Median (IQR)	11 (7)	11.5 (8)	0.209
Total Oxygen Duration (Days)	23 (18%)	23 (22.3%)	0.832
Age At Start of Support (Hours)	2.1 (1.9%)	2.3 (1.9%)	0.783
Intubation at Any Time, n (%)	15 (15.8%)	16 (17.0%)	0.819
BPD at 36 Weeks PMA, n (%)	24 (25.3%)	26 (27.7%)	0.709
Mortality Before Discharge, n (%)	9 (9.5%)	8 (8.5%)	0.817
Length of NICU Stay (days)	37 (22%)	39 (25%)	0.690
Discharge Weight (g)	2002 ± 373	1919 ± 481	0.187

The frequency of major neonatal complications did not differ significantly between the two respiratory support modalities. Rates of pneumothorax, nasal trauma, feeding intolerance, necrotizing enterocolitis, severe intraventricular hemorrhage, and retinopathy of prematurity requiring treatment were similar between the HFNC and CPAP groups (Table 3).

Table 3: Neonatal Complications

Complications	HFNC (n=95), n (%)	CPAP (n=94), n (%)	p-value
Pneumothorax	6 (6.3%)	3 (3.2%)	0.497
Nasal trauma	11 (11.6%)	14 (14.9%)	0.501
Feeding intolerance	20 (21.1%)	20 (21.3%)	0.970
NEC (Bell ≥ II)	5 (5.3%)	5 (5.3%)	1.000
Severe IVH	4 (4.2%)	8 (8.5%)	0.250
ROP requiring treatment	6 (6.3%)	7 (7.4%)	0.782

The multivariable logistic regression model demonstrated adequate fit according to the Hosmer–Lemeshow goodness-of-fit test, and no significant multicollinearity was observed among predictor variables. Multivariable logistic regression analysis was performed to identify independent predictors of bronchopulmonary dysplasia. After adjustment for relevant clinical covariates, respiratory modality (HFNC vs CPAP) was not independently associated with BPD (aOR 1.41, 95% CI 0.69–2.90; p=0.348). However, intubation at any time during NICU stay emerged as a strong independent predictor of BPD (aOR 19.30, 95% CI 2.42–154.04; p=0.005*). Conversely, absence of antenatal steroid exposure was associated with significantly higher odds of BPD compared with complete steroid exposure (aOR 0.24, 95% CI 0.07–0.76; p=0.016*) (Table 4).

Table 4: Multivariable Predictors of Bronchopulmonary Dysplasia

Variables	Adjusted OR (95% CI)	p-value
HFNC vs CPAP	1.41 (0.69–2.90)	0.348
Partial vs Complete Steroids	0.40 (0.16–1.05)	0.063
None vs Complete Steroids	0.24 (0.07–0.76)	0.016*
Gestational Age	1.09 (0.93–1.27)	0.289
Birth Weight	0.999 (0.998–1.000)	0.155
Surfactant Therapy	1.16 (0.57–2.36)	0.686
Baseline FiO_2	0.92 (0.02–37.10)	0.964
Intubation (Any)	19.30 (2.42–154.04)	0.005*
Sepsis	0.54 (0.23–1.25)	0.151
PDA	1.25 (0.57–2.78)	0.577

*Indicates statistically significant difference at p ≤ 0.050

DISCUSSION

The present study compared high-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) as primary non-invasive respiratory support in preterm neonates <34 weeks' gestation. The results demonstrated no significant difference in bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age between the two groups, and respiratory modality was not independently associated with BPD after multivariable adjustment. These findings are consistent with previous systematic reviews evaluating HFNC compared with CPAP in preterm infants. A Cochrane review reported that HFNC likely results in little or no difference in death or BPD compared with CPAP, although treatment failure may occur slightly more frequently in certain populations [6]. Similarly, a systematic review published in 2021 found no statistically significant difference in BPD risk between HFNC and CPAP [12], and a recent meta-analysis focusing on BPD prevention also concluded that neither modality demonstrated clear superiority [14]. Together, these findings suggest that the choice between HFNC and CPAP alone may not be a major determinant of BPD risk when other aspects of respiratory management are optimized. Although the respiratory modality itself was not associated with BPD in our adjusted model, intubation at any time during NICU stay emerged as a strong independent predictor of BPD. This finding is biologically plausible and consistent with previous literature demonstrating that exposure to invasive mechanical ventilation contributes to lung injury through volutrauma, barotrauma, and oxidative stress. International neonatal respiratory guidelines, therefore, emphasize early and effective non-invasive respiratory support strategies aimed at minimizing invasive ventilation whenever possible [15]. The current study findings reinforce the importance of preventing escalation to mechanical ventilation as a key strategy in reducing the risk of BPD. The study also observed a protective association of complete antenatal steroid exposure, which is biologically plausible because antenatal corticosteroids promote fetal lung maturation and improve early pulmonary adaptation [14-16]. Although there was a higher proportion of complete steroid exposure in the HFNC group at baseline, adjustment in the multivariable model confirmed that respiratory modality itself was not

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independently associated with BPD. Major neonatal complications were similar between HFNC and CPAP, including pneumothorax, necrotizing enterocolitis, severe intraventricular hemorrhage, and retinopathy of prematurity, consistent with previously reported safety profiles for both modalities [17, 18]. Some studies have suggested that HFNC may result in lower rates of nasal trauma because of the less intrusive interface; however, treatment failure rates may be slightly higher in certain populations, emphasizing the need for careful patient selection and clear escalation criteria [19, 20]. The sample size calculation assumed BPD incidences of 30% in the CPAP group and 15% in the HFNC group based on earlier neonatal studies reporting BPD rates of approximately 20–30%. However, more recent meta-analyses suggest that the true difference between modalities may be smaller, which should be considered when interpreting the findings.

This study has several limitations. This cohort design limits causal inference, and respiratory modality selection was based on clinician judgment, introducing potential confounding by indication. In addition, the study was conducted at a single tertiary-care NICU, which may limit generalizability. Physiologic oxygen reduction testing and standardized NICHD BPD severity grading were also not routinely performed. Future multicenter prospective studies and randomized controlled trials are needed to further evaluate the comparative effectiveness of HFNC and CPAP in preventing bronchopulmonary dysplasia.

CONCLUSIONS

In preterm neonates <34 weeks' gestation, HFNC and CPAP were associated with similar rates of bronchopulmonary dysplasia, mortality, and major neonatal complications. Respiratory modality was not independently associated with BPD, whereas intubation increased BPD risk, and complete antenatal steroid exposure appeared protective. Because this was an observational study with clinician-driven modality selection, the findings should be interpreted as demonstrating association rather than equivalence between HFNC and CPAP. Further prospective research is required to confirm these results.

Authors' Contribution

Conceptualization: WI
Methodology: SZ, MKK
Formal analysis: JI, SSA
Writing and Drafting: WI, SZ, JI, FA, MKK, SSA
Review and Editing: WI, SZ, JI, FA, MKK, SSA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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