Nasal HFOV Versus Nasal IPPV as a Post Extubation Respiratory Support in Preterm Infants - a Randomised Controlled Trial

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Abstract

Early and successful extubation prevents several morbidities in preterm newborns. Several secondary noninvasive respiratory modalities exists but with their merits and demerits. Given the superior respiratory efficacy of nasal high frequency oscillatory ventilation (nHFOV), we tried to examine whether nHFOV could reduce reintubation rates compared to nasal intermittent positive pressure ventilation (NIPPV) during the postextubation phase in preterm infants. Stratified randomisation based on gestational age was done for 86 mechanically ventilated preterm infants between 26 - 37 weeks of gestation within 2 weeks of age, to receive either nHFOV or NIPPV post extubation. The main objective was to compare extubation failure within 72 hours following extubation and secondarily feed intolerance, necrotising enterocolitis (NEC) (> stage 2), hemodynamically significant patent ductus arteriosus (hsPDA), intraventricular haemorrhage (IVH) (> grade 3), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), death, hospital stay duration. No statistical difference was noted for primary outcome (RR 0.8, 95% CI: 0.23 to 2.78**;** *p* = 1.00) and secondary outcomes . However nHFOV appeared superior in respect to feed tolerance rates, pCO2 washout and hospital stay duration.

Conclusion: Extubation failure within 72 hours in infants less than 37 weeks of gestation did not differ between the two groups. However nHFOV seems promising in reducing enteral feeding issues and hospital stay duration . Larger multicentre studies are required for exploring benefits of nHFOV.

Trial registration: www.ctri.nic.in id CTRI/2019/07/020055, registration date July 5, 2019

Introduction

The transition of intrauterine to extra-uterine environment is marked by complex pulmonary and hemodynamic changes which occur smoothly and uneventfully in most babies[1]. Disturbed adaptation to extra-uterine life leading to respiratory distress occurs in about 7% of neonates[2]. Preterm neonates are at a greater risk for developing respiratory distress due to myriad of causes. Most of these babies therefore require some form of respiratory support to aid their breathing effort. With advancement of medical research and science, it has been proved that mechanical ventilation, though the gold standard and probably the best mode of ventilation, is crippled with long term respiratory morbidities. Therefore in the quest for various non invasive methods, the present day has seen a balanced arsenal of tools starting from synchronized non invasive positive pressure ventilation (SNIPPV) to high flow nasal cannula (HFNC), each of which has its pros and cons. The idea of this study is to highlight another brick in the wall, the nasal high frequency oscillatory ventilation (nHFOV).

Time and again, it has been proved that lesser the time a baby spends on invasive ventilation, lesser the risk of chronic lung injury. Moreover, preterm babies need to tolerate extubation successfully. Till date, nasal IPPV is considered the best modality post extubation to enable babies to have a smooth transition from invasive to non invasive modes.· However, synchronization which is difficult to achieve in most cases, may provide better results[3]. The beauty of nHFOV lies primarily in the fact that it does not need

synchronization[4]. Theoretically, nasal HFOV combines the benefits of both invasive high frequency oscillatory ventilation (HFOV) and nasal continuous positive airway pressure (nCPAP)[4].

Added advantages include reduced episodes of bradycardia and desaturation[5], enhanced alveolar ventilation due to better alveolar recruitment and improved functional residual capacity (FRC), theoretically lesser ventilator induced lung injury (VILI) and reduced gastroesophageal reflux[6]. Various physiological and benchmark studies have demonstrated positive results in favour of nHFOV, viz. the feasibility of nHFOV in extreme low birth weight (ELBW) infants[7], effectiveness of different interfaces delivering nHFOV[8,9,10], the efficiency in eliminating carbon dioxide (CO_2)[11,12,13], the effect of different parameters and leak on CO_2 removal[9,14,15], the transmission of oscillation and tidal volume delivery in the airways[14]. De Luca et al. suggested working parameters for nHFOV in different clinical scenarios, which needs verification in adequately powered studies[8]. Few cross over and randomized control trials using nHFOV as a primary mode in RDS have been undertaken but large scale data is still lacking [11,16,17,18,19,20]. In most of these studies nHFOV was compared with nCPAP. nHFOV is being presently practised in some European countries, Canada and China. However a worldwide acclamation of this novel method is yet to happen[13,21]. Only two studies have evaluated the efficacy of nHFOV post extubation[13,22]. SNIPPV might be the most effective non invasive respiratory support modality in the immediate post extubation phase but is not readily available[23]. Currently a large multicentric trial is being conducted in China which aims to select the superior secondary mode of non invasive ventilation amongst nCPAP, NIPPV and nHFOV[24].

We hypothesized that using nHFOV as a post extubation mode will improve patient - ventilator synchrony, enable easy weaning of a baby from ventilator and reduce the need for re-intubation. Comparison of nHFOV with NIPPV is still in its early stages and more studies are required to reach consensus statement. Therefore we planned to compare nHFOV versus NIPPV as a post extubation respiratory mode in preterm neonates between 26-37 weeks gestational age admitted in a tertiary care centre . To the best of our knowledge, such a study has not yet been carried out. Given the advantages of nHFOV over NIPPV, this modality can provide an added advantage in future newborn respiratory care.

Material And Methods

Trial design, settings and participants

This randomized control trial was conducted in level III neonatal intensive care unit (NICU) in a tertiary care hospital in Kolkata, India from July 2019 to September 2020. All preterm newborns (26-37 weeks) with respiratory distress, presenting within 15 days of life requiring invasive ventilatory support for at least 12 hours were enrolled in the study. Babies with major congenital anomalies or known/suspected chromosomal anomalies, upper airway anomalies, severe perinatal asphyxia or born outside the institute were excluded.

Intervention

Informed consent from parents was taken. Post extubation respiratory support was provided in intervention (nHFOV) and comparator (NIPPV) groups, after randomization by simple online randomization done at time of intubation. Blinding was not possible because of the nature of the study. nHFOV was provided by SLE 6000 ventilator (Surrey, UK) via appropriate Fisher-Paykel nasal interface. NIPPV was given via Dragger Babylog 8000 plus ventilator (Lübeck, Germany) with appropriate Fisher-Paykel nasal interface. Cycling of prongs and masks was done as per unit protocol. Prong or mask size was chosen to have a snug fitting. The oxygen saturation probe placement was standardized on pre-ductal location. Necessary outcome parameters were observed and noted from time to time and followed up till discharge or death. Arterial blood gas was obtained at 12 hours post intervention. Pre-extubation mode of invasive ventilation was at the treating physician's discretion. Settings used in the two arms is depicted in Table I.

Outcomes

Primary outcome: Extubation failure within 72 hours.

Secondary outcomes:

i) Re-intubation rate

ii) Invasive ventilator free days[25]

iv) Days on assisted ventilation

v) Number of days on O_2

vi) pCO_2 12 hours post intervention

vii) Incidence of hsPDA[26]

viii) IVH (above grade3)[27]

ix) Broncho Pulmonary Dysplasia (BPD)[28]

x) Retinopathy of Prematurity (ROP) requiring laser[29]

xi) Culture positive sepsis

xii) Necrotizing Enterocolitis (NEC) above stage2[30]

xiii) Rate of feed intolerance[31]

xiv) Time taken to full enteral feeds

xv) Gastrointestinal perforation

xvi) Pulmonary air leaks

xvii) Length of NICU stay

xviii) Mortality due to any cause

Sample size

Considering a need for re-intubation in studies using NIPPV as a post extubation secondary mode in newborn of 35%[3], and hypothesizing a reduction of need for re-intubation in the intervention group to 10%, a sample size of 86 is required keeping an alpha error of 5% and power of 80%.

Randomization

Randomization was done by computer-generated random sequence number (Research Randomizer (Version 4.0)). The allocation ratio was 1:1 and concealment was done by using a serially numbered opaque sealed envelope. The generation of random numbers and assignment was done by a person not involved in the study. .

Statistical analysis

Analysis was done using GraphPad Prism version 7.0.0 for Windows, (GraphPad Software, San Diego, California USA), MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). Data was summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables that were normally distributed, median and interquartile range for skewed numerical variables, and counts and percentages for categorical variables. Numerical variables were compared between subgroups by Student's independent samples t test if normally distributed, or by Mann-Whitney U test if otherwise. Fisher's exact test was employed along with calculation of relative risk (RR) and 95% confidence interval (CI) for intergroup comparison of categorical variables. Analyses were two-tailed and statistical significance level was set at $p < 0.05$ for all comparisons.

Ethics

This study was approved by institutional ethics committee of the Institute of Post Graduate Medical Education and Research, Kolkata, India (IPGME&R/IEC/2019/434). Written informed consent was obtained from all legal guardians before participation in the study. This trial was registered in Clinical trial registry of India (Registration number CTRI/2019/07/020055).

Results

Out of 650 total preterm live births during the study period 112 infants were assessed for eligibility . After exclusion of 26 , a total of 86 infants were subjected to stratified randomisation into one of the two

groups of nHFOV and NIPPV , stratification done based on gestational age in two subgroups 26-31^{+6}weeks and 32-36^{+6} weeks. The flow of participants in the study is summarised in Figure I. Both groups were comparable with the baseline variables (Table II). The median gestation age of the infants was 31.5 weeks with an average birth weight of 1660 g. The duration of invasive ventilation before being extubated to the respective intervention arms were a median of 29 hours for nHFOV and 27 hours for NIPPV. The results of primary and secondary outcomes are depicted in Table III & IV.

There was a reduction in need of reintubation at 72 hours between the nHFOV group (9.3%) and the NIPPV group (11.6%) but no statistical significance (RR with nHFOV, 0.8; 95% CI, 0.23 to 2.78). In subgroup analysis also, statistical significance was not found for the primary outcome (In 26-31^{+6} w, 14.2% vs 9.09% with RR 1.43 , 95% CI 0.27 to 7.73 for nHFOV and in 32-36^{+6} w, 4.5% vs 14.2% RR 0.32 with 95% CI 0.04 to 2.82 for nHFOV). Overall reintubation rate was reduced but not statistically significant (16.2% vs 18.6% with RR 0.88 and 95% CI 0.35 to 2.2 for nHFOV). Days of assisted ventilation seemed less for nHFOV with median (IQR) of 7 days (4 to 16) versus 8 days (4 to 15) for NIPPV (U 889, p=0.764). Similar observation for days spent on oxygen with median 8 days (IQR 4 to 19.75) for nHFOV and 9 days (IQR 5 to 18) for NIPPV (U 916, p=0.944). nHFOV seemed superior in pCO2 elimination and pH optimisation 12 hours after the start of intervention with mean of 35.53 $\pm$ 8.57 vs 38.82 $\pm$ 9.82 mmHg (p = 0.097) and 7.38 $\pm$ 0.07 vs 7.36 $\pm$ 0.07 (p = 0.073). No differences were observed between the two groups as well as sub groups for sepsis , hsPDA, IVH , air leaks , BPD, ROP requiring laser and mortality before discharge. Feed intolerance seemed lesser in the nHFOV group (37.2 % vs 58.13 % , RR 0.64 95% CI 0.4 to 1.02, p=0.084). Moreover infants in the nHFOV arm appeared to achieve full enteral feeds earlier (median 7 days (IQR 5 to 10) vs median 8 days (5.75 to 10.25) , p = 0.503). In the 26-31+6 weeks subgroup also, full enteral feeds was attained earlier in nHFOV arm by around 1.8 days (8.89$\pm$3.67 vs 10.61$\pm$6.65 days, p = 0.503). For babies discharged home, the length of hospital stay seemed shorter in the nHFOV arm by around 4 days (30.61$\pm$22.58 vs 34.31+28.68 days, p= 0.538). In the subgroup analysis of less than 32 weeks , babies were discharged atleast 3 days earlier (49.5+20.6 days vs 52.4+29.8 days, p=0.745). Similar observation for more than 32 weeks gestation too (16+9.21 vs 17.22+13.05 days, p= 0.731). We did not find any difference in the number of ventilator free days between the two groups.

Discussion

In our randomised controlled trial, there was a reduction in reintubation rates within 72 hours in nHFOV group, however without any statistical significance. The consideration of higher NIPPV failure rates based on western literature and the desired reduction led to relatively smaller sample size estimation than ideally required for a statistical significant reduction of primary outcome. Need for mechanical ventilation was significantly reduced in many studies and two meta-analysis using nHFOV as a primary mode, however all of them used nCPAP as the comparator arm[12,16,17]. nCPAP is still considered the standard of care post extubation, while NIPPV now appears to be the better modality, with its own pitfalls[23]. nHFOV is adjudged in benchmark studies as a better respiratory support modality[4]. One RCT by Chen et al. with 206 infants showed lesser reintubation and pCO2 in 6 hours time with nHFOV post extubation

against nCPAP[22]. Malakian et al., however did not find any difference in rate of intubation within 72 hours[20]. To the best of our knowledge , this is the first randomised controlled trial comparing nHFOV versus NIPPV as a post extubation modality in preterm babies worldwide. The only trial (NCT02543125) comparing nHFOV with NIPPV as a post extubation modality was initiated in China in the year 2016 and is yet to complete. Another large multicentric triple arm RCT is underway in China by Shi et al., comparing nCPAP versus NIPPV versus nHFOV as a post extubation modality to choose the best out of the three , results of which are awaited[24].

The days on assisted ventilation and on oxygen in both groups were similar in the study. Another factor which might help prevent extubation failure is efficacious clearance of pCO2. Our study also showed better clearance of pCO2 and normalisation of blood gases but failed to achieve statistical significance. Mukherjee et al., Colaizy et al., and Czernik et al., also showed similar significant reductions in pCO2[13,[32],[33]]. There was a time dependant variation in pCO2 levels in many studies probably because of different amplitudes used. In our study we used a mean airway pressure of 10.9$\pm$2.06 and a median amplitude of 15 which was similar to most studies done with nHFOV[4,9,12,16,22].

In this study, we found infants in the nHFOV arm seemed to have better feed tolerance rates and earlier full enteral feeds by 1 day. Given the advantage of nHFOV over NIPPV in the aspect of no need for synchronisation[4], no glottic constrictions during breaths[[34]], and active expiration it is not surprising that nHFOV seems to lower feed intolerance rates. Unfortunately majority of the studies have not focused on the feed tolerance issues while the baby is on nHFOV except Iranpour et al., Malakian et al., and Chen et al., who showed no difference in NEC rates[18,20,22]. Because of lack of synchronised machines from this part of the world, we need to strike a fine balance between non invasive ventilation and feed intolerance issues and in this regard nHFOV seems promising. We also noted that for infants discharged home, those in the nHFOV arm were discharged much earlier compared to their NIPPV couterparts by around 4 days. This can be attributed to better nutrition buildup and early discharge readiness which also takes care of cost-benefit ratio. Chen et al., showed a similar shorter duration of hospital stay with nHFOV by around 5 days[22] however Malakian et al., showed no difference in days of hospitalisation[20]. Early full enteral feeds and early discharge from the unit is a boon for mother-infant dyad and is therefore encouraged.

As for secondary outcomes like sepsis , hsPDA, IVH, NEC, airleaks, ROP, BPD, ventilator free days and mortality there was not much to choose between the two among groups as well as subgroups . Interestingly most studies done on nHFOV including the two meta-analysis failed to show any difference in PDA, BPD, NEC, airleaks, ROP, IVH and mortality[12,16,17,18,20,22]. We also did not find any significant side effects with nHFOV. We cycled between short binasal prongs and mask, both of which have been shown to be efficacious[8,9,14]. However none of the previous studies have used both simulatenously. Mask delivered nHFOV has more dampening effect, therefore theoretically would require more aggressive ventilatory parameters[10]. In our case, cycling of the interfaces were done for comfort of the babies and whether it caused a drop in efficacy of nHFOV cannot be ascertained. It will require more studies to evaluate this aspect.

The major limitations of this study are firstly a small sample size to derive any statistical significance. The higher NIPPV failure rate consideration at the onset of study probably led to a relatively smaller sample size estimation. Secondly, comfort level of babies were not quantified objectively. Thirdly, whether intermittent use of mask led to lesser efficacy needs to be investigated further. Fourthly, long term side effects and neurodevelopmental outcome is something to look forward to. Finally a multicentre study is the need of the hour for formulating standard operating protocols as well as better utilisation of this novel respiratory modality.

In summary, among preterm ventilated infants, nHFOV did bring about a reduction in reintubation rates within 72 hours post extubation however without any statistical significance, it also seemed promising in reducing feed intolerance, days to full enteral feed and hospital stay. Arterial blood pH and pCO2 seemed to achieve a better normalisation in the nHFOV group. Most secondary outcomes however were similar between the two groups. Further multicentric studies need to be planned to explore further benefits of this novel respiratory support as well as formulate standard operating protocols.

Abbreviations

BPD brochopulmonary dysplasia

CI confidence interval

CO_2 carbon dioxide

ELBW extreme low birth weight

FiO2 fraction of inspired oxygen

FRC functional residual capacity

HFNC high flow nasal cannula

HFOV high frequency oscillatory ventilaton

hsPDA hemodynamically significant patent ductus arteriosus

IQR interquartile range

IVH intraventricular hemmorhage

IVH Gr3+ intraventricular hemmorhage more than grade3

MV mechanical ventilation

nCPAP nasal continuous postive airway pressure

NEC necrotising enterocolitis

NEC St2+ necrotising enterocolitis above stage 2

nHFOV nasal high frequency oscillatory ventilation

NICU neonatal intensive care unit

NIPPV nasal intermittent positive pressure ventilation

PIP peak inspiratory pressure

PEEP positive end expiratory pressure

RDS respiratory distress syndrome

ROP retinopathy of prematurity

RR relative risk

SNIPPV synchronised nasal intermittent positive pressure ventilation

VILI ventilator induced lung injury

Declarations

Funding -

N/A

Conflicts of interest/Competing interests -

The authors declare that they have no conflict of interest.

Ethics approval -

The ethical approval for the study was taken from the Institutional Ethics Committee, Institute of Post Graduate Medical Education and Research,, Kolkata, India(IPGME&R/IEC/2019/434, dated 03.07.2019).

Consent to participate -

Informed consent was obtained from the legal guardian of all included participants.

Consent to publication -

Informed consent was obtained from the legal guardian of all included participants.

Availability of data and material -

Available for viewing at https://drive.google.com/file/d/198bnLzXK_ZWfBfzdzLlDHr8ZgFvBCp17/view?usp=sharing

Code availability -

N/A

Authors' contributions -

Dr. Soutrik Seth conceptualised and designed the study, developed the protocol, patient management and prepared the first draft. Dr. Bijan Saha helped in protocol development ,co-ordinated, supervised data collection, reviewed and revised the manuscript at all stages of its production. Dr. Anindya Kumar Saha , critically reviewed and revised the manuscript. Dr. Suchandra Mukherjee helped in protocol development and critically reviewed the manuscript for improving the content. Dr. Avijit Hazra performed the statistical analysis of the data. All the authors approved the final manuscript as submitted and agree to be accountable for all aspect of the work.

References

1. Martin RJ, Crowley MA (2013) Respiratory problems. In: Fanaroff AA, Fanaroff JM (ed) Care of the high risk neonate, 6th edn, Elsevier Saunders, Philadelphia, pp 244
2. Agarwal R, Deorari A, Paul V, Sankar MJ, Sachdeva A (2019) AIIMS Protocols in Neonatology, 2nd edn, Delhi, Noble Vision
3. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. (2014) Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev.;(9):CD003212.
4. De Luca D, Dell'Orto V.(2016) Non-invasive high-frequency oscillatory ventilation in neonates: review of physiology, biology and clinical data, Arch Dis Child Fetal Neonatal Ed;101 :F565–F570
5. Rüegger CM, Lorenz L, Kamlin OC, Manley BJ, Owen LS, Bassler D et al.(2018) The Effect of Noninvasive High-Frequency Oscillatory Ventilation on Desaturations and Bradycardia in Very Preterm Infants: A Randomized Crossover Trial, J Pediatr. ;201:269-273.e2
6. Cantin D, Djeddi D, Samson N, Nadeau C, Praud JP.(2018) Nasal high-frequency oscillatory ventilation inhibits gastroesophageal reflux in the neonatal period. Respiratory Physiology & Neurobiology. ;251:28-33
7. Aktas S, Unal S, Aksu M, Ozcan E, Ergenekon E, Turkyilmaz C et al.,(2016) Nasal HFOV with Binasal Cannula Appears Effective and Feasible in ELBW Newborns, Journal of Tropical Pediatrics, Volume 62, Issue 2, Pages 165–168
8. De Luca D, Carnielli VP, Conti G, Piastra M., (2010) Noninvasive high frequency oscillatory ventilation through nasal prongs: bench evaluation of efficacy and mechanics, Intensive Care Med.;36(12):2094-

100

9. De Luca, D., Piastra, M., Pietrini, D. and Conti, G. (2012), Effect of amplitude and inspiratory time in a bench model of non-invasive HFOV through nasal prongs. Pediatr. Pulmonol., 47: 1012-1018.
10. Centorrino R, Dell'Orto V, Gitto E, Conti G, De Luca D. (2019)Mechanics of nasal mask-delivered HFOV in neonates: A physiologic study. PediatrPulmonol.;54(8):1304-1310.
11. Bottino R, Pontiggia F, Ricci C, Gambacorta A, Paladini A, Chijenas V et al (2018) Nasal high-frequency oscillatory ventilation and CO2 removal: A randomized controlled crossover trial. PediatrPulmonol. ;53(9):1245-1251
12. Li, J., Li, X., Huang, X. Zhang Z. (2019) Noninvasive high-frequency oscillatory ventilation as respiratory support in preterm infants: a meta-analysis of randomized controlled trials. Respir Res20, 58
13. Mukerji A, Singh B, Helou SE, Fusch C, Dunn M, Belik J, Shah V (2015) Use of noninvasive high-frequency ventilation in the neonatal intensive care unit: a retrospective review. Am J Perinatol; 30:171–6
14. De Luca, D., Costa, R., Visconti, F., Piastra, M. and Conti, G. (2016), Oscillation transmission and volume delivery during face mask-delivered HFOV in infants: Bench and in vivo study. PediatrPulmonol., 51: 705-712
15. Klotz D, Schaefer C, Stavropoulou D, Fuchs H, Schumann S. (2017) Leakage in nasal high-frequency oscillatory ventilation improves carbon dioxide clearance-A bench study. PediatrPulmonol. ;52(3):367-372
16. Haidar Shehadeh AM (2019) Non-invasive high flow oscillatory ventilation in comparison with nasal continuous positive pressure ventilation for respiratory distress syndrome, a literature review. J Matern Fetal Neonatal Med. 7:1-10
17. Zhu XW, Zhao JN, Tang SF, Yan J, Shi Y. (2017) Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: A preliminary report. PediatrPulmonol. ;52(8):1038-1042
18. Iranpour R, Armanian AM, Abedi AR, Farajzadegan Z (2019) Nasal high-frequency oscillatory ventilation (nHFOV) versus nasal continuous positive airway pressure (NCPAP) as an initial therapy for respiratory distress syndrome (RDS) in preterm and near-term infants. BMJ Paediatr Open. 14;3(1):e000443
19. Klotz D, Schneider H, Schumann S, Mayer B, Fuchs H. (2018) Non-invasive high-frequency oscillatory ventilation in preterm infants: a randomised controlled cross-over trial. Arch Dis Child Fetal Neonatal Ed. ;103(4):F1-F5. doi: 10.1136/archdischild-2017-313190
20. Malakian A, Bashirnezhadkhabaz S, Aramesh MR, Dehdashtian M. (2020) Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: a randomized controlled trial. J Matern Fetal Neonatal Med. ;33(15):2601-2607

21. Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C. (2015) Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. Eur J Pediatr. ;174(4):465-71
22. Chen L, Wang L, Ma J, Feng Z, Li J, Shi Y. (2019) Nasal high-frequency os-cillatory ventilation in preterm infants with respiratory distress syn-drome and ARDS after extubation: a randomized controlled trial.Chest. ;155(4):740-748
23. Ramaswamy VV, Bandyopadhyay T, Nanda D, Bandiya P, More K, Oommen VI, et al. (2020) Efficacy of noninvasive respiratory support modes as postextubation respiratory support in preterm neonates: A systematic review and network meta-analysis. Pediatric Pulmonology.; 55: 2924– 2939
24. Shi Y, De Luca D, (2019) NASalOscillatioN post-Extubation (NASONE) study group. Continuous positive airway pressure (CPAP) vs noninvasive positive pressure ventilation (NIPPV) vs noninvasive high frequency oscillation ventilation (nHFOV) as post-extubation support in preterm neonates: protocol for an assessor-blinded, multicenter, randomized controlled trial. BMC Pediatrics. ;19(1):256
25. Schoenfeld DA, Bernard GR; ARDS Network. (2002) Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. ;30(8):1772-7
26. Sehgal A, McNamara PJ (2009) Does echocardiography facilitate determination of hemodynamically significance attributable to the ductus arteriosus ? Eur J Pediatr 168(8):907–914
27. Papile LA, Burstein J,Brustein R, Koffler H. (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500gm.pediatrics 92:529-34
28. Jobe AH, Bancalari E (2001) Bronchopulmonary dysplasia: NICHD/NHLBI/ORD workshop summary. Am J Respir Crit Care Med.163:1723-9
29. Classification of Retinopathy of Prematurity.(2005) The International Classification of Retinopathy of Prematurity Revisited. Arch Ophthalmol. ;123(7):991–999
30. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T (1978). Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. Ann Surg.;187(1):1-7
31. Moore TA, Wilson ME. (2011) Feeding intolerance: a concept analysis. Adv Neonatal Care.;11(3):149-54
32. Colaizy TT, Younis UM, Bell EF, Klein JM.(2008) Nasal high-frequency ventilation for premature infants. Acta Paediatr. 97(11):1518-22
33. Czernik C, Schmalisch G, Bührer C, Proquitté H.(2012) Weaning of neonates from mechanical ventilation by use of nasopharyngeal high-frequency oscillatory ventilation: a preliminary study. J Matern Fetal Neonatal Med. 25(4):374-8
34. Hadj-Ahmed MA, Samson N, Nadeau C, Boudaa N, Praud JP. (2015) Laryngeal muscle activity during nasal high-frequency oscillatory ventilation in nonsedated newborn lambs. Neonatology. ;107(3):199-205.

Tables

Table I. Parameters of nHFOV and NIPPV arm used in the study.

PARAMETERS	nHFOV	NIPPV
INITIAL	Frequency – 10–12 Hz, I:E ratio 1:1, amplitude 25–35 cm H_2O titrated based on visible chest oscillations & pCO2, Pmean 8–10 cm H_2O titrated on oxygenation, FiO_2 to maintain SpO_2 at 90–95%.	PIP = 2 cm H_2O above the pre-extubation set PIP on mechanical ventilation Positive endexpiratory pressure (PEEP) = 4–6 cm H_2O or identical to PEEP during MV Inspiratory Time (Ti) = 0.30-0.45s. Respiratory rate (RR) = 40–50 breaths/min Flow = 8–10 L/min FiO2 = adjusted to maintain SpO_2 between 90% and 95%
WEANING	FiO2 weaned first by 3–5% while maintaining target saturation until it reaches 30%, then Pmean tapered by 1 cm till 6 cm H_2O.	FiO_2 was decreased by 3–5% while maintaining target SpO_2 in range of 90–95% till it reached 30%; then PIP was tapered by 1–2 cm.
DISCONTINUATION	Minimal or no signs of respiratory distress and hemodynamically stable for 24 hours. Discontinued to nCPAP or O2 or room air.	Minimal or no signs of respiratory distress on NIV pressure (PIP < 13, PEEP < 5 cm H_2O), FiO2 < 0.3 and hemodynamic stability for 24 hours. Discontinued to nCPAP or O2 or room air.
UPGRADATION	Pmean was increased upto a maximum of 12cm and FiO_2 upto 60%	PIP was increased upto a maximum of 25, with simultaneous increase of PEEP to a maximum of 6 and FiO_2 to 60% to maintain target saturation.
FAILURE	Pmean > 12 and/or FiO2 > 60%, pH < 7.20 and/or pCO_2 > 60 mm Hg, frequent bradycardia (< 100 bpm) and desaturation (SpO_2 < 85%) or apnea (defined as three or more apneic episodes of any degree of severity within a period of 1 hour), shock requiring inotropes and Silverman Anderson score of > 6 as per unit protocol In case of failure, babies were intubated.	PIP > 25, PEEP > 6, FiO2 > 60%, pH < 7.20 and/or pCO_2 > 60 mm Hg, frequent bradycardia (< 100 bpm) and desaturation (SpO_2 < 85%) or apnea (defined as three or more apneic episodes of any degree of severity within a period of 1 hour), shock requiring inotropes and Silverman Anderson score of > 6 as per unit protocol In case of failure, babies were intubated.

Table II. Baseline variables of the enrolled subjects

Variable	nHFOV(n = 43)	NIPPV(n = 43)	SIGNIFICANCE
Age of mother, years, mean (SD)	26.83(7.02)	27.18(6.07)	p = 0.403
Gestation, weeks, mean (SD	31.9(3.6)	31.7(3.5)	p = 0.785
Number of fetuses(single/twin), n(%)	32(74.4)/11(25.6)	27(62.8)/16(37.2)	p = 0.24
Maternal PIH, n(%)	5(11.6)	4(9.3)	p = 0.12
Maternal GDM, n(%)	6(13.9)	4(9.3)	p = 0.5
Maternal PROM, n(%)	14(32.5)	10(23.2)	p = 0.33
Maternal APH, n(%)	3(6.9)	2(4.6)	p = 0.64
Maternal Hypothyroidism, n(%)	2(4.6)	2(4.6)	p = 1.00
Maternal Oligohydromnios, n(%)	7(16.2)	3(6.9)	p = 0.17
Antenatal steroids(complete/incomplete), n(%)	5(11.6)/21(48)	4(9.3)/22(51.1)	p = 1.00
LUCS, n(%)	19(44.2)	19(44.2)	p = 1.00
Birth weight, grams, mean(SD)	1722.25(873.66)	1599.39 + 688.55	p = 0.47
Appropriateness of Gestational age (SGA/AGA/LGA), n(%)	6(13.9)/35(81.5)/2(4.6)	3(6.9)/40(93.1)/0	p = 0.29 p = 0.1
Male, n(%)	24(55.9)	24(55.9)	p = 1.00
Apgar 1min, mean (SD)	5.79(1.35)	5.51(1.72)	p = 0.4
Apgar 5min, mean (SD)	7.11(1.13)	7.02(1.22)	p = 0.71
PPV, n(%)	21(48.8)	21(48.8)	p = 1.00
Intubation, n(%)	7(16.3)	13(30.23)	p = 0.12
SA score, Median(IQR)	4(4 to 5)	4(3 to 5)	p = 0.472
RDS, n(%)	26(60.4)	29(67.4)	p = 0.5
Surfactant, n(%)	25(58.1)	28(65.1)	p = 0.5
Duration of IMV,hours, median(IQR)	29(22 to 54)	27(14 to 52)	p = 0.222
Pco2 before, mmHg, mean (SD)	39.96(9.04)	40.32(10.2)	p = 0.86
pH before intervention, mean (SD)	7.33(0.09)	7.31(0.08)	p = 0.43
SNAPPE 2 scores, mean (SD)	22.95(18.33)	24.79(19.27)	p = 0.65

Table III. Primary outcome measures

Variable	nHFOV(n = 43)	NIPPV(n = 43)	Relative Risk(95% Confidence Interval)	Significance
Reintubation within 72hrs, n(%)	4 (9.3)	5 (11.6)	0.8 (0.23 to 2.78)	p = 1.000
Reintubation within 72hrs, n(%) Subgroup 26 to 31 + 6 weeks	3 (14.2) (n = 21)	2 (9.09) (n = 22)	1.43 (0.27 to 7.73)	p = 1.000
Reintubation within 72hrs, n(%) Subgroup 32 to 36 + 6 weeks	1 (4.5) (n = 22)	3 (14.2) (n = 21)	0.32 (0.04 to 2.82)	p = 0.345

Table IV. Secondary outcome measures

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Comparison	Significance
Reintubation rate, n(%)	7 (16.2)	8 (18.6)	RR = 0.88, 95% CI (0.35 to 2.2)	p = 1.000
Reintubation rate, n(%) Subgroup 26 to 31 + 6 weeks	6 (27.2) (n = 21)	4 (18.18) (n = 22)	RR = 1.57, 95% CI (0.52 to 4.79)	p = 0.488
Reintubation rate, n(%) Subgroup 32 to 36 + 6 weeks	1 (4.5) (n = 22)	4 (19.04) (n = 21)	RR = 0.24, 95% CI (0.03 to 1.97)	p = 0.185
Days of assisted ventilation, median(IQR)	7 (4 to 16)	8 (4 to 15)	u = 889	p = 0.764
Days of assisted ventilation, mean (SD) Subgroup 26 to 31 + 6 weeks	21.4(21.34)	22.95(24.8)	t = to 0.21	p = 0.835
Days of assisted ventilation, median(IQR) Subgroup 32 to 36 + 6 weeks	5 (4 to 8)	5 (3 to 9)	u = 200	p = 0.459
Days on oxygen, median(IQR)	8 (4 to 19.75)	9 (5 to 18)	u = 916	p = 0.944
Days on oxygen, mean (SD) Subgroup 26 to 31 + 6 weeks	25(22.82)	23.18(24.74)	t = 0.25	p = 0.804
Days on oxygen, median(IQR) Subgroup 32 to 36 + 6 weeks	5.5 (4 to 8)	5(4 to 11)	u = 229.5	p = 0.984
pCO2 after intervention, mmHg, mean (SD)	35.53(8.57)	38.82(9.48)	t=-1.68	p = 0.097
pCO2 after intervention, mmHg, mean (SD) Subgroup 26 to 31 + 6 weeks	35.21(7.84)	36.98(9.16)	t=-0.68	p = 0.500

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Comparison	Significance
pCO2 after intervention, mmHg, mean (SD) Subgroup 32 to 36 + 6 weeks	35.85(9.38)	40.85(9.64)	t=-1.7	p = 0.096
pH post intervention, mean (SD)	7.38(0.07)	7.36(0.07)	t = 1.81	p = 0.073
pH post intervention, mean (SD) Subgroup 26 to 31 + 6 weeks	7.38(0.07)	7.37(0.07)	t = 0.51	p = 0.609
pH post intervention, mean (SD) Subgroup 32 to 36 + 6 weeks	7.39(0.07)	7.34(0.06)	t = 2.19	p = 0.034
Sepsis, n(%)	5 (11.6)	9 (20.9)	RR = 0.56,95%CI (0.2 to 1.52)	p = 0.382
Sepsis, n(%) Subgroup 26 to 31 + 6 weeks	4 (19) (N = 21)	5 (22.7) (N = 22)	RR = 0.84,95%CI (0.26 to 2.7)	p = 1.000
Sepsis, n(%) Subgroup 32 to 36 + 6 weeks	1 (4.5) (N = 22)	4 (19) (N = 21)	RR = 0.24,95%CI (0.03 to 1.97)	p = 0.185
hsPDA, n(%)	22 (51.16)	23 (53.48)	RR = 0.96,95%CI (0.64 to 1.43)	p = 1.000
hsPDA, n(%) Subgroup 26 to 31 + 6 weeks	16 (76.2) (n = 21)	17 (77.2) (n = 22)	RR = 0.99,95%CI (0.71 to 1.37)	p = 1.000
hsPDA, n(%) Subgroup 32 to 36 + 6 weeks	6 (27.2) (n = 22)	6 (28.6) (n = 21)	RR = 0.95,95%CI (0.37 to 2.49)	p = 1.000
IVH Gr3+, n(%)	1 (2.3)	2 (4.3)	RR = 0.5,95%CI (0.05 to 5.31)	p = 1.000
IVH Gr3+, n(%) Subgroup 26 to 31 + 6 weeks	1 (4.7) (n = 21)	2 (9.1) (n = 22)	RR = 0.52,95%CI (0.05 to 5.36)	p = 1.000

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Comparison	Significance
IVH Gr3+, n(%) Subgroup 32 to 36 + 6 weeks	0 (n = 22)	0 (n = 21)	----------	
NEC St2+, n(%)	2 (4.3)	5 (11.6)	RR = 0.4,95%CI (0.08 to 1.95)	p = 0.433
NEC St2+, n(%) Subgroup 26 to 31 + 6 weeks	2 (9.5) (n = 21)	4 (18.1) (n = 22)	RR = 0.52,95%CI (0.11 to 2.57)	p = 0.664
NEC St2+, n(%) Subgroup 32 to 36 + 6 weeks	0 (n = 22)	1 (4.7) (n = 21)	----------	p = 0.488
Feed intolerance, n(%)	16 (37.2)	25 (58.13)	RR = 0.64,95%CI (0.40 to 1.02)	p = 0.084
Feed intolerance, n(%) Subgroup 26 to 31 + 6 weeks	11 (52.4) (n = 21)	16 (72.7) (n = 22)	RR = 0.72,95%CI (0.44 to 1.17)	p = 0.215
Feed intolerance, n(%) Subgroup 32 to 36 + 6 weeks	5 (22.7) (n = 22)	9 (42.8) (n = 21)	RR = 0.53,95%CI (0.21 to 1.32)	p = 0.203
Full feed day of life, days, median(IQR)	7 (5 to 10)	8 (5.75 to 10.25)	u = 673.5	p = 0.503
Full feed day of life, days, mean(SD) Subgroup 26 to 31 + 6 weeks	8.89(3.67)	10.61(6.65)	t=-0.96	p = 0.343
Full feed day of life, days, median(IQR) Subgroup 32 to 36 + 6 weeks(days)	6.5 (5 to 8)	6 (6 to 8)	u = 192	p = 0.667
Air leaks, n(%)	5 (11.6)	1 (2.3)	RR = 5, 95%CI (0.61 to 41.06)	p = 0.202
Air leaks, n(%) Subgroup 26 to 31 + 6 weeks	2 (9.5) (N = 21)	0 (N = 22)	----------	p = 0.233

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Comparison	Significance
Air leaks, n(%) Subgroup 32 to 36 + 6 weeks	3 (13.6) (N = 22)	1 (4.7) (N = 21)	RR = 2.86, 95%CI (0.32 to 25.42)	p = 0.607
ROP requiring treatment, n(%)	0 (0)	1 (2.17)	----------	p = 1.000
ROP requiring treatment, n(%) Subgroup 26 to 31 + 6 weeks	0 (N = 21)	1 (4.54) (N = 22)	----------	p = 1.000
ROP requiring treatment, n(%) Subgroup 32 to 36 + 6 weeksS	0 (N = 22)	0 (N = 21)	----------	p = 1.000
BPD, n(%)	8 (18.6)	8 (18.6)	RR = 1, 95%CI (0.41 to 2.42)	p = 1.000
BPD, n(%) Subgroup 26 to 31 + 6 weeks	7 (33.3) (N = 21)	7 (31.8) (N = 22)	RR = 1.05, 95%CI (0.44 to 2.48)	p = 1.000
BPD, n(%) Subgroup 32 to 36 + 6 weeks	1 (4.5) (N = 22)	1 (4.7) (N = 21)	RR = 0.95, 95%CI (0.06 to 14.31)	p = 1.000
Death, n(%)	4 (9.3)	8 (18.6)	RR = 0.5, 95%CI (0.16 to 1.54)	p = 1.000
Death, n(%) Subgroup 26 to 31 + 6 weeks	4 (19) (N = 21)	5 (22.7) (N = 22)	RR = 0.84,95%CI (0.26 to 2.70)	p = 1.000
Death, n(%) Subgroup 32 to 36 + 6 weeks	0 (N = 22)	3 (14.3) (N = 21)	----------	p = 0.108
Discharge, days, mean(SD)	30.61(22.58)	34.31(28.68)	t=-0.62	p = 0.538
Discharge, days, mean(SD) Subgroup 26 to 31 + 6 weeks	49.53(20.65)	52.41(29.84)	t=-0.33	p = 0.745

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Comparison	Significance
Discharge, days, mean(SD) Subgroup 32 to 36 + 6 weeks	16(9.21)	17.22(13.05)	t=-0.34	p = 0.731
Ventilator free days, days, mean(SD)	26.05(23.24)	26.48(28.72)	t=-0.07	p = 0.944
Ventilator free days, days, mean(SD) Subgroup 26 to 31 + 6 weeks	38.87(26.76)	39.49(33.72)	t=-0.06	p = 0.947
Ventilator free days, days, median(IQR) Subgroup 32 to 36 + 6 weeks	12.37(8.79 to 14.37)	8.59(6.48 to 13.16)	u = 171.5	p = 0.153

Figures

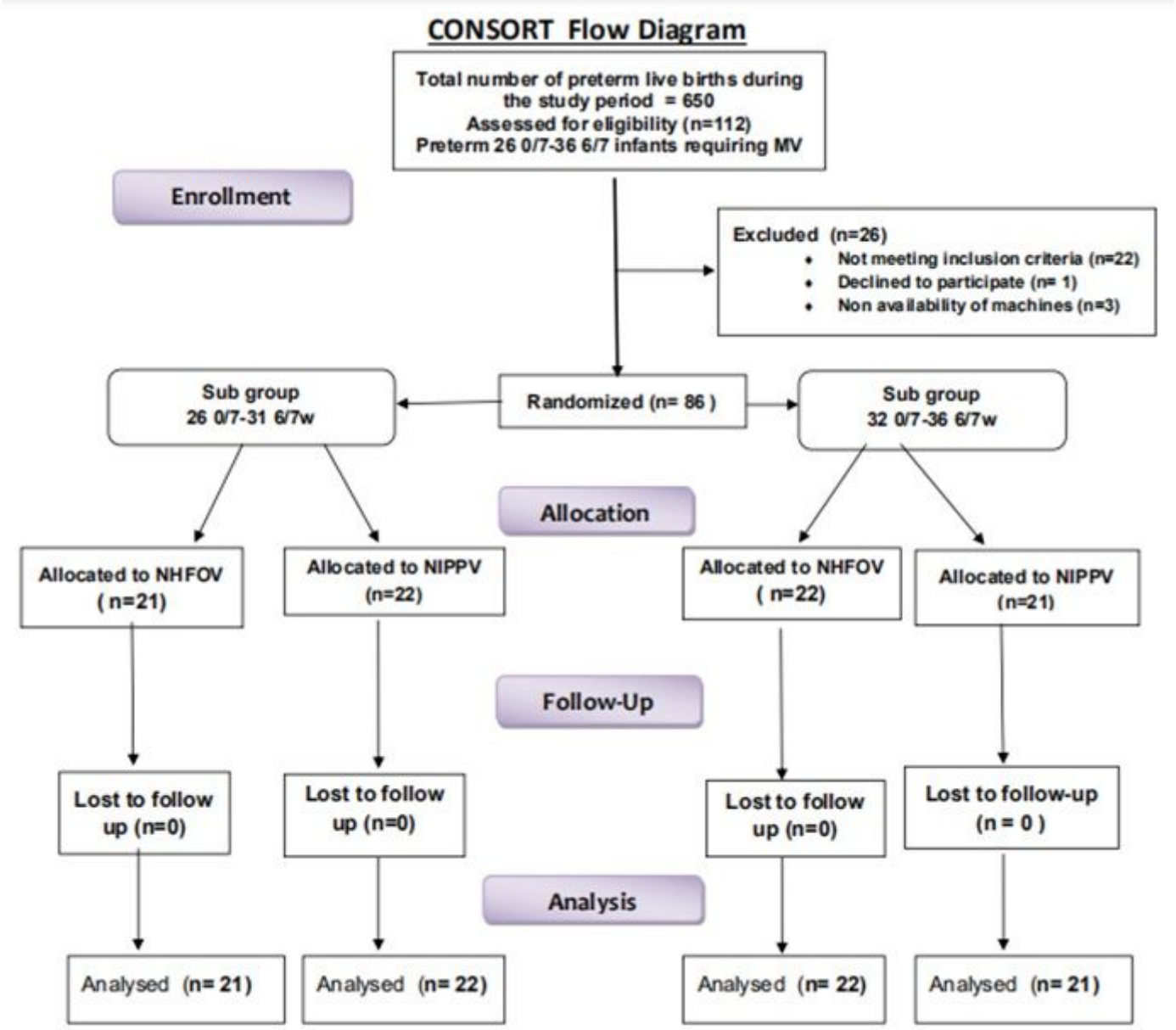

Figure 1

Flow of participants in the study