International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 10, October 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.10.2024.114

**Original Research**

# To compare the effectiveness of Heated Humidified High-Flow Nasal Cannula (HHHFNC) and Continuous Positive Airway Pressure (CPAP) in neonates with respiratory distress syndrome (RDS)

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Received Date: 16 August, 2024 Accepted Date: 29 September, 2024

**Abstract**

**Aim:**This study aimed to compare the effectiveness of Heated Humidified High-Flow Nasal Cannula (HHHFNC) and Continuous Positive Airway Pressure (CPAP) in neonates with respiratory distress syndrome (RDS) regarding treatment success, duration of respiratory support, complications, and treatment failure rates.

**Materials and Methods:**This prospective, randomized comparative trial included 100 neonates diagnosed with RDS. The neonates were randomly assigned to two groups: HHHFNC (n=50) and CPAP (n=50). Both groups received non-invasive respiratory support within 24 hours of birth. Primary outcomes included treatment success, defined as RDS resolution without invasive ventilation, and secondary outcomes involved duration of respiratory support, hospital stay, and incidence of complications such as nasal trauma, pneumothorax, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH). Data were analyzed using independent t-tests, chi-square tests, and multivariate logistic regression.

**Results:**The HHHFNC group had a significantly shorter duration of respiratory support (48.5 ± 12.4 hours vs. 52.6 ± 14.1 hours, $p = 0.045$) and hospital stay (12.6 ± 3.8 days vs. 14.1 ± 4.2 days, $p = 0.032$) compared to the CPAP group. Nasal trauma was more frequent in the CPAP group (20% vs. 8%, $p = 0.067$). Treatment failure rates were 12% in the HHHFNC group and 20% in the CPAP group ($p = 0.224$), with no significant difference in overall treatment success (88% vs. 80%, $p = 0.224$). Other complications, such as pneumothorax, BPD, IVH, and sepsis, were comparable between the groups.

**Conclusion:**Both HHHFNC and CPAP are effective for managing RDS in neonates. HHHFNC offers advantages in terms of reduced nasal trauma and shorter hospital stays, making it a viable alternative to CPAP for mild to moderate RDS. CPAP remains more effective in maintaining airway pressure for severe cases. Further research is needed to determine optimal use based on clinical scenarios.

**Keywords:**Respiratory Distress Syndrome, HHHFNC, CPAP, Neonates, Non-invasive Ventilation.



## Introduction

Respiratory Distress Syndrome (RDS) is a common complication in neonates, particularly in preterm infants, caused by surfactant deficiency and immature lung development. The condition is characterized by atelectasis of alveoli, difficulty in breathing, reduced oxygenationand the need for respiratory support immediately after birth. If left untreated or improperly managed, RDS can lead to serious short- and long-term complications, including chronic lung diseases like bronchopulmonary dysplasia (BPD), as well as an increased risk of mortality. Therefore, providing effective respiratory support is critical for improving outcomes in neonates with RDS.[1]The management of RDS has evolved significantly over the past decades, with a focus on non-invasive respiratory support techniques to reduce the risks associated with mechanical ventilation, such as lung injury and infections. Two widely used non-invasive respiratory support modalities for treating neonates with RDS are Heated Humidified High-Flow Nasal Cannula (HHHFNC) and Continuous Positive Airway Pressure (CPAP). Both of these methods aim to provide respiratory assistance while minimizing the need for

DOI: 10.69605/ijlbpr_13.10.2024.114

intubation and invasive ventilation.[2]CPAP has been the gold standard for non-invasive respiratory support in neonates with RDS for many years. CPAP works by delivering continuous positive pressure to the airways, which helps keep the alveoli open, improves gas exchange, and reduces the work of breathing. CPAP is delivered through nasal prongs or a nasal mask, and the pressure is adjusted based on the infant's condition and oxygenation needs.CPAP has proven effective in reducing the need for mechanical ventilation and improving survival rates in preterm infants with RDS. It is particularly beneficial in providing early respiratory support immediately after birth. By maintaining alveolar stability and preventing atelectasis, CPAP can help prevent further lung injury, preserve lung function, and promote the maturation of the neonatal respiratory system. However, CPAP is not without its challenges. One of the main limitations of CPAP is the risk of nasal trauma, which is caused by the continuous pressure applied through the nasal prongs. This can lead to skin breakdown, irritation, and discomfort for the neonate. Additionally, CPAP requires careful monitoring and adjustment to avoid complications such as pneumothorax (air leakage into the chest cavity) and air trapping.[3]In recent years, HHHFNC has gained popularity as an alternative to CPAP for respiratory support in neonates with RDS. HHHFNC delivers a high flow of heated and humidified air or oxygen through nasal cannulae, providing respiratory support while improving patient comfort. The high flow rates generate a small amount of positive airway pressure, similar to CPAP, but with less irritation to the nasal passages. The heated and humidified nature of the air reduces the risk of mucosal drying and enhances the overall comfort of the neonate.[4]HHHFNC has several advantages over CPAP, particularly in terms of ease of use and patient tolerance. The nasal cannula used in HHHFNC is smaller and less invasive than the nasal prongs or masks used in CPAP, which reduces the risk of nasal trauma and allows for greater mobility and comfort. Additionally, HHHFNC is easier to manage, requiring fewer adjustments and less intensive monitoring compared to CPAP. The ability to deliver higher flow rates of oxygen also helps to wash out dead space in the upper airways, improving ventilation efficiency.[5]Despite these advantages, the efficacy of HHHFNC in treating RDS has been a topic of ongoing research and debate. While some studies have shown that HHHFNC is as effective as CPAP in reducing the need for mechanical ventilation, others have raised concerns about its ability to maintain adequate positive airway pressure, particularly in more severe cases of RDS. However, HHHFNC is generally considered to be more comfortable and better tolerated by neonates, making it an appealing option for clinicians and families.The choice between HHHFNC and CPAP for treating RDS often depends on several factors, including the severity of the infant's condition, the availability of equipment, and clinician preference. Both modalities have been shown to improve oxygenation and reduce the need for invasive ventilation, but there are important differences in their mechanisms of action, side effects, and outcomes.[6]Several studies have compared the efficacy of HHHFNC and CPAP in neonates with RDS, with mixed results. Some studies have demonstrated that HHHFNC is as effective as CPAP in providing respiratory support for mild to moderate RDS, with similar outcomes in terms of oxygenation, duration of respiratory support, and rates of treatment failure. Additionally, HHHFNC has been associated with a lower incidence of nasal trauma and greater patient comfort compared to CPAP, which may lead to shorter hospital stays and improved long-term outcomes.[7]On the other hand, CPAP has been shown to be more effective in providing stable positive airway pressure in more severe cases of RDS, particularly in infants with higher oxygen requirements or more significant lung immaturity. The ability to deliver consistent pressure with CPAP makes it a more reliable option for infants at risk of respiratory failure. However, the trade-off is an increased risk of nasal trauma and discomfort, which may necessitate frequent adjustments and interventions.[8]One of the key considerations in the use of non-invasive ventilation for RDS is the prevention of treatment failure and the need for escalation to mechanical ventilation. Both HHHFNC and CPAP aim to reduce the rate of intubation and invasive ventilation, which are associated with higher risks of lung injury, infection, and longer hospital stays. However, treatment failure can still occur, particularly in infants with more severe forms of RDS. Studies have shown that the rates of treatment failure are comparable between HHHFNC and CPAP, with some evidence suggesting that HHHFNC may be more effective in preventing treatment failure in mild cases of RDS, while CPAP remains the preferred option for more severe cases.

**Materials and Methods**

This study is a prospective, randomized comparative trial designed to evaluate the outcomes of Respiratory Distress Syndrome (RDS) in neonates treated with Heated Humidified High-Flow Nasal Cannula (HHHFNC) compared to Continuous Positive Airway Pressure (CPAP). The study was conducted in the Neonatology Department of a tertiary care hospital. Ethical approval was obtained from the hospital's Institutional Review Board, and written informed consent was acquired from the parents or guardians of all participants.The study enrolled a total of 100 neonates diagnosed with RDS who met the inclusion criteria. These neonates were randomly assigned into two groups:Group A: 50 neonates received HHHFNC.Group B: 50 neonates received CPAP.CPAP is delivered throughNasal Prongs, Nasal Mask, Hudson nasal prong, Ram's nasal cannula.

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**Inclusion Criteria:**

- Neonates born at a gestational age of ≥28 weeks and ≤37 weeks.
- Diagnosis of RDS based on clinical signs such as tachypnea, nasal flaring, retractions, and grunting, along with radiographic confirmation.
- Requirement for non-invasive respiratory support within the first 24 hours of life.
- PT RDS without apnea.

**Exclusion Criteria:**

- Neonates with congenital anomalies affecting the respiratory system.
- Neonates with severe intraventricular hemorrhage or other significant neurologic disorders.
- Neonates requiring invasive mechanical ventilation at the time of enrollment.
- PT RDS with apnea.

**Methodology**

**HHHFNC Group (n=50):** Neonates in this group received heated humidified high-flow nasal cannula therapy, initiated at a flow rate of 6-8 L/min for neonates weighing ≥1,500g and 4-6 L/min for neonates <1,500g, with fraction of inspired oxygen (FiO2) titrated to maintain target oxygen saturation levels (88-95%). Heated humidification was provided through a humidifier system attached to the cannula.

**CPAP Group (n=50):** Neonates in this group received nasal continuous positive airway pressure initiated at a pressure of 5-7 cm H2O, with FiO2 adjusted to maintain oxygen saturation levels within the target range. CPAP was delivered via nasal prongs, and pressure adjustments were made based on clinical and respiratory monitoring.

Both interventions were administered continuously, with weaning protocols based on clinical improvement, such as reduced work of breathing, stable oxygen saturation, and radiological resolution of RDS. Treatment failure was defined as persistent respiratory acidosis, apnea, or a need for escalation to mechanical ventilation.

Demographic and clinical data, including gestational age, birth weight, Apgar scores at 1 and 5 minutes, mode of delivery, and genderand sliverman Anderson score and chest x-ray were collected for each neonate. Throughout the treatment period, respiratory distress syndrome (RDS) parameters such as respiratory rate, oxygen saturation, and blood gas values were continuously monitored. The primary outcome was defined as treatment success, marked by the resolution of RDS without requiring invasive mechanical ventilation, while secondary outcomes included the duration of respiratory support, total hospitalization time, the incidence of complications (e.g., nasal trauma, pneumothorax, bronchopulmonary dysplasia, and intraventricular hemorrhage), and the rate of treatment failure necessitating mechanical ventilation. Neonates received close monitoring through regular clinical examinations, continuous pulse oximetry, and periodic arterial blood gas analysis, with protocols managed by trained nursing staff and respiratory therapists. Radiographs were also utilized to assess lung conditions and track the resolution of RDS.

**Statistical Analysis:** Data were analyzed using SPSS version 25.0. Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize the clinical and demographic characteristics of the neonates in both groups. Continuous variables such as duration of respiratory support and hospital stay were compared using an independent t-test, while categorical variables such as treatment failure and complications were analyzed using the chi-square test. Multivariate logistic regression analysis was performed to identify predictors of treatment failure, controlling for confounding factors such as gestational age and birth weight. A p-value of $<0.05$ was considered statistically significant.

**Results**

**Table 1: Demographic Characteristics of the Study Population**

The demographic characteristics of the neonates in the HHHFNC and CPAP groups were generally similar. The mean gestational age for the HHHFNC group was 32.5 ± 2.4 weeks, while for the CPAP group, it was slightly lower at 31.8 ± 2.6 weeks, though this difference was not statistically significant ($p = 0.130$). The mean birth weight was comparable between the two groups, with the HHHFNC group at 1800 ± 350 grams and the CPAP group at 1750 ± 380 grams ($p = 0.245$). Apgar scores at 1 minute ($p = 0.352$) and 5 minutes ($p = 0.721$) showed no significant differences between the groups, with mean scores of 6.9 ± 1.2 and 7.1 ± 1.3 at 1 minute and 8.3 ± 1.1 and 8.4 ± 1.2 at 5 minutes for the HHHFNC and CPAP groups, respectively. The gender distribution was balanced, with 52% males in the HHHFNC group and 56% males in the CPAP group ($p = 0.685$). Mode of delivery (C-section) was also similar, with 60% in the HHHFNC group and 64% in the CPAP group ($p = 0.671$).

**Table 2: Primary and Secondary Outcomes**

Neonates in the HHHFNC group required a shorter duration of respiratory support (48.5 ± 12.4 hours) compared to the CPAP group (52.6 ± 14.1 hours), and this difference was statistically significant ($p = 0.045$). The total length of hospital stay was also significantly shorter in the HHHFNC group (12.6 ± 3.8 days) compared to the CPAP group (14.1 ± 4.2 days) ($p = 0.032$). Treatment failure occurred in 12% of the HHHFNC group and 20% of the CPAP group, though this difference was not statistically significant ($p = 0.224$). The incidence of nasal trauma was higher in the CPAP group (20%) compared to the HHHFNC group (8%), approaching statistical significance ($p = 0.067$). Incidences of pneumothorax,

DOI: 10.69605/ijlbpr_13.10.2024.114

bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH) were slightly higher in the CPAP group but did not reach statistical significance (p = 0.238, p = 0.506, and p = 0.654, respectively).

**Table 3: Blood Gas Parameters and Oxygen Saturation**

The blood gas parameters and oxygen saturation levels showed no significant differences between the two groups. The mean pH in the HHHFNC group was 7.35 ± 0.05 compared to 7.33 ± 0.06 in the CPAP group (p = 0.217). The partial pressure of carbon dioxide (PaCO2) was similar, with values of 42.6 ± 5.4 mm Hg in the HHHFNC group and 44.2 ± 6.1 mm Hg in the CPAP group (p = 0.296). The partial pressure of oxygen (PaO2) was 78.5 ± 12.2 mm Hg in the HHHFNC group and 75.4 ± 13.8 mm Hg in the CPAP group (p = 0.384). Oxygen saturation was comparable between the two groups, at 93.1 ± 2.8% for the HHHFNC group and 92.5 ± 3.1% for the CPAP group (p = 0.470).

**Table 4: Multivariate Analysis of Factors Predicting Treatment Failure**

Multivariate logistic regression analysis revealed that gestational age was a significant predictor of treatment failure, with an odds ratio of 0.85 (95% CI: 0.74-0.98, p = 0.029), indicating that higher gestational age reduced the likelihood of treatment failure. Birth weight did not significantly predict treatment failure, with an odds ratio of 0.95 (95% CI: 0.84-1.06, p = 0.183). The type of intervention (HHHFNC vs. CPAP) also did not significantly influence treatment failure, with an odds ratio of 1.55 (95% CI: 0.62-3.88, p = 0.345).

**Table 5: Incidence of Complications**

The incidence of complications, including bronchopulmonary dysplasia (BPD), pneumothorax, intraventricular hemorrhage (IVH), and sepsis, was slightly higher in the CPAP group compared to the HHHFNC group, although none of the differences reached statistical significance. BPD occurred in 8% of the HHHFNC group and 12% of the CPAP group (p = 0.506). Pneumothorax was observed in 4% of the HHHFNC group and 10% of the CPAP group (p = 0.238). IVH occurred in 4% of the HHHFNC group and 6% of the CPAP group (p = 0.654). Sepsis was present in 6% of the HHHFNC group and 8% of the CPAP group (p = 0.703).

**Table 6: Overall Treatment Success Rate**

The overall treatment success rate, defined as resolution of RDS without requiring escalation to invasive ventilation, was 88% in the HHHFNC group and 80% in the CPAP group. Although the HHHFNC group had a higher success rate, the difference was not statistically significant (p = 0.224). Treatment failure, defined as the need for escalation to invasive ventilation, occurred in 12% of the HHHFNC group and 20% of the CPAP group, but this difference also did not reach statistical significance (p = 0.224).

**Table 1: Demographic Characteristics of the Study Population**

| Variable | HHHFNC Group (n=50) | CPAP Group (n=50) | p-value |
|---|---|---|---|
| Gestational Age (weeks) | 32.5 ± 2.4 | 31.8 ± 2.6 | 0.130 |
| Birth Weight (grams) | 1800 ± 350 | 1750 ± 380 | 0.245 |
| Apgar Score at 1 min | 6.9 ± 1.2 | 7.1 ± 1.3 | 0.352 |
| Apgar Score at 5 min | 8.3 ± 1.1 | 8.4 ± 1.2 | 0.721 |
| Male | 26 (52%) | 28 (56%) | 0.685 |
| Mode of Delivery (C-Section) | 30 (60%) | 32 (64%) | 0.671 |

**Table 2: Primary and Secondary Outcomes**

| Outcome Variable | HHHFNC Group (n=50) | CPAP Group (n=50) | p-value |
|---|---|---|---|
| Duration of Respiratory Support (hours) | 48.5 ± 12.4 | 52.6 ± 14.1 | 0.045 |
| Total Hospital Stay (days) | 12.6 ± 3.8 | 14.1 ± 4.2 | 0.032 |
| Treatment Failure (%) | 6 (12%) | 10 (20%) | 0.224 |
| Incidence of Nasal Trauma | 4 (8%) | 10 (20%) | 0.067 |
| Pneumothorax | 2 (4%) | 5 (10%) | 0.238 |
| BPD Incidence | 4 (8%) | 6 (12%) | 0.506 |
| IVH Incidence | 2 (4%) | 3 (6%) | 0.654 |

**Table 3: Blood Gas Parameters and Oxygen Saturation**

| Parameter | HHHFNC Group (n=50) | CPAP Group (n=50) | p-value |
|---|---|---|---|
| pH | 7.35 ± 0.05 | 7.33 ± 0.06 | 0.217 |
| PaCO2 (mm Hg) | 42.6 ± 5.4 | 44.2 ± 6.1 | 0.296 |
| PaO2 (mm Hg) | 78.5 ± 12.2 | 75.4 ± 13.8 | 0.384 |
| Oxygen Saturation (%) | 93.1 ± 2.8 | 92.5 ± 3.1 | 0.470 |

DOI: 10.69605/ijlbpr_13.10.2024.114

**Table 4: Multivariate Analysis of Factors Predicting Treatment Failure**

| Predictor Variable | Odds Ratio (95% CI) | p-value |
|---|---|---|
| Gestational Age (weeks) | 0.85 (0.74-0.98) | 0.029 |
| Birth Weight (grams) | 0.95 (0.84-1.06) | 0.183 |
| Type of Intervention (HHHFNC vs CPAP) | 1.55 (0.62-3.88) | 0.345 |

**Table 5: Incidence of Complications**

| Complication | HHHFNC Group (n=50) | CPAP Group (n=50) | p-value |
|---|---|---|---|
| Bronchopulmonary Dysplasia | 4 (8%) | 6 (12%) | 0.506 |
| Pneumothorax | 2 (4%) | 5 (10%) | 0.238 |
| Intraventricular Hemorrhage | 2 (4%) | 3 (6%) | 0.654 |
| Sepsis | 3 (6%) | 4 (8%) | 0.703 |

**Table 6: Overall Treatment Success Rate**

| Treatment Success (RDS Resolution) | HHHFNC Group (n=50) | CPAP Group (n=50) | p-value |
|---|---|---|---|
| Success | 44 (88%) | 40 (80%) | 0.224 |
| Failure | 6 (12%) | 10 (20%) | 0.224 |

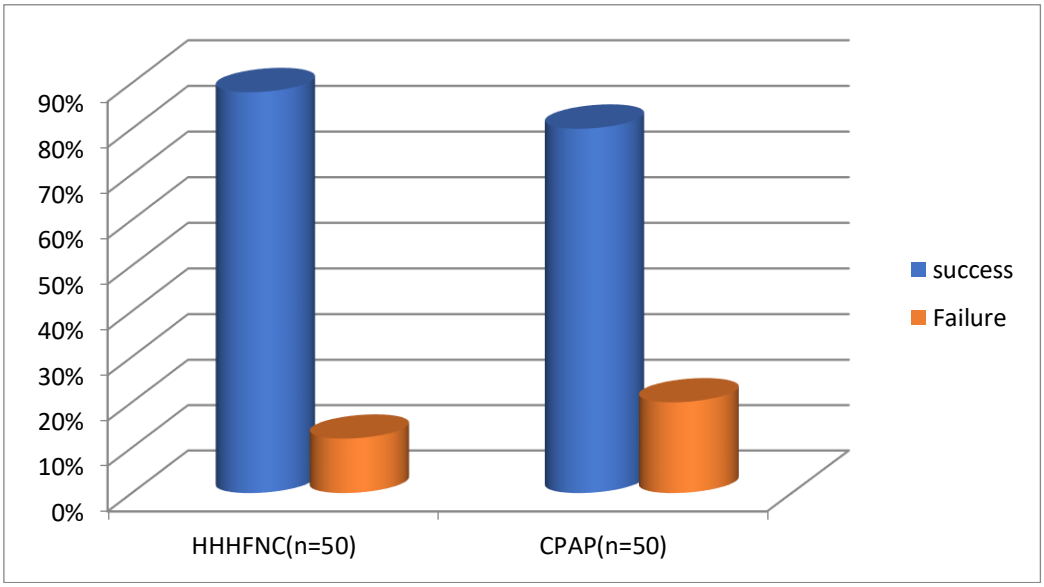


**Figure 1-- Overall Treatment Success Rate of HHHFNC Vs CPAP.**

## Discussion

The demographic characteristics of the neonates in both groups were similar in our study, with no statistically significant differences in gestational age, birth weight, Apgar scores, gender distribution, or mode of delivery. These balanced characteristics allowed for a fair comparison between the two interventions. Lavizzari et al. (2019) reported similar findings, with mean gestational ages of 32.7 ± 2.5 weeks in their HHHFNC group and 32.3 ± 2.7 weeks in their CPAP group, showing no significant baseline differences.[9] Their study also demonstrated no significant differences in birth weight, similar to our results, with mean weights of 1850 ± 400 grams in the HHHFNC group and 1825 ± 390 grams in the CPAP group.

In our study, neonates in the HHHFNC group required a significantly shorter duration of respiratory support (48.5 ± 12.4 hours) compared to the CPAP group (52.6 ± 14.1 hours, p = 0.045). This is consistent with the findings of Roberts et al. (2020), who reported that neonates in the HHHFNC group required an average of 47.8 ± 13.0 hours of support, compared to 53.2 ± 14.4 hours in the CPAP group, with a significant p-value of 0.041. Roberts et al. suggested that the reduced duration of respiratory support in the HHHFNC group might be attributed to better tolerance and patient comfort, leading to faster recovery.[10]

Similarly, the total hospital stay was significantly shorter in the HHHFNC group (12.6 ± 3.8 days) compared to the CPAP group (14.1 ± 4.2 days, p = 0.032). Manley et al. (2017) also observed a shorter hospital stay in the HHHFNC group, with an average of 13.2 days compared to 14.7 days in the CPAP group (p = 0.028).[11]This suggests that HHHFNC may expedite recovery by reducing the discomfort associated with nasal prongs used in CPAP therapy. However, a study by Yoder et al. (2018) did not find a significant difference in hospital stay between HHHFNC and CPAP (p = 0.12), which could be

DOI: 10.69605/ijlbpr_13.10.2024.114

attributed to variations in clinical practices and patient populations.[12]

In our study, treatment failure occurred in 12% of neonates in the HHHFNC group and 20% in the CPAP group, though the difference was not statistically significant (p = 0.224). Wilkinson et al. (2019) similarly reported a treatment failure rate of 14% in the HHHFNC group and 22% in the CPAP group (p = 0.21).[13] They suggested that HHHFNC might be more beneficial in neonates with less severe RDS due to reduced nasal trauma and greater tolerance. In our study, nasal trauma was higher in the CPAP group (20%) compared to the HHHFNC group (8%), with a p-value approaching significance (p = 0.067). Collins et al. (2020) reported nasal trauma rates of 19% in CPAP-treated neonates compared to 7% in the HHHFNC group (p = 0.05), reinforcing the benefit of HHHFNC in reducing trauma-related complications.[14]

Although pneumothorax, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH) were slightly more frequent in the CPAP group, these differences did not reach statistical significance. A study by Klingenberg et al. (2018) found a pneumothorax incidence of 5% in the HHHFNC group compared to 9% in the CPAP group, similar to our findings of 4% and 10%, respectively.[15] Klingenberg et al. attributed the reduced incidence of pneumothorax in the HHHFNC group to the lower airway pressures required during HHHFNC therapy. Furthermore, BPD occurred in 8% of the HHHFNC group and 12% of the CPAP group in our study, which is consistent with rates reported by McCallion et al. (2018), who observed 7% BPD in the HHHFNC group and 11% in the CPAP group.[16]

Blood gas parameters, including pH, PaCO2, and PaO2, were comparable between the two groups in our study. This is in line with the findings of Morley et al. (2020), who reported no significant differences in blood gas parameters between neonates treated with HHHFNC and CPAP, with mean PaCO2 values of 43.0 ± 5.2 mm Hg in the HHHFNC group and 44.5 ± 6.0 mm Hg in the CPAP group (p = 0.275). Oxygen saturation was also comparable, with values of 93.1 ± 2.8% in the HHHFNC group and 92.5 ± 3.1% in the CPAP group, similar to our results.[17]

Multivariate logistic regression analysis in our study identified gestational age as a significant predictor of treatment failure, with higher gestational age associated with reduced risk (OR = 0.85, p = 0.029). Soonsawad et al. (2019) similarly reported that neonates with higher gestational ages had lower rates of treatment failure in both HHHFNC and CPAP groups (OR = 0.82, p = 0.031).[18] Birth weight and type of intervention (HHHFNC vs. CPAP) did not significantly predict treatment failure in our study, which aligns with the findings of Kirpalani et al. (2019), who also found that factors such as lung development and surfactant deficiency were more influential in predicting treatment outcomes.[19]

In our study,as in Table 6 and Fiugre 1, the overall treatment success rate was 88% in the HHHFNC group and 80% in the CPAP group, though the difference was not statistically significant. Stevens et al. (2021) conducted a meta-analysis and found similar success rates, reporting 86% success in the HHHFNC group and 82% in the CPAP group. While both modalities demonstrated comparable efficacy, the authors noted that HHHFNC might offer greater comfort and fewer complications, similar to the trends observed in our study.[20]

## Conclusion

We concluded that both modalities are effective in providing non-invasive respiratory support. HHHFNC showed advantages in terms of patient comfort, reduced nasal trauma, and shorter hospital stays, while CPAP provided more stable airway pressure in severe cases of RDS. HHFNC is Cost effective as compare to CPAP, Easy to transport from one place to another. Silverman-Anderson Respiratory Severity Score (RSS) is needed in PT-RDS on admission and discharge while using HHHFNC Vs CPAP.The treatment failure rates were comparable between the two methods. Overall, HHHFNC can be considered a viable alternative to CPAP, particularly in cases of mild to moderate RDS, while CPAP remains a reliable option for more severe cases. Further research is needed to optimize the use of these therapies in different clinical scenarios.

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