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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

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ABSTRACT

Background Currently, various forms of non-invasive respiratory support have been used in the management of respiratory distress syndrome (RDS) in preterm neonates. However, nasal high-frequency oscillatory ventilation (nHFOV) has not yet been applied commonly as an initial treatment.

Objectives This study was designed to investigate the efficacy and safety of nHFOV compared with nasal continuous positive airway pressure (NCPAP) in preterm and near-term infants with RDS.

Methods In a randomised clinical trial, a total of 68 neonates (gestational age (GA) between 30 and 36 weeks and 6 days) with a clinical diagnosis of RDS were randomly assigned to either the NCPAP (n=34) or the nHFOV (n=34) group. The primary outcome was the duration of non-invasive respiratory support (duration of using NCPAP or nHFOV).

Result The median (IQR) duration of non-invasive respiratory support, was significantly shorter in the nHFOV group than that in the NCPAP group (20 (15–25.3) versus 26.5 (15–37.4) hours, respectively; p=0.02). The need for a ventilator occurred in 4 out of 34 (11.8%) neonates in the NCPAP group and in none of the neonates in the nHFOV group (p=0.03). In addition, intraventricular haemorrhage (IVH) occurred in nine cases (6.9%) in the NCPAP group and two cases (3.3%) in the nHFOV group, which showed a significant difference (p=0.04). The incidence of pneumothorax, chronic lung disease, pulmonary haemorrhage and necrotising enterocolitis was similar between the two groups.

Conclusion This study showed that nHFOV significantly reduced the duration of non-invasive respiratory support and decreased the need for intubation compared with NCPAP in infants with RDS. Furthermore, nHFOV seems to reduce the incidence of IVH without increasing other complications.

Trial registration number IRCT2017062734782N1.

What is known about the subject?

- In recent years, attempts have been made to use non-invasive methods for management of respiratory distress syndrome (RDS) in preterm newborns.
- Nasal continuous positive airway pressure (NCPAP) is a relatively simple and effective therapy in the early management of RDS but some patients who are initially treated with NCPAP need mechanical ventilation.
- The application of high-frequency ventilation with the strategy of lung recruitment improves gas exchange and decreases lung injury.

What this study adds

- Nasal high-frequency oscillatory ventilation (nHFOV) reduced the duration time of non-invasive respiratory support.
- nHFOV decreased the need for intubation compared with NCPAP in neonates with RDS.

INTRODUCTION

Premature infants with respiratory distress syndrome (RDS) usually require respiratory support.[1] Due to the complications of intubation and mechanical ventilation, in the last decade, attempts have been made to use non-invasive methods in the management of these patients.[2] Over the past few decades, nasal ventilation has been used to control and improve respiratory failure in infants with RDS.[3 4] One of the most commonly used non-invasive methods is nasal continuous positive airway pressure (NCPAP).[5] NCPAP is a relatively simple and effective therapy in the early management of RDS in newborns.[6 7]

NCPAP is the application of positive pressure to the airways of spontaneously breathing neonates throughout the respiratory cycle.[8] However, some neonates with this

therapeutic approach also develop respiratory failure and need mechanical ventilator support.[9] According to some investigations, 43%–80% of infants with moderate to severe respiratory failure who are initially treated with NCPAP need mechanical ventilation.[10]

In recent years, the beneficial effects of high-frequency ventilators have been shown in the management of RDS as well as the use of these ventilators as the initial mode of support or as a rescue treatment after failure of conventional mechanical ventilation.[11]

In high-frequency ventilation (HFV), a low tidal volume with a higher frequency than that of physiological respiration is produced.[12] This technique is very effective in eliminating carbon dioxide (CO_2) and is independent of dead space.[13] Adequate recruitment of lung volume in this mechanical mode has the main role of protecting and preserving lung architecture as well as potentiating surfactant therapy.[14]

Although HFV has been applied in many neonatal intensive care units, nasal high-frequency oscillatory ventilation (nHFOV) is a relatively new non-invasive modality, and evidence for its use is limited.[15] nHFOV is effective and superior to nasal intermittent positive pressure ventilation in terms of lung CO_2 elimination in a model using newborn manikins. The nHFOV is a non-invasive ventilation mode that applies an oscillatory pressure waveform to the airways using a nasal interface. This mode has been shown to facilitate CO_2 expiration, but little is known about its use in neonates.[16]

There is increasing evidence of beneficial effects of nHFOV in reducing the duration of respiratory distress compared with the effects of NCPAP in RDS.[17]

In this study, we compared the efficacy and safety of nHFOV and NCPAP in the treatment of RDS in preterm and near-term infants.

METHODS AND MATERIALS

Study design and patients

This study was a prospective randomised clinical trial carried out in neonatology wards of two different hospitals (Beheshti and Alzahra) affiliated with Isfahan University of Medical Sciences, Iran, from October 2017 to March 2018.

Due to the novelty of nHFOV being used in the treatment of premature infants, the ethics committee were concerned about its use in very premature infants. It was therefore agreed that this study would be undertaken in premature neonates who are 30 weeks or more gestation. This trial was registered at IRCT.ir (reference number IRCT2017062734782N1). Informed written consent was obtained from all parents before the infants were enrolled in the study.

The inclusion criteria included newborns with a gestational age between 30 and 36 weeks and 6 days; newborns with an appropriate weight for the gestational age; newborns with spontaneous breathing and clinical signs and symptoms of RDS, such as grunting, cyanosis and intercostal and subcostal retraction with RDS suggestive of chest X-rays. The exclusion criteria included major congenital abnormalities at birth, diaphragmatic hernia, cyanotic heart disease, intrauterine growth retardation, a need for intubation and mandatory ventilation on the first day of life and perinatal asphyxia (umbilical cord pH <7 and umbilical cord bicarbonate <12 mEq/L).

Intervention

Shortly after birth, all neonates with respiratory distress syndrome according to the inclusion criteria were randomised into two groups: the NCPAP (control) group, which had treatment with nasal CPAP, and the nHFOV (intervention) group, which had support with nasal HFV. Randomisation was performed using a sequentially numbered computerised randomisation algorithm. The allocation to treatment was concealed until study entry.

In the control group, CPAP was started at a pressure of 6–7 cm of water with binasal midline prongs (Fisher & Paykel Healthcare, New Zealand). NCPAP was generated with the use of a mechanical ventilator (Fabian, Autromic Medical Systems AG) based in Hirzel (Zurich, Switzerland). Fractional inspired oxygen (FiO_2) levels were adjusted to maintain the oxygen (O_2) saturation of patients from 89% to 95%.

In the nHFOV group, neonates were treated with a nasal high-frequency ventilator (Fabian, Autromic Medical Systems AG) based in Hirzel (Zurich, Switzerland) shortly after birth. The mean pressure was 8 cm H_2O, and the FiO_2 levels was adjusted to maintain the O_2 saturation of patients from 89% to 95%. The initial frequency was set at 10 Hz. Amplitude was set based on the vibration of the upper chest wall and the neck of patients, and it was increased to a maximum of 20 cm H_2O.

Surfactant (curosurf; Chiesa pharmaceuticals, Parma, Italy) was administered if patients had FiO_2 levels>35% to maintain the desired oxygen saturation levels. The first dose of surfactant was 200 mg/kg, and the second dose, if needed, was 100 mg/kg. Surfactant was administered according to the INtubation-SURfactant-Extubation (INSURE) method In the both groups, if the FiO_2 level decreased below 30%, patients were weaned to a humidified high-flow nasal cannula (HHFNC); furthermore, when FiO_2 levels reached 21% and respiratory distress improved, the HHFNC was discontinued. NCPAP or nHFOV failure was defined as apnoea or pH <7.2 and partial pressure of CO_2 >60 mm Hg.

Outcomes

The duration of using NCPAP or nHFOV was considered the primary outcome. Failure of treatment or need for intubation and ventilator (NCPAP or nHFOV failure); the presence of a patent ductus arteriosus (PDA), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), chronic lung disease (CLD) or pneumothorax, pulmonary haemorrhage and time to full enteral feeding were considered secondary outcomes. The patient was

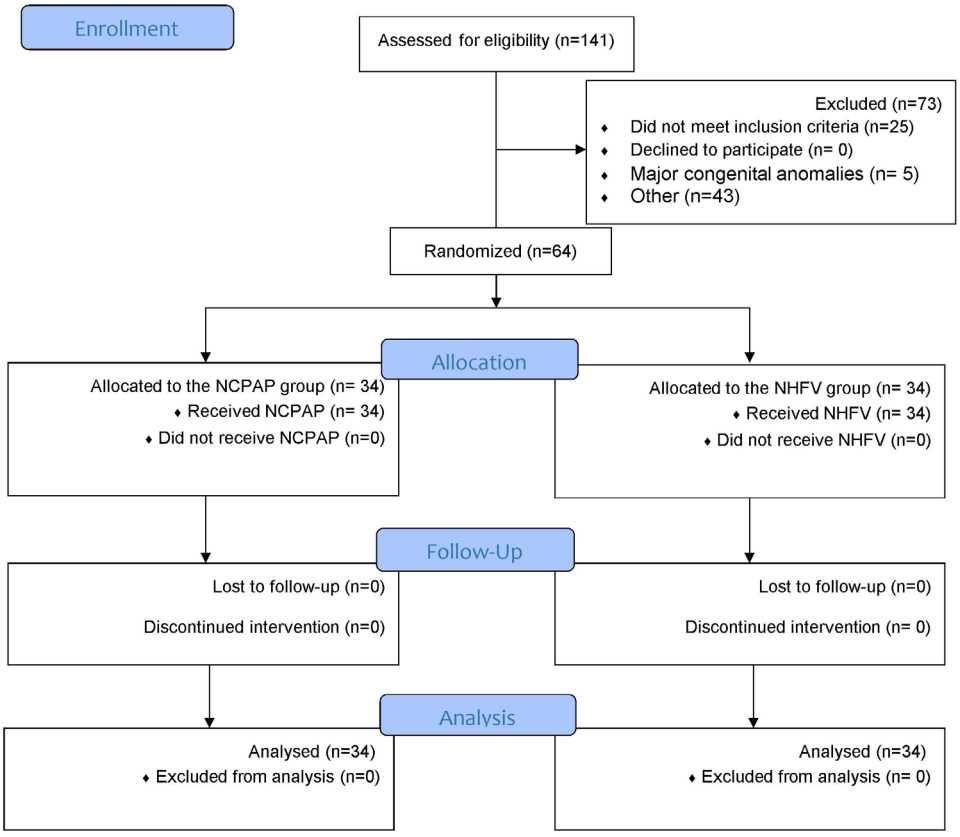

Figure 1 Flow diagram of the participants. NCPAP, nasal continuous positive airway pressure; NHFV, nasal high-frequency ventilation.

considered to have CLD when oxygen dependency was continued after 28 days of life.[18] NEC was diagnosed in combination with pneumatosis intestinalis, or it required a related surgical intervention. IVH was detected by brain ultrasound, which was carried out by a trained neonatologist 72 hours after birth. IVH was defined by using the Papile classification.[19] PDA was confirmed by echocardiography.

Primary and secondary outcomes were monitored daily by a neonatology fellow. The data were extracted from the case records and documented in the patients' forms and then compared between the two groups.

Patient involvement

Patients were not directly involved in the design of this study.

Statistical analysis

A sample size of 68 infants was considered for this study. For the calculation of sample size, we used the following formula: $N= (z_{1-\alpha/2}+z_{1-\beta})^2(2p(1p))/d^2$, where, based on type one error rate $\alpha=0.05$; ($Z_{1-\alpha/2}=1.96$), statistical power $1-\beta=0.8$; ($Z_{1-\beta}=0.84$); p is an estimate of the incidence rate of main study outcomes in both groups, in which it was considered to be 0.5 and d was considered to be 0.8P as the minimum detectable difference in terms of the incidence rate of main outcomes between the two groups. Categorical and continuous data have been presented as frequency (percentage) and mean SD for normally distributed, and for non-normal data we also reported the median (IQR; first quartile, third quartile) too. Normality of continuous data was evaluated using Kolmogorov-Smirnov and Q-Q plot. Non-normally right skewed distributed continuous data were subjected to logarithmic transformation in order to normalise them. Categorical data (or proportions) were compared between two study groups by χ^2 or Fisher exact tests. Independent samples t-test was applied for comparing normally distributed continuous variables and non-parametric statistical test was used for comparing continuous non-normally distributed data. All analyses were performed using SPSS V.20.

RESULTS

Patients' characteristics

During the study period, a total of 141 preterm infants with a gestational age between 30 and 36 weeks and 6 days were assessed for study eligibility. Overall, 73 neonates were excluded due to various reasons (figure 1). Of the 68 neonates who participated in the study, 34 were randomly assigned to the NCPAP group and 34 to the nHFOV group. Neonates had at least 30 weeks and maximum 36.5 weeks in both groups. Among the 34 patients in the NCPAP group, 13 were female and 21 were male. Of the 34 patients in the nHFOV group, 15 were male and 19 were female. The demographic and basic characteristics

Table 1 Comparison of demographic data in NCPAP and nHFOV groups

Newborn demographic factors and characteristics	NCPAP (n=34)	nHFOV (n=34)
Sex		
Female	13 (38.2%)	15 (44.1%)
Male	21 (61.8%)	19 (55.9%)
Method of delivery		
Caesarian	31 (91.2%)	31 (91.2%)
Vaginal delivery	3 (8.8%)	3 (8.8%)
Gestational age, weeks	33 (30–34)	33 (31–35)
Weight, g	1959.26 (613.57)	2161.76 (764.74)
Height, cm	45.75 (7.43)	45.55 (4.57)
Head circumference, cm	30.44 (2.38)	31.41 (3.02)
First minute Apgar Score	6.35 (2.28)	6.26 (2.28)
Fifth minute Apgar Score	8.44 (1.25)	8.64 (1.65)

Values in table are frequency (%) for categorical, mean (SD) for normally distributed continuous variables and median (IQR; Q1: first quartile, Q3: third quartile) for non-normally distributed continuous variables.
NCPAP, nasal continuous positive airway pressure; nHFOV, nasal high-frequency oscillatory ventilation.

Table 2 Comparison of the baseline characteristics in NCPAP and nHFOV groups

Newborn characteristics	NCPAP (n=34)	nHFOV (n=34)
PO_2 before intervention, mm Hg	37 (13.30)	36.35 (12.49)
PCO_2 before intervention, mm Hg	42.57 (7.68)	43.78 (9.94)
HCO_3 before intervention	19.18 (3.15)	20.04 (5.74)
BE before intervention	−5.94 (3.15)	−6.37 (2.58)
pH before intervention	7.30 (7.27–7.34)	7.28 (7.24–7.35)
Received prenatal steroids	10 (29.4%)	8 (23.5%)
Type of steroid		
Dexamethasone	6 (60%)	6 (75%)
Betamethasone	4 (40%)	2 (25%)
Received surfactant	18 (52.9%)	18 (52.9%)
Age when received surfactant	5.43 (6.20)	7.16 (6.45)
Number of surfactant received		
1	13 (72.2%)	17 (94.4%)
2	4 (22.3%)	1 (5.6%)
3	1 (5.6%)	0

Values in table are frequency (%) for categorical, mean (SD) for normally distributed continuous variables and median (IQR; Q1: first quartile, Q3: third quartile) for non-normally distributed continuous variables.

BE, base excess; HCO_3, bicarbonate; NCPAP, nasal continuous positive airway pressure; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; nHFOV, nasal high-frequency oscillatory ventilation.

of the patients are summarised in table 1. After randomisation, the distributions of sex, method of delivery, gestational age, height, weight, head circumference and Apgar scores at the first and fifth minute after birth were comparable between the two groups (table 1). Moreover, at beginning of study before applying interventions, after randomisation, the participants in NCPAP and nHFOV groups were statistically comparable in terms of distribution of the arterial blood gas parameters and the therapeutic measurements. The baseline values of main study outcomes and therapeutic measurements for the two groups are summarised in table 2.

A total of 29.4% of mothers in the NCPAP group had received prenatal steroids (betamethasone=40%, dexamethasone=60%) compared with (betamethasone=25%, dexamethasone=75%) the mothers in the nHFOV group; the difference was statistically comparable. The need for surfactant administration, the number of surfactant administrations and the age of neonates at the time of surfactant therapy also were comparable between two groups (table 2).

Outcome evaluations

The primary outcome (table 3), the median (IQR) duration of non-invasive respiratory support, was significantly shorter in the nHFOV group than that in the NCPAP group (20 (15–25.3) vs 26.5 (15–37.4) hours, respectively; p=0.02).

The mean (SD) age of neonates when the intervention started was not significant difference between the NCPAP and nHFOV groups (1.8 (0.7) vs 1.9 (1.5) hours, respectively). The median (IQR) age of neonates after the completion of respiratory support was 28.5 (17–39.5) and 22 (17.7–27) hours in the NCPAP and nHFOV groups, respectively, which was significantly different (p=0.03).

Treatment failure (intubation and need for a ventilator) occurred in 4 out of 34 (11.8%) neonates in the NCPAP group and none of the neonates in the nHFOV group, which was statistically significant (p=0.03). Other secondary outcomes, such as the incidence of PDA, pneumothorax, pulmonary haemorrhage, CLD and NEC, were similar in the two groups (table 3).

Intraventricular haemorrhage was slightly more frequent among patients in the NCPAP group than that among patients in the nHFOV group, showing a statistically significant difference (p=0.04; table 3). In addition, there was no mortality in the two groups.

As shown in table 4, the arterial blood gas parameters 1 hour after intervention were comparable between two groups.

DISCUSSION

In our prospective randomised controlled trial, nHFOV decreased the mean duration of non-invasive respiratory

Table 3 Primary and secondary outcomes in NCPAP and nHFOV groups

Outcomes	NCPAP (n=34)	nHFOV (n=34)	P value
Duration of non-invasive support (primary outcome), hours	26.5 (15–37.4)	20 (15–25.2)	0.02*
Failure of intervention (need to intubation and ventilator)	4 (11.8%)	0 (0%)	0.03
Intraventricular haemorrhage, 72 hours after birth			
Normal	25 (93)	31 (86.7)	0.04
Grade 1	0	1 (10)	
Grade 2	9 (6.9)	2 (3.3)	
Grade 3	0	0	
PDA	6 (17.6%)	4 (11.8%)	0.49
CLD	2 (5.9%)	5 (14.7%)	0.23
NEC	3 (8.8%)	1 (2.9%)	0.30
Pulmonary haemorrhage	1 (2.9%)	0	0.31
Age when oral feeding began, hours	27.7 (12.4)	22.7 (10.6)	0.08†
Age when full oral feeding received, hours	118.9 (58.5)	108.2 (48.9)	0.41†
Pneumothorax	0	0	/

Data are presented as frequency (percentage) for categorical, mean (SD) for normally distributed continuous variables and median (IQR; Q1: first quartile, Q3: third quartile) for non-normally distributed continuous variables.
*Resulted from non-parametric Mann-Whitney U test.
†Resulted from independent samples t-test and other p values are based on applying χ^2 or Fisher's exact test.
CLD, chronic lung disease; NCPAP, nasal continuous positive airway pressure; NEC, necrotising enterocolitis ; PDA, patent ductus arteriosus; nHFOV, nasal high-frequency oscillatory ventilation.

support (primary outcome) in neonates with RDS. The need for mechanical ventilation was also significantly lower in the nHFOV group compared with NCPAP as was the incidence of intraventricular haemorrhage. There were no other significant differences between the two groups for the other secondary outcomes (table 3).

A few trials have evaluated the efficacy and safety of early nHFOV for respiratory support in preterm neonates with RDS.[20 21] A similar study was performed by Malakian *et al*[20] in 124 neonates with RDS between 28and 34 weeks of gestational age. Sixty-three and 61 neonates were studied with nHFOV and NCPAP groups, respectively, and like our study, they showed that the duration of non-invasive ventilation in the nHFOV group was significantly less with nHFOV than with NCPAP (p=0.01).[20] Unlike our study, Malakian *et al*[20] showed that there is no significant difference between the nHFOV (6.5%) and NCPAP (14.1%) groups in need for mechanical ventilation (p=0.13). Whether nHFOV can effectively reduce the need for mechanical ventilation in preterm infants requires further studies with larger sample size.

Zhu *et al*[21] reported a similar study, in which, after surfactant administration via the INSURE method, 81 infants with gestational age of 28–34 weeks and moderate–severe RDS were randomised to NCPAP (n=42) or to nHFOV (n=39). The primary outcome was the need for intubation and mechanical ventilation (failure of intervention) within 72 hours after birth. Like our study, the need for mechanical ventilation was significantly lower in the nHFOV group than that in the NCPAP group (24.3% vs 56.4%, p<0.01). They did not report the mean duration of non-invasive respiratory support in both groups.

Table 4 Post hoc secondary outcomes in NCPAP and nHFOV groups

Newborn characteristics	NCPAP (n=34)	nHFOV (n=34)	P value
PO_2 1 hour after intervention, mmHg	59.88 (14.87)	58.17 (21.66)	0.70
PCO_2 1 hour after intervention, mmHg	38.59 (8.30)	40.79 (7.82)	0.26
HCO_3 1 hour after intervention	21.83 (2.46)	22.07 (2.51)	0.69
BE 1 hour after intervention	–2.9 (–3.9 to –1.9)	–2.1 (–4.1 to –1.09)	0.57*
pH 1 hour after intervention	7.36 (0.07)	7.36 (0.06)	0.73

Values in table are frequency (%) for categorical, mean (SD) for normally distributed continuous variables and median (IQR; Q1: first quartile, Q3: third quartile) for non-normally distributed continuous variables.
*Resulted from non-parametric Mann-Whitney U test and other p values are based on applying independent samples t-test. Multiple testing adjustment based on Bonferroni approach was applied for calculating the p values.
BE, base excess; HCO_3, bicarbonate; NCPAP, nasal continuous positive airway pressure; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; nHFOV, nasal high-frequency oscillatory ventilation.

HFOV is a type of mechanical ventilation that utilises a respiratory rate that is at least four times greater than the normal value (>150 breaths per minute) and very small tidal volumes that avoid large cycle changes in lung volume. Data from the past decades support the early use of HFOV in intubated neonates, which can lead to earlier extubation compared with infants on conventional mechanical ventilation.[22 23] The application of HFV with the strategy of lung recruitment improves gas exchange and decreases lung injury.[24] Therefore, we can assume that a similar mechanism of action is at play with nHFOV and that non-invasive (nasal) HFOV appears to be more effective than other types of non-invasive respiratory support. Our study and one similar study by Zhu *et al*[21] supported this hypothesis that the early use of nHFOV is more effective than the early use of NCPAP because less treatment failure occurs in nHFOV.

In the current study, grade 2 intraventricular haemorrhage (IVH) occurred in nine cases (6.9%) in the NCPAP group and two cases (3.3%) in the nHFOV group, which showed a significant difference (p=0.04). In general, complications of high-frequency techniques have been reported to be rare. Until recently, the major concern with the use of HFOV in intubated preterm neonates was its possible contribution to an increase in periventricular leucomalacia (PVL) or severe IVH.[25 26] However, major multicentre trials of invasive HFOV did not show an increase in IVH or PVL,[22 27] and studies about this morbidity in non-invasive HFOV are limited. This study revealed that when HFOV is used as a non-invasive respiratory support, it might even reduce intraventricular haemorrhage in comparison with NCPAP. In other similar studies, the incidence of IVH between the two groups (NCPAP vs nHFOV) showed no significant difference.[20 21]

In our study, there were no significant increases in the incidence of apnoea, PDA, air leakage or NEC in the nHFOV group. In the studies performed by Zhu *et al*[21] and Malakian *et al*,[20] the incidence of serious complications was not significantly different between the nHFOV and NCPAP groups. It is assumed that early non-invasive HFOV is safe for respiratory support as an initial therapy in premature neonates with RDS and a gestational age of more than 30 weeks although further studies are needed to confirm this.

Our study had some limitations. First, the number of participants in this study was small, and although the results were significant, they should be taken with caution. For routine and widespread use of nHFOV as a primary mode of respiratory support in premature neonates with RDS, more trials, especially multicentre studies, are required. Second, due to a lack of sufficient facilities and financial constraints, some premature neonates were eligible for our study, but we could not include them all, as we did not have enough ventilators for nHFOV.

CONCLUSION

This prospective, randomised controlled study showed that nHFOV significantly reduced the duration time of non-invasive respiratory support and decreased the need for intubation compared with NCPAP in preterm and near-term infants with RDS. However, to suggest the routine use of nHFOV as an initial therapy in the management of preterm neonates, further studies are required.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The ethical committee of the Isfahan University of Medical Sciences approved the study protocol (Ethics committee reference number: IR.MUI.REC.1396.3.336).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

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