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ORIGINAL ARTICLE

Nasal HFOV versus nasal IPPV as a post-extubation respiratory support in preterm infants—a randomised controlled trial

Soutrik Seth[1] · Bijan Saha[1] · Anindya Kumar Saha[1] · Suchandra Mukherjee[1] · Avijit Hazra[2]

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Abstract

Early and successful extubation prevents several morbidities in preterm newborns. Several secondary non-invasive respiratory modalities exist but with their merits and demerits. Given the benefits 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 post-extubation phase in preterm infants. Stratified randomisation based on gestational age was done for 86 mechanically ventilated preterm infants between 26 and 36^{+6} 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 h following extubation and secondarily feed intolerance, intraventricular haemorrhage (IVH) (> grade 3), composite bronchopulmonary dysplasia (BPD)/mortality, composite duration of oxygen supplementation/ventilation support and SpO2/FiO2 ratio. 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 possibly better in respect to feed tolerance rates and pCO2 washout.

Conclusion: Extubation failure within 72 h 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 pCO2 elimination. 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

What is Known:
- *NIPPV is superior to nCPAP as a secondary mode of respiratory support.*
- *Synchronisation is preferred for optimum ventilation.*

What is New:
- *nHFOV, a novel non-invasive respiratory modality without need for synchronisation, appears promising as a secondary mode subject to further trials.*
- *It seems promising in reducing enteral feeding issues and pCO2 elimination.*

Keywords nHFOV · NIPPV · Extubation failure · Respiratory distress · Preterm · Neonates

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✉ Bijan Saha
bijansaha18@gmail.com

Soutrik Seth
soutrik.nrs@gmail.com

Anindya Kumar Saha
sahaanindya09@gmail.com

Suchandra Mukherjee
drsmukherjee70@gmail.com

Avijit Hazra
deanipgmerkolkata@gmail.com

[1] Department of Neonatology, Institute of Post Graduate Medical Education & Research and SSKM Hospital, 244, A J C Bose Road, Kolkata PIN-700020, India

[2] Department of Pharmacology, Institute of Post Graduate Medical Education & Research and SSKM Hospital, 244, A J C Bose Road, Kolkata PIN-700020, India

Abbreviations

BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CO_2	Carbon dioxide
ELBW	Extreme low birth weight
FiO2	Fraction of inspired oxygen
FRC	Functional residual capacity
GER	Gastroesophageal reflux
HFOV	High-frequency oscillatory ventilation
IQR	Interquartile range
IVH	Intraventricular haemorrhage
IVH Gr3+	Intraventricular haemorrhage more than grade 3
MV	Mechanical ventilation
nCPAP	Nasal continuous positive airway pressure
nHFOV	Nasal high-frequency oscillatory ventilation
NICU	Neonatal intensive care unit
NIPPV	Nasal intermittent positive pressure ventilation
pCO2	Partial pressure of carbon dioxide
PIP	Peak inspiratory pressure
PEEP	Positive end-expiratory pressure
RDS	Respiratory distress syndrome
RR	Relative risk
S/F ratio	Saturation to fraction of inspired oxygen ratio
SNIPPV	Synchronised nasal intermittent positive pressure ventilation
VILI	Ventilator-induced lung injury

Introduction

The transition of intrauterine to extra-uterine environment is marked by complex pulmonary and haemodynamic changes which occur smoothly and uneventfully in most infants [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 infants therefore require some form of respiratory support to aid their breathing effort. With the 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 nasal continuous positive airway pressure (nCPAP), 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 the lesser the time an infant spends on invasive ventilation, the lesser the risk of chronic lung injury. Moreover, preterm infants need to tolerate extubation successfully. To date, nasal IPPV is considered the best modality post-extubation to enable infants 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]. De Luca et al. suggested working parameters for nHFOV in different clinical scenarios, which need verification in adequately powered studies [4].

Few crossover and randomized control trials using nHFOV as a primary mode in RDS have been undertaken, but large-scale data is still lacking [5–9]. 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 [10]. Only two studies have evaluated the efficacy of nHFOV post-extubation [11, 12]. SNIPPV might be the most effective non-invasive respiratory support modality in the immediate post-extubation phase but is not readily available [13]. 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 [14].

We hypothesized that using nHFOV as a post-extubation mode will enable easy weaning of an infant from the ventilator and reduce the need for reintubation. 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 and 36^{+6} 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 a 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 (26–36^{+6} weeks) with respiratory distress, presenting within 15 days of life requiring invasive ventilatory support for at least 12 h were enrolled in the study. Small for gestational age infants were identified according to Fenton's preterm growth chart [15]. Infants 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. Infants were intubated and put on Drager Babylog 8000 plus ventilator (Lübeck, Germany) using synchronised intermittent positive pressure ventilation with volume guarantee mode primarily for absent, weak, or intermittent spontaneous effort , frequent (> 6 events/h) or severe apnoea requiring positive pressure ventilation, marked retractions, severe tachypnea > 100/min, Silverman Anderson score > 7, pH < 7.2 and not improving, pCO2 > 65 on days 0–3, > 70 beyond day 3, shock requiring inotropic support. Extubation was done when working Pmean < 8 cm H_2O, FiO2 < 0.3 and tidal volume < 4 ml/kg. Post-extubation respiratory support was provided in intervention (nHFOV) and comparator (NIPPV) groups, after randomization by simple online randomization done at the time of intubation. Blinding was not possible because of the nature of the study. nHFOV was provided by SLE 6000 ventilator (Surrey, UK) via Fisher Paykel FlexiTrunk™ interface. NIPPV was given via Dragger Babylog 8000 plus ventilator (Lübeck, Germany) via Fisher Paykel FlexiTrunk™ interface. Cycling of prongs and masks was done every 4 h. Chin straps were not used. Prong or mask size was chosen to have a snug fitting as per recommendations of Fisher Paykel FlexiTrunk™ interface. Caffeine was given to infants with birth weight less than 1250 g and continued till 5 days post-weaning from respiratory support. The oxygen saturation probe placement was standardized on pre-ductal location and was monitored continuously. Arterial blood gas was obtained at 12 h post-intervention. Infant's respiratory condition was monitored with Silverman Anderson scoring every 2 h. Haemodynamic condition was assessed every 2 h in form of saturation, perfusion, and capillary refill time. Assessment for feed tolerance was done every 3 h. Echocardiographic assessment of haemodynamics and patent ductus arteriosus and transcranial ultrasound for intraventricular haemorrhage was done as per unit protocol. Sepsis workup was done on clinical basis and based on risk factors as and when needed. Respiratory morbidity was assessed at appropriate time frame. Infants were followed up as specified in the foregoing until discharge from unit or death. Pre-extubation mode of invasive ventilation was at the treating physician's discretion. Settings used in the two arms are depicted in Table 1.

Outcomes

Primary outcome: Extubation failure within 72 h.

Secondary outcomes:

(i) Reintubation rate
(ii) Invasive ventilator free days [16]
(iii) SpO2/FiO2 ratio
(iv) Composite duration of oxygen supplementation/ventilation support
(v) pCO_2 and pH 12 h post-intervention
(vi) IVH (above grade 3) [17]
(vii) Composite bronchopulmonary dysplasia/mortality [18]
(viii) Rate of feed intolerance [19]
(ix) Time taken to full enteral feeds
(x) Pulmonary air leaks

Sample size

NIPPV failure rate in our NICU ranges between 25% and 35%. From the Cochrane review by Lemyre et al. [3], we identified 5 studies with the use of non-synchronous NIPPV which had varied heterogeneity amongst the study populations in respect to gestational age but all of them belonged uniformly to preterm gestation. Kirpalani et al. studied the maximum number of infants in this context [20]. However, in their study, NIPPV was supposed to be delivered via mixed devices and due to unavailability of any Food and Drug Administration (FDA)–approved synchronised devices, as acknowledged by the author, it can be considered that non-synchronised machines were used mostly. From these studies, the failure rate of NIPPV was cumulatively around 33% which, along with our internal NICU data, prompted us to consider a 35% failure rate for secondary mode of NIPPV. We, therefore, chose to study 43 subjects in each group in order to have 80% power to reduce the extubation failure rate from this baseline rate of 35 to 10% with a significance level of 0.05% (two-tailed), using uncorrected chi-square test to evaluate the null hypothesis. Sample size was calculated using PS: Power and Sample Size Calculation (Version 3.1.6, Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, USA).

Randomization

Randomization was done by computer-generated random sequence number (Research Randomizer (Version 4.0)); further stratification was done based on gestational age into two subgroups $26–31^{+6}$weeks and $32–36^{+6}$ weeks. 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. The infants and personnel could not be blinded due to the nature of intervention; however, the outcome assessor was blinded.

Statistical analysis

Analysis was done using GraphPad Prism version 7.0.0 for Windows, (GraphPad Software, San Diego, CA, USA), MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). Data was summarized by routine descriptive

Table 1 Parameters of nHFOV and NIPPV arm used in the study (also added in online supplement)

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 and pCO_2, 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 end-expiratory pressure (PEEP) = 4–6 cm H_2O or identical to PEEP during mechanical ventilation Inspiratory time (Ti) = 0.30–0.45 s Pmean 8–10 cm H_2O 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 every 6 h by 1 cm until 6 cm H_2O	FiO_2 was decreased by 3–5% while maintaining target SpO_2 in range of 90–95% until it reached 30%; then PIP was tapered every 6 h by 1–2 cm till 12 cm H_2O. Subsequently, Pmean lowered to 6 cm H_2O
Discontinuation	FiO2 < 30%, Pmean < 6 cm H_2O Minimal or no signs of respiratory distress and haemodynamically stable for 24 h Discontinued to nCPAP or O_2 or room air	Minimal or no signs of respiratory distress on NIV pressure (PIP < 13, PEEP < 5 cm H_2O), FiO_2 < 0.3, Pmean < 6 cm H_2O and haemodynamic stability for 24 h. Discontinued to nCPAP or O_2 or room air
Upgradation	Pmean was increased by 1 cm H_2O at a time up to a maximum of 12 cm and FiO_2 increased up to 60%	PIP was increased up to a maximum of 25, with simultaneous increase of PEEP to a maximum of 6 and FiO_2 to 60% to maintain target saturation. Pmean increased to 12 cm H_2O
Failure	Pmean > 12 and/or FiO_2 > 60%, pH < 7.20 and/or pCO_2 > 60 mm Hg, frequent bradycardia (< 100 bpm) and desaturation (SpO_2 < 85%) or apnoea (defined as three or more apneic episodes of any degree of severity within a period of 1 h), shock requiring inotropes and Silverman Anderson score of >6 as per unit protocol In case of failure, infants were intubated	PIP > 25, PEEP > 6, FiO_2 > 60%, Pmean > 12 cm H_2O, pH < 7.20 and/or pCO_2 > 60 mm Hg, frequent bradycardia (< 100 bpm) and desaturation (SpO_2 < 85%) or apnoea (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, infants were intubated

statistics, median and interquartile range for 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 inter-group 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 carried out in accordance with the Declaration of Helsinki and was approved by the 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 Fig. 1. Both groups were comparable with the baseline variables (Table 2). The median gestation age of the infants was 31.5 weeks with a median birth weight of 1500 g. The duration of invasive ventilation before being extubated to the respective intervention arms was a median of 29 h for nHFOV and 27 h for NIPPV. The results of the primary and secondary outcomes are depicted in Tables 3, 4 and 5.

There was no reduction in need of reintubation at 72 h between the nHFOV group (9.3%) and the NIPPV group (11.6%) ($p = 1.000$). In a subgroup analysis also, statistical significance was not found for the primary outcome. Overall reintubation rate was reduced but not statistically significant (16.2 vs. 18.6%). Composite duration of oxygen supplementation/ventilation support and Spo2/FiO2 ratio was similar between the two groups.. There was a possible trend towards better pCO2 elimination ($p = 0.097$) and pH optimisation ($p = 0.073$) 12 h after the start of intervention. No differences were observed between the two groups as well as sub groups for IVH (> grade 3), air leaks, composite BPD/mortality before discharge. There was a possible trend towards

Table 2 Baseline variables of the enrolled subjects

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Significance
Age of mother, years, median (IQR)	25 (21 to 31)	26 (23 to 30)	p = 0.403
Gestation, weeks, median (IQR)	32 (28 to 35)	31 (29 to 35)	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 pregnancy-induced hypertension, n (%)	5 (11.6)	4 (9.3)	p = 0.12
Maternal gestational diabetes, n (%)	6 (13.9)	4 (9.3)	p = 0.5
Maternal PROM, n (%)	14 (32.5)	10 (23.2)	p = 0.33
Maternal antepartum haemorrhage, n (%)	3 (6.9)	2 (4.6)	p = 0.64
Maternal hypothyroidism, n (%)	2 (4.6)	2 (4.6)	p = 1.00
Maternal oligohydramnios, 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
Birth weight, grams, median (IQR)	1500 (1120 to 2140)	1495 (980 to 2214)	p = 0.47
Small for gestational age, n (%)	6 (13.9)	3 (6.9)	p = 0.29
Male, n (%)	24 (55.9)	24 (55.9)	p = 1.00
Apgar 5 min, median (IQR)	7 (6 to 8)	7 (6 to 8)	p = 0.71
Positive pressure ventilation, n (%)	21(48.8)	21(48.8)	p = 1.00
Intubation, n (%)	7 (16.3)	13 (30.23)	p = 0.12
Silverman Anderson score, median (IQR)	4 (4 to 5)	4 (3 to 5)	p = 0.472
Respiratory distress syndrome, n (%)	26 (60.4)	29 (67.4)	p = 0.5
Surfactant, n (%)	25 (58.1)	28 (65.1)	p = 0.5
Duration of invasive ventilation, hours, median (IQR)	29 (22 to 54)	27 (14 to 52)	p = 0.222
pCO2 before, mm Hg, median (IQR)	41.3 (32.02 to 47.4)	38.9 (34.1 to 45)	p = 0.86
pH before intervention, median (IQR)	7.349 (7.268 to 7.386)	7.328 (7.27 to 7.357)	p = 0.43
SNAPPE 2 scores, median (IQR)	17 (6.25 to 35.75)	21 (6.25 to 35.25)	p = 0.65
Mean airway pressure before extubation, median (IQR)	9.6 (9 to 10.6)	10 (9.3 to 11)	p = 0.184
FiO2 before extubation, median (IQR)	21 (21 to 30)	21 (21 to 25)	p = 0.568

Abbreviations: *PROM*, premature rupture of membranes; *SNAPPE 2*, score for neonatal acute physiology with perinatal extension 2; *FiO2*, fraction of inspired oxygen; *IQR*, inter quartile range

lesser feed intolerance in the nHFOV group (37.2 vs. 58.13%, p = 0.084). However, time to achieve full enteral feeds was similar amongst the groups as well as subgroups. 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 no difference in reintubation rates within 72 h in nHFOV group, compared with NIPPV group. 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 [5, 6, 21]. nCPAP is still considered the standard of care post-extubation, while NIPPV now appears to be the better modality, with its own pitfalls [13]. 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 h time with nHFOV post-extubation against nCPAP [11]. Malakian et al., however, did not find any difference in rate of intubation within 72 h [9]. To the best of our knowledge, this is the first randomised controlled trial comparing nHFOV versus NIPPV as a post-extubation modality in preterm infants worldwide. The only trial (NCT02543125) comparing nHFOV with

Table 3 Primary outcome measures

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Relative risk (95% confidence interval)	Significance
Reintubation within 72 h, n (%)	4 (9.3)	5 (11.6)	0.8 (0.23 to 2.78)	p = 1.000

Table 4 Secondary outcome measures

Variable	nHFOV (n = 43)	NIPPV (n = 43)	Relative risk (95% confidence interval)	Significance
Reintubation rate, n (%)	7 (16.2)	8 (18.6)	0.88 (0.35 to 2.2)	p = 1.000
pCO2 after intervention, mm Hg, median (IQR)	33.8 (29.125 to 41)	37.9 (32 to 42.5)		p = 0.097
pH post-intervention, median (IQR)	7.39 (7.348 to 7.438)	7.35 (7.313 to 7.406)		p = 0.073
IVH Gr3+, n (%)	1 (2.3)	2 (4.3)	0.5 (0.05 to 5.31)	p = 1.000
Feed intolerance, n (%)	16 (37.2)	25 (58.13)	0.64 (0.40 to 1.02)	p = 0.084
Full feed day of life, days, median (IQR)	7 (5 to 10)	8 (5.75 to 10.25)		p = 0.503
Air leaks, n (%)	5 (11.6)	1 (2.3)	5 (0.61 to 41.06)	p = 0.202
Ventilator free days, days, median (IQR)	26.54 (24.75 to 26.92)	26.67 (22 to 27.42)		p = 0.944
Composite BPD/mortality, n (%)	12 (27.9)	15 (34.8)	0.80 (0.426 to 1.503)	p = 0.485
Composite O2 supplementation/ventilatory support, days, median (IQR)	8 (4 to 21)	9 (5 to 18)		p = 0.944
SpO2/FiO2 ratio, median (IQR)	310 (260 to 316.67)	306.67 (260 to 368)		p = 0.198

NIPPV as a post-extubation modality was initiated in China in the year 2016 and is yet to be completed. The composite duration of oxygen supplementation/ventilation support, SpO2/FiO2 ratio during the intervention in both groups was also similar in the study. These, along with no difference in primary outcome can be explained by the fact that both the interventions were working at similar mean airway pressures which is unlikely to bring about a difference in oxygenation.

Assessment of extubation readiness should be done with lung mechanics, pressure time index, minute ventilation test apart from clinical tests and assessment of dynamics of biological signals. One of the key factors for successful extubation depends on the mode of respiratory support provided post-extubation, so as to keep the lungs open. Synchronised form of NIPPV seems to be the best choice but unavailability seems to be an issue. The pre-extubation mean airway pressure (MAP), FiO2 and tidal volume in volume ventilation play key roles in the success of extubation. Though failure rates increase with decreasing gestation and weight, secondary measures can be taken to sustain a successful extubation. Another factor which might help prevent extubation failure is efficacious clearance of pCO2. Our study showed possible trend towards 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 [12, 22, 23]. There was a time-dependent 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 ± 2.06 and a median amplitude of 15 which was similar to most studies done with nHFOV [4, 5, 11, 21, 24]. The MAP was similar in the two groups and this was an advantage since it allowed us to compare the effect of the pressure waveform and the active expiration as these seem to be the only real difference between groups. On the contrary, low MAPs in nHFOV probably failed to recruit the lung effectively.

Added advantages of nHFOV include reduced episodes of bradycardia and desaturation [25], enhanced alveolar ventilation due to better alveolar recruitment and improved functional residual capacity (FRC), theoretically lesser ventilator-induced lung injury (VILI) [26], and reduced gastroesophageal reflux [27]. 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 [28], effectiveness of different interfaces delivering nHFOV [24, 29, 30], the efficiency in eliminating carbon dioxide (CO_2) [12, 21, 26], the effect of different parameters and leak on CO_2 removal [24, 29, 31, 32], the transmission of oscillation and tidal volume delivery in the airways [31].

In this study, we found that 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 [33], and an active expiration, it is not surprising that nHFOV seems to lower feed intolerance rates. 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.

As for secondary outcomes like IVH, more than grade 3, air leaks, ventilator free days, composite BPD/mortality, composite oxygen supplementation/ventilation support, S/F ratio did not differ much between the groups as well as subgroups. Interestingly, most studies done on nHFOV including the two meta-analysis failed to show any difference in BPD, air leaks, IVH and mortality [5–7, 9, 11, 21]. Though the literature suggests viscid secretions interfering with efficacy of nHFOV [10], we did not find this alarming side effect probably because of good nursing care and maintenance of oral hygiene while on ventilation. We cycled between short binasal prongs and mask every 4-hourly, both of which have been shown to be efficacious [24, 29–31]. However, none of the

Table 5 Subgroup analysis - primary and secondary outcomes

Variable	Subgroup 26 to 31^{+6} weeks			Subgroup 32 to 36^{+6} weeks		
	nHFOV (n = 21)	NIPPV (n = 22)	RR (95%CI), p-value	nHFOV (n = 22)	NIPPV (n = 21)	RR (95% CI), p-value
Reintubation within 72 h, n (%)	3 (14.2)	2 (9.09)	1.43 (0.27 to 7.73), p = 1.000	1 (4.5)	3 (14.2)	0.32 (0.04 to 2.82), p = 0.345
Reintubation rate, n (%)	6 (27.2)	4 (18.18)	1.57 (0.52 to 4.79), p = 0.488	1 (4.5)	4 (19.04)	0.24 (0.03 to 1.97), p = 0.185
pCO2 after intervention, mm Hg, median (IQR)	35.6 (29.75 to 41.25)	36.4 (32 to 39.1)	p = 0.500	32.35 (29 to 41)	40.3 (32.35 to 45.3)	p = 0.096
pH post-intervention, median (IQR)	7.387 (7.349 to 7.423)	7.381 (7.329 to 7.431)	p = 0.609	7.395 (7.343 to 7.441)	7.336 (7.305 to 7.378)	p = 0.034
IVH Gr3+, n (%)	1 (4.7)	2 (9.1)	0.52 (0.05 to 5.36), p = 1.00	0	0	------
Feed intolerance, n (%)	11 (52.4)	16 (72.7)	0.72 (0.44 to 1.17), p = 0.215	5 (22.7)	9 (42.8)	0.53 (0.21 to 1.32), p = 0.203
Full feed day of life, days, median (IQR)	8 (6 to 12)	8.5 (5 to 13)	p = 0.343	6.5 (5 to 8)	6 (6 to 8)	p = 0.667
Air leaks, n (%)	2 (9.5)	0	p = 0.233	3 (13.6)	1 (4.7)	2.86 (0.32 to 25.42), p = 0.607
Ventilator free days, days, median (IQR)	26.5 (24.56 to 26.92)	26.92 (25.34 to 27.09)	p = 0.947	26.73 (25.34 to 27.1)	26.59 (21.96 to 27.06)	p = 0.153
Composite BPD/mortality, n (%)	11(52.38)	11 (50)	1.047 (0.58 to 1.88), p = 0.875	1 (4.54)	4 (19.04)	0.238,(0.03 to 1.96), p = 0.182
Composite O2 supplementation/ventilatory support, days, median (IQR)	16 (7 to 40.5)	12 (5.75 to 34.25)	p = 0.804	5.5 (4 to 9.25)	5 (4 to 11)	p = 0.984
SpO2/FiO2 ratio, median (IQR)	310 (267.14 to 326.66)	306.67 (262.14 to 369)	p = 0.798	265.71 (218.33 to 313.33)	310 (235 to 370)	p = 0.137

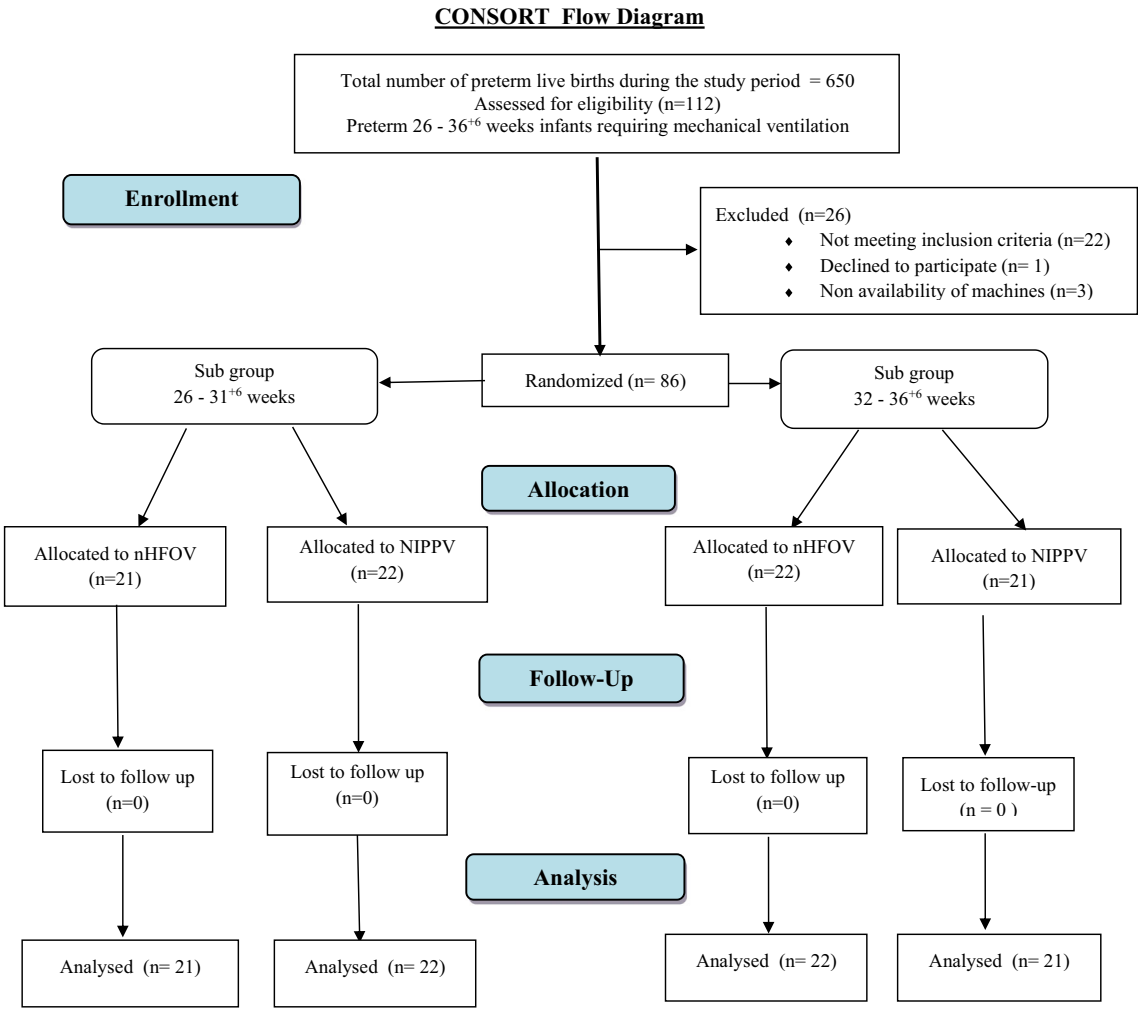

Fig. 1 Flow of participants in the study

previous studies have used both simultaneously. Mask-delivered nHFOV has more dampening effect, therefore, theoretically would require more aggressive ventilatory parameters [30]. In our case, cycling of the interfaces was done for the comfort of the infants 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 the study probably led to a relatively smaller sample size estimation. Further, comfort level of infants were not quantified objectively, neither GER could be documented. Also, whether intermittent use of mask led to lesser efficacy needs to be investigated further. Moreover, long-term side effects and neurodevelopmental outcome are something to look forward to. As far as blinding was concerned, neither the infants nor the personnel were blinded. However, the person performing the final analysis was blinded to the intervention. In this regard, we acknowledge that the data compilation could have been blinded. The Pmean pressures used in nHFOV arm was possibly sub-optimal without any effective alveolar recruitment as per available evidences [4]. Unfortunately, this was done as per our pre-planned study protocol. 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 not bring about a significant reduction in reintubation rates within 72 h of post-extubation. It seemed promising in reducing feed intolerance and optimising arterial blood pH and pCO2. 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.

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Authors' contributions Dr. Soutrik Seth conceptualized and designed the study, developed the protocol, patient management and prepared the first draft. Dr. Bijan Saha helped in protocol development, coordinated, 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.

Data and materials availability Available for viewing at https://drive.google.com/file/d/1ZH7jElbBkzTvwrpdQLi_AgnJ3413Aq73/view?usp=sharing

Code availability N/A.

Declarations

Ethics approval and consent to participate Informed consent was obtained from the legal guardian of all included participants.

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

Conflict of interest The authors declare no competing interests.

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