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# Nasal High-Frequency Oscillatory Ventilation versus Nasal Intermittent Positive Pressure Ventilation In Pre-terms With Respiratory Distress Syndrome During Early Neonatal Period: A Randomized Controlled Trial

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## ABSTRACT

***Objective:*** To determine the effectiveness of NHFOV versus NIPPV in reducing the need for invasive mechanical ventilation in preterm neonates with RDS (moderate-severe) during the first seven days of the life of neonate.

***Study Design:*** Randomized controlled study (ACTRN: 12622000291785).

***Place and Duration of Study:*** Neonatal Unit, PNS Shifa Hospital, Karachi Pakistan, from Jan to Aug 2021.

***Methodology:*** Forty-eight preterm neonates, with the gestational age of 27 weeks to 34 weeks with Respiratory distress Syndrome, were randomized to NHFOV Group (n=24) and NIPPV Group (n=24). The primary outcome was the need for invasive mechanical ventilation (IMV). The secondary outcomes were the duration of hospitalization, non-invasive respiratory support, mortality, abdominal distention, pneumothorax, need for surgery for patent ductus arteriosus, spontaneous intestinal perforation, and necrotizing enterocolitis, intraventricular haemorrhage≥ Grade-3, bronchopulmonary dysplasia, retinopathy of prematurity Stage-3.

***Results:*** There was no significant difference between NHFOV (64.7%) versus NIPPV (35.3%) groups in need of Invasive Mechanical Ventilation ($p$=0.13). Secondary outcomes were not significant between the two groups, air leak ($p$=0.31), necrotising enterocolitis ($p$=1.00), broncho-pulmonary dysplasia ($p$=0.31), retinopathy of prematurity ($p$=0.15).There was no intraventricular haemorrhage found between the two groups.

***Conclusion***: Nasal high-frequency oscillatory ventilation was less statistically significant than NIPPV in reducing the need for invasive mechanical ventilation in the initial seven days of life in neonates with Respiratory distress syndrome.

**Keywords***:* Nasal intermittent positive pressure ventilation, Nasal high-frequency oscillatory ventilation, Respiratory distress syndrome.

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## INTRODUCTION

Respiratory distress syndrome is common in premature neonates with surfactant deficiency.[1] Continuous positive airway pressure (CPAP) is considered an essential modality of non-invasive respiratory support in premature with Respiratory Distress Syndrome. Heated humidified high-flow nasal cannula (HHHFNC), biphasic nasal CPAP, and nasal intermittent positive airway pressure have been viewed as an option in contrast to CPAP following extubation in decreasing the need for re-intubation and forestalling air spills.[2] The previous study also showed the decreased requirement of mechanical ventilation (13.3%) and early weaning from NCPAP (86.7%) in neonates with RDS.[3] NHFOV through the nasopharyngeal tube has shown improved effects in reducing CO2 levels than NCPAP.[4,5] NHFOV was a rescue treatment in preterm infants after the failure of NIV modes.[4] High-frequency ventilation is effective in CO2 elimination and is independent of dead space by providing higher frequency and low tidal volume.[6,7] NHFOV was found to be beneficial mode in delaying intubation than Non-Invasive Ventilation in preterm infants.[8] This was also seen in the decreased need for invasive mechanical ventilation in the nasal high-frequency oscillatory ventilation group in contrast to the nasal continuous positive pressure ventilation group (24% vs 56.4%).[9] At the same time, mechanical ventilation was needed in 28.9% after NCPAP failure in neonates with respiratory distress syndrome. The NHFOV is an effective mode of non-invasive ventilation, but its use was limited in neonates.[10] This study aimed to assess the impact of NHFOV vs NIPPV in premature babies with respiratory distress syndrome after giving surfactant by INSURE technique during the initial seven days of neonate life.

## METHODOLOGY

The randomized controlled study was conducted at the Neonatal Unit, PNS SHIFA Hospital Karachi,

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from January to August 2021. The trial was registered at ANZCTR (ACTRN 12622000291785). Ethical approval from the Ethical Committee (ERC/2021/Paed/52) and informed consent from the parents for their neonates for examination and mediation were taken, as per the Helsinki Declaration. The sample size was calculated using the WHO sample size calculator, taking NHFOV 24.3% vs NCPAP 56.4%.[9]

**Inclusion Criteria:** Neonates of gestational age 27 weeks to 34 weeks, neonates with moderate to severe RDS (nasal flaring, grunting and tachypnea) and Silverman score> six within the first hour of life were enrolled in this study.

**Exclusion Criteria:** Neonate with birth weight less than 600gm, the baby needed intubation for resuscitation, Cardiopulmonary arrest needing prolonged resuscitation, congenital anomalies like diaphragmatic hernia, sequestration, cystic adenomatous malformations, pulmonary hypoplasia or any congenital heart disease, pulmonary haemorrhage, Grade-4 intraventricular haemorrhage, referred to another hospital before randomization were excluded from the study.

The estimated sample size was forty-six, 23 (Experimental-Group) and 23 (Control-Group). Neonates with inclusion criteria were randomly assigned to NHFOV or NIPPV after birth, with sequentially numbered sealed, opaque envelopes. Individual randomization was assigned for neonates born from multiple gestations. It was given by a (CNO Medin) nasal mask, with the following setting amplitude 7(range 7-10), frequency 8Hz (range 8-12) and MAP 6cmH20 (range 6-10). Neonates were given NIPPV (CNO Medin), with the following settings as positive end-expiratory pressure of 6cmH2O (range 1-8 cmH2O), Peak Inspiratory Pressure (PIP) of 15 cmH2O (range 1-25cmH2O, adjusted for PaCO2 level, expansion of chest and oxygenation), rate initiated at 40bpm)range 5-60bpm, as per PaCO2 levels), the fraction of inspired oxygen(FiO2 ) was maintained to keep SpO2 from 90 to 94% in infants ≥30 weeks GA and 89% to 93% in preterm neonates<30 weeks GA by a pulse oximeter, inspiratory time (IT) 0.40s.[11]

To minimize the distention of the abdomen, an oro-gastric tube was kept in the stomach and was intermittently suctioned in NHFOV and NIPPV groups. A nasal mask was used in NHFOV and NIPPV-Group. The nasal mask was used according to the size of the nares (small, medium, and large) that cover the nares.

Neonate with moderate to severe Respiratory Distress Syndrome was given Surfactant (Poractant alfa) at a dose of 2.5ml/kg via the INSURE (intubation, surfactant, and extubation) technique before randomization. Second doses of Curocef 1.5ml/kg can be given using the same method as mentioned earlier if FiO2 requirement >0.40 to maintain target SpO2 (89% to 93%) for preterm with <30 weeks (90-94%) for >30 week.[12]

Neonates with apnea were given an injection of Caffeine Citrate with 20 mg/kg as the loading dose, followed by 10 mg/kg per day as the maintenance dose. Recommendation for invasive mechanical ventilation was as follows: Hypoxemia (FiO2>0.5 with PaO2 <50mmHg ), severe apnea & bradycardia, severe respiratory distress, pulmonary haemorrhage, cardiopulmonary arrest, severe respiratory acidosis (PaCO2 >65mmHg with pH<7.20). Weaning from non-invasive respiratory support was included if FiO2 <0.25 to maintain SpO2, mean airway pressure <6cm H2o for NHFOV or NIPPV and no respiratory distress sign.[13]

Demographic data were collected on a structured proforma by the researcher. The primary outcome included the reduced need for mechanical ventilation during the initial seven days of life in the neonate with respiratory distress syndrome randomized in NHFOV and NIPPV groups. Secondary outcomes included hospitalization days, Non-Invasive Ventilation days, pre-discharge mortality, need for surgery for patent ductus arteriosus, abdominal distention, air leaks such as pneumothorax, pneumomediastinum, and pneumopericardium, spontaneous intestinal perforation, necrotizing enter colitis, intraventricular haemorrhage ≥Grade 3, retinopathy of prematurity Stage 3, bronchopulmonary dysplasia. BPD was classified as mild, moderate, or severe per the National Institutes of Health consensus.[13] An intraventricular haemorrhage was graded as Papile *et al*.[14] and Bell *et al*.[15] staging was used for necrotizing entero-colitis.

Statistical Package for the social sciences (SPSS) version 23.00 was used to analyze data. Student's t-test was used to analyze the continuous data. Chi-squared test was used for comparing categorical data. The *p*-value of ≤0.05 was considered statistically significant.

## RESULTS

Forty-eight neonates with respiratory distress syndrome were randomly divided into two groups (NHFOV and NIPPV). There was no significant change in the other general characteristics of neonates in the two groups, as shown in (Table-I).

In NHFOV-Group 11(64.7%) and in NIPPV-Group 6(35.3%) preterm babies required IMV during first 7 days ($p$=0.131) as shown in (Figure).

**Table–I: Characteristics of Patients on NHFOV and NIPPV Groups (n=48)**

| Characteristics | NHFOV (n=24), n(%) | NIPPV (n=24), n(%) | *p*-value |
|---|---|---|---|
| **Gender** | | | |
| Female<br>Male | 11(57.9)<br>13(44.8) | 8(42.1)<br>16(55.2) | 0.376 |
| Cesarean section | 16(42.1) | 22(57.9) | 0.094 |
| Spontaneous Vaginal Delivery | 7(77.8) | 2(22.2) | 0.094 |
| Prenatal Corticosteroids | 24(51.1) | 23(48.9) | 0.312 |
| Premature rupture of membrane | 7(58.3) | 5(41.7) | 0.505 |
| | Mean±SD | Mean±SD | - |
| Gestational age (weeks) | 29.96±2.38 | 43.58±61.03 | 0.28 |
| Weight (g) | 1347±458 | 1672±534 | 0.028 |
| Apgar Score @5mins | 8.62±1.20 | 8.83±1.30 | 0.569 |

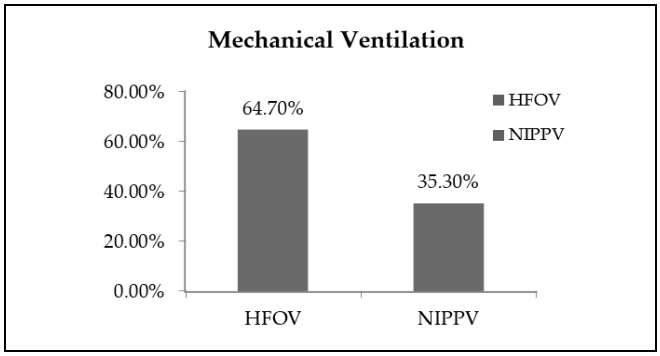


**Figure: Need of Mechanical Ventilation in NHFOV versus NIPPV Groups (n=48)**

The reason for respiratory failure was hypoxia, bradycardia and respiratory acidosis [NHFOV; 8 (34.7%) versus NIPPV; 6(26.0%]. Secondary outcomes were not significant between NHFOV and NIPPV Groups, as shown in (Table-II). NHFOV was not statistically significant than NIPPV in reducing the need for invasive mechanical ventilation in the initial seven days of life in neonates with Respiratory distress.

## DISCUSSION

Nasal high-frequency oscillatory ventilation is an emerging non-invasive mode; very few trials have been done to compare this modality with NIPPV. A multicentre retrospective cohort study was conducted in China that showed mechanical ventilation need was fundamentally reduced in NHFOV versus NIPPV group as novel non-invasive ventilation in premature with respiratory distress syndrome.[16] A study was done by Chen et al. in which NHFOV significantly reduced the need for reintubation rate at 6 hours compared to NCPAP, especially in neonates with a gestational age of ≤ 32 weeks.[17] NHFOV were found to decrease pCo2 and pH after 12 hours of respiratory support.[18] Another study showed that no neonate needs NHFOV.[19] In a prospective randomized control trial, the need for IMV was least in NHFOV vs NCPAP group(24.3% vs 56.4% $p$<0.01) in premature neonates with respiratory distress syndrome, whereas IVH, BPD or air leaks were similar between the groups9. Seth et al. did not assess a major change in the requirement of reintubation at 72 hours in NHFOV vs NIPPV group among neonates with gestational age 26 and 36+6 weeks18.NHFOV was least effective than NIPPV in 42 neonates as post-extubation respiratory support.[18]

**Table -II Primary and Secondary Outcomes in NHFOV and NIPPV Groups (n=48)**

| Outcomes | NHFOV (n=24) | NIPPV (n=24) | *p*-value |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| | 6.29±4.33 | 5.62±2.85 | 0.533 |
| Need of Non-invasive ventilation (hours) | 156.08±105 | 135±68 | 0.416 |
| | n (%) | n (%) | |
| Mechanical Ventilation need | 11(64.7) | 6(35.3) | 0.131 |
| Mortality | 13(65) | 7(35) | 0.079 |
| Abdominal distention | 3(50) | 3(50) | 1.000 |
| Air Leak | 1(100) | 0(.0) | 0.312 |
| Necrotizing Enterocolitis | 1(50) | 1(50) | 1.000 |
| Retinopathy of Prematurity | 1(25) | 3(75) | 0.154 |
| Bronchopulmonary Dysplasia | 1(100) | 0(.0) | 0.312 |
| Patent Ductus Arteriosus | 0 | 0 | - |
| Intraventricular Hemorrhage | 0 | 0 | - |
| Spontaneous Intestinal Perforation | 0 | 0 | - |

However, in our study, there were no huge contrasts found between the NHFOV (64.7%) and NIPPV (35.3%) groups needing mechanical ventilation during the first seven days of life ($p$=0.13). This was the prin cipal, randomized, controlled study in premature neonates utilizing NHFOV as an essential method of respiratory support in Pakistan. This study did not show a statistical difference in reducing the need for mechanical ventilation as the primary outcome. This also has been seen in another randomized controlled trial with no major difference in the two groups NHFOV and NCPAP $p$=0.13. Furthermore, this study did not show a significant result for the incidence of BPD and mortality in preterm babies with GA 28wk to 34 wk, similar to our study ($p$>0.05)19.

Whereas no major difference was seen in the incidence of mortality, abdominal distention, NEC, ROP and BPD in our study, similar to previous studies.[18,20]. No Air leak was seen in that study. However, in our

study, one neonate developed pneumothorax within 24 hours of NHFOV and needed chest tube placement and immediate mechanical ventilation. Pneumothorax was also a complication in the NHFOV Vs NIPPV group study trial.[18] However, we did not find any haemodynamically significant PDA or complications like intraventricular haemorrhage or spontaneous intestinal perforation in NHFOV and NIPPV groups.

The non-invasive ventilation and hospitalization days were insignificant between NHFOV and NIPPV groups, similar to previous studies.[19] This was also found significantly reduce the need for respiratory support in the NHFOV Group in randomized control trials.[20] Although the mean airway pressure between NHFOV vs NIPPV group was not statistically different in our study, pH value was significantly maintained in the NHFOV group and effectively reduced PaCO2.

Gestational age and weight were the two main confounders which could not be removed where, as selection bias was minimized by random selection.

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## CONCLUSION

In our study, NHFOV was not statistically significant than NIPPV in reducing the need for mechanical ventilation during the first seven days of life in preterm neonates with Respiratory distress syndrome, nullifying our hypothesis. Therefore, further large-scale studies are required to analyze the advantages of this modernistic respiratory support.

**Conflict of Interest:** None.

**Authors' Contribution**

Following authors have made substantial contributions to the manuscript as under:

RA: Conception, data acquisition, data analysis, drafting the manuscript, approval of the final version to be published.
SM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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