Non-invasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in extremely preterm infants with respiratory distress syndrome: study protocol for a multicentre randomised controlled, superiority trial

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ABSTRACT

Introduction Tracheal intubation and invasive mechanical ventilation (IMV) significantly decreased mortality of respiratory distress syndrome (RDS) in extremely preterm infants (28 weeks’ gestational age) whereas bronchopulmonary dysplasia increased. Thus, consensus guidelines recommend the use of non-invasive ventilation (NIV), as the preferred first-line approach for these infants. This trial aims to compare the effect of nasal continuous positive airway pressure (NCPAP) and non-invasive high-frequency oscillatory ventilation (NHFOV) as the primary respiratory support in extremely preterm infants with RDS.

Methods and analysis We designed a multicentre, randomised, controlled, superiority trial investigating the effect of NCPAP and NHFOV as the primary respiratory support in extremely preterm infants with RDS in neonatal intensive units in China. At least 340 extremely preterm infants with RDS will be randomised to NHFOV or NCPAP as a primary mode of NIV. The primary outcomes will be the respiratory support failure determined by the need for IMV within 72 hours from birth.

Ethics and dissemination Our protocol has been approved by the Ethics Committee of Children’s Hospital of Chongqing Medical University. We will present our findings at national conferences and peer-reviewed paediatrics journals.

Trial registration number NCT05141435.

INTRODUCTION

Respiratory distress syndrome (RDS) is one of the leading causes of mortality and morbidity in extremely preterm infants (≤28 weeks’ gestational age (GA)).1 Tracheal intubation and invasive mechanical ventilation (IMV) significantly improve the survival rate of extremely preterm infants with RDS, however, prolonged IMV also increases ventilator-induced lung injury leading to bronchopulmonary dysplasia (BPD).3 Thus, consensus guidelines recommend the use of non-invasive ventilation (NIV), as the preferred first-line approach for these infants.3

Nasal continuous positive airway pressure (NCPAP) has been the mainstay of NIV in the neonatal intensive care unit (NICU), for over decade years. Nonetheless, extremely preterm infants have a high risk of NCPAP treatment failure due to collapsing chest wall and poor diaphragmatic strength.4 The recently large cohort study showed up to 40% of extremely preterm infants fail to sustain on NCPAP and require IMV.5 To minimise the need of IMV, a relatively newer form of NIV that is emerging is non-invasive high-frequency oscillatory ventilation (NHFOV). NHFOV is an unconventional NIV mode trying to mimic, whenever possible, the high-frequency oscillations superimposed on NCPAP (NIV), as the preferred first-line approach for these infants.
on spontaneous tidal breathing. Compared with NCPAP, potential advantages of NHFOV include efficiency in CO₂ removal, easy alveolar recruitment.⁵ An European survey showed that NHFOV is gaining wider acceptance in some countries and no major side effects are reported.⁶

Several randomised controlled trials comparing NCPAP and NHFOV have yielded inconsistent results with regards to effectiveness in treatment of RDS.⁸⁻¹⁰ We recently completed a multicentre randomised controlled trial to find NHFOV seemed to reduce the rate of treatment failure than NCPAP in preterm infants <30 weeks of GA.¹¹ However, the small population may have limited the interpretation of the results. Therefore, we conduct this multicentre, randomised controlled trial to compare the effect of NCPAP and NHFOV as the primary respiratory support in extremely preterm infants with RDS. Our hypothesis is that NHFOV would reduce the rate of treatment failure, compared with NCPAP, as the primary respiratory support in extremely preterm infants with RDS.

METHODS

Aims
This trial aims to compare the effect of NCPAP and NHFOV as the primary respiratory support in extremely preterm infants with RDS.

Study design
This will be a multicentre, randomised controlled, superiority trial conducted in 20 tertiary NICUs in China from August 2022 to August 2024. The trial will be performed in accordance with the prospective trial flow (figure 1).

Setting
We plan to enrol preterm infants born between 24 weeks+0 day and 28 weeks+6 days of GA from 20 tertiary NICUs in China. These 20 tertiary NICUs have more than 1000 NICU beds and annual admissions of nearly 1000 extremely preterm infants with RDS each year.

Patient and public involvement
Patients and the public did not participate in the study design. Participation is entirely voluntary. The study results will be disseminated to guardians and the public through public health education and neonatal academic conferences.

Inclusion criteria
(1) GA between 24⁰/⁷ and 28⁰/⁷ weeks and (2) diagnosis of RDS. The diagnosis of RDS will be based on clinical manifestations (tachypnea, nasal flaring and or grunting) and a fraction of inspired oxygen (FiO₂) greater than 0.25 for target saturation of peripheral oxygen (SpO₂) 89%–94%; (3) Age <2 hours; (4) informed parental consent has been obtained.

Exclusion criteria
(1) Intubated for any reasons at birth; (2) major congenital malformations or known complex congenital heart disease; (3) transferred out of the NICU before randomisation.

Randomisation
Neonates will be randomised and assigned either to NCPAP or NHFOV arms with a 1:1 ratio, when patients fulfil all inclusion criteria. Simple randomisation will be done according to a computer-generated random number table and will be posted in a specific secured website available on 24/7. Twins will all be allocated in the same treatment group. Infants randomised to one arm cannot crossover to the other or vice-versa during the study.

Blinding
Operators and care providers will not be blinded, and the outcome assessors and data analysts will be blinded to the intervention.

Study intervention
In the delivery room, all eligible infants with spontaneously breathing should be supported by NCPAP
(pressure: 6–8 cm H2O) and transferred to NICUs on NCPAP immediately.

**Nasal continuous positive airway pressure**

The infants assigned to NCPAP will be provided by either variable flow or continuous flow devices. The starting pressure will be set at 6 cmH2O and can be raised in steps of 1 cmH2O up to 10 cmH2O. If this is not enough to maintain SpO2 between 90% and 95%, FiO2 will be added up to 0.40.

**Non-invasive high-frequency oscillatory ventilation**

NHFOV will only be provided with piston/membrane oscillators able to provide a real oscillatory pressure with active expiratory phase (Acutronic FABIAN-III, SLE 5000, Lowenstein Med LEONI+). Infants assigned to NHFOV will be started with the following boundaries: (1) mean airway pressure (MAP) of 6 cmH2O (can be changed in steps of 1 cmH2O within the range range 6–10 cmH2O); MAP will be titrated (within the range) according to open lung strategy, performing alveolar recruitment, similar to what is done in endotracheal high frequency oscillatory ventilation targeting a FiO2 ≤25% to 30%.12 (2) frequency of 10 Hz (can be changed in steps of 1 Hz within the range 8–12 Hz). (3) Inspiratory time 50% (1:1). (4) amplitude 15 cmH2O (can be changed in steps of 5 cmH2O within the range 15–30 cmH2O). In case of hypoaxemia, MAP and FiO2 will be increased (within the above-described ranges). In case of hypercarbia, amplitude will be increased first and then frequency will be lowered (within the above-described ranges).

**Interface**

NCPAP and NHFOV will be all administered through short, binal prongs. Nasal prongs size will be chosen according to the nares' diameter as the best fitting ones (the largest ones that fit the nares without blanching the surrounding tissues) and following manufacturer's recommendations.

**Surfactant treatment**

Surfactant (Curosurf; 200 mg/kg) will be administered if infants have FiO2 >30% to maintain the target SpO2 89%–94% by less invasive surfactant administration.3

**Caffeine treatment**

Caffeine (Caffeine Citrate Injection. Chiesi Pharmaceuticals, Parma, Italy) will be prophylactically administered. The initial loading dose is 20 mg/kg, and the maintenance dose is 5 mg/kg per day. Caffeine treatment will be stopped when no apneas occur or corrected GA 36 weeks was reached.

**Other treatments or tests**

1. Heart ultrasound to evaluate cardiac morphology, pulmonary pressures and patent ductus arteriosus (PDA), within the first 3 days of life and subsequently repeated, if needed; (2) Cerebral ultrasound within 48 hours of life and weekly thereafter, until discharge, if needed; (3) Routine measures to prevent BPD; routine fluid/nutritional policy; (4) Placement of umbilical central venous catheter and/or peripherally inserted central venous lines. Placement of arterial lines if needed, according to local policies and (5) Routine therapies according to local policies (ie, antibiotics, PDA closure drugs...).

**Indication for non-invasive support weaning**

The criteria for weaning non-invasive respiratory will be: (1) minimal or no signs of respiratory distress; (2) NHFOV MAP or NCPAP pressure <6 cmH2O and (3) FiO2 <0.25 to achieve target SpO2.

**Primary outcomes**

The primary outcomes will be the respiratory support failure determined by the need for IMV within 72 hours from birth. The respiratory support failure will be considered if one of the following occurs: (1) severe respiratory acidosis (defined as PaCO2 >60 mm Hg with pH<7.2) for at least 1 hour; (2) hypoxia refractory to study intervention (defined as SpO2 <90%, with FiO2=0.4 and maximal pressures allowed in the study arm) for at least 1 hour after the administration of surfactant; (3) severe apnoea (defined as recurrent apnoea with >3 episodes/hour associated with heart rate <100/min or a single episode of apnoea requiring bag and mask ventilation) and (4) attending physician determined that urgent intubation is necessary.

**Secondary outcomes**

1. Airleaks (pneumothorax and/or pneumomediastinum) occurred during treatment of RDS.
2. BPD, defined according to the NICHD definition.13
3. Haemodynamically significant PDA, defined according to local NICU protocols.
4. Retinopathy of prematurity (ROP) ≥2nd stage.14
5. Necrotising enterocolitis (NEC) ≥2nd stage.15
6. Intracranial haemorrhage (IVH) ≥3rd grade.16
8. Composite mortality/BPD.
9. Weekly weight gain (in grams/day) for the first 4 weeks of life or until NICU discharge, whichever comes first.
10. Duration of non-invasive respiratory assistance.
11. Duration of hospitalisation.
12. Rate of surfactant treatment.
13. Rate of thick secretions causing an airway obstruction.
14. Rate of nasal trauma.

**End of the study**

A patient may exit from the study for any of the following reasons:

1. Death.
2. In any case, when the 36 weeks' postconceptional age is reached.
3. If parents or guardians withdraw an already given consent for the participation (in that case the patient will keep receiving the whole routine clinical assistance;
data acquired up to that point will be immediately destroyed).

**Sample size calculation**

According to the results of our last multicentre study, the risk of failure while receiving NCPAP for extremely preterm infants with RDS was 30%, and a reduction of 20% for babies receiving NHFOV.11 We decide to aim a difference of 15% in the rate of the respiratory support failure. Considering an alpha error of 0.05 and a power of 90%, 170 neonates would be needed in each group.

**Data collection**

All data for trial analysis are routine clinical items that can be obtained from the clinical notes. Data will be recorded in real time (every day) on web-based case report forms provided by OpenCDMS. The website will be tested with fictitious data before the actual enrolment. Data will be collected at the following schedule (figure 2).

Before the intervention begins: information on eligibility; baseline clinical informations, Silverman score, Critical risk index for babies-II score.17

Following study intervention: ventilator parameters, SpO2, blood gas values (PaO2, PaCO2, SpO2 and pH) before intervention and intubation.

Follow-up: failed on assigned NIV at 72 hours or 7 days, surfactant treatment, duration of the study intervention (NCPAP or NHFOV), airleaks, PDA, BPD, ROP >2nd stage, NEC ≥2nd stage, IVH >2nd grade, in-hospital mortality, composite mortality/BPD, weekly weight gain (in grams/day), duration of hospitalisation, thick secretions causing an airway obstruction, nasal trauma.

**Statistical methods**

Outcomes will be analysed on an intention-to-treat basis. We will calculate a risk difference (with 95% CI) for dichotomous outcomes and mean (with 95% CI) or median (25–75th percentile, using Hodges-Lehmann) differences for continuous outcomes between the study

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groups. Continuous variables will be compared using Student's t test or the Mann-Whitney rank sum test as appropriate. Categorical variables were compared using the χ² test. P values <0.05 were considered statistically significant. Analyses were performed with SPSS V.16 (IBM).

Data monitoring board
An independent data monitoring committee belonging to the Central Ethics Committee of Children’s Hospital of Chongqing Medical University has been established for the trial. This committee will perform interim data analysis, investigate compliance with the trial and monitor adverse events. Formal interim analyses of efficacy will be carried out by the DMB when 25%, 50% and 75% of the outcome data were available. The board will advise the principal investigator (YS) who will remain the only responsible for the trial conduction and for any eventual decision to stop or continue it.

Ethics and dissemination
The study protocol was approved by the Ethics Committee of Children’s Hospital of Chongqing Medical University (n.2019.161) and registered in the ClinicalTrials.gov registry (ID: NCT05141435). The trial was performed in accordance with the approved guidelines and regulations of the participating institutions. Informed consent will be obtained antenatally or on NICU admission from parents or guardians. Hospitals participating in the study will share the findings and results of the study, which will be presented at national conferences and peer-reviewed paediatrics journals.

DISCUSSION
In the recent years, several randomised controlled trials have compared the effects between NHFOV and NCPAP in treatment of RDS. Malakian et al randomised 124 infants with RDS between 28 and 34 weeks to NHFOV vs NCPAP and reported that NHFOV did not decrease the need for IMV (NCPAP 14.1% vs NHFOV 6.5%, p=0.13). In contrast with the study by Malakian et al, Iranpour et al demonstrated NHFOV significantly decreased the need for IMV compared with NCPAP (NCPAP 11.8% vs NHFOV 0%, p=0.03) in preterm and near-term infants as an initial therapy. Similarly, Zhu et al published a pilot study on NHFOV versus NCPAP as primary treatment in preterm infants with moderate to severe RDS. They observed NHFOV significantly decreased the need for IMV (24.3% vs 56.4%, p<0.01). The discrepancy of these results may be ascribed to different study design.

We performed a multicentre randomised controlled trial comparing NHFOV and NCPAP as a primary mode of respiratory support in preterm infants (260/7 –336/7 weeks GA) with RDS. A total of 302 preterm infants were analysed in this trial. Treatment failure occurred in 15 of 152 infants (9.9%) in the NHFOV group and in 26 of 150 infants (17.3%) in the NCPAP group (p=0.06). Despite our trial showed no significant benefit of NHFOV with respect to primary outcomes in general, NHFOV resulted in a significantly lower rate of treatment failure in the strata of 26/7–29/7 weeks (11.9% vs 32.4%, p=0.03) and BW <1500g (10.4% vs 29.6%, p=0.01). NHFOV seemed to improve effectiveness than NCPAP in smaller preterm infants. Recently we published a multicentre, randomised controlled trial investigating, from primary extubation until NICU discharge, the use of NHFOV versus NCPAP versus non-invasive intermittent positive pressure ventilation to reduce IMV. The result showed NHFOV had significantly fewer reintubations and shorter IMV than the NCPAP in very preterm infants. However, the finding of this trial could not be translated to the acute phase of RDS, when lung derecruitment and the trend to alveolar collapse play an important role in the pathogenesis of respiratory failure.

Thus, a large population and rigorous design, including physiologically targeted ventilatory management is necessary for better evaluation of NHFOV as a primary mode of non-invasive support in extremely preterm infants with RDS. Our trial may help contribute to establish guidelines for NHFOV in extremely preterm infants with RDS to minimise the need for IMV, and to decrease significant pulmonary and non-pulmonary morbidities associated with IMV.

Trial status
At the time of this manuscript submission, the enrolment is ongoing.

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Contributors YL conceptualised the study, and drafted the initial study protocol, XZ participated in the study design, and recruitment of other centres to participate in this trial, YS critically reviewed the manuscript, recruited members for the data safety and monitoring board, and approved the final version of the manuscript. All authors of the NHFOV study group read and approved the final version, and agreed to participate in this study.

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REFERENCES