

**Noninvasive Ventilation for Preterm Neonates With
Respiratory Distress Syndrome: a Multi-center Randomized
Controlled Trial**

(NCT03099694)

13 July 2017

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STUDY PROTOCOL

Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: Study protocol for a multi-center, prospective, randomized, controlled trial. For the Noninvasive High-Frequency Oscillatory Ventilation Study Group (NHFOV Study Group*).

Abstract

Background: Invasive mechanical ventilation is associated with development of adverse pulmonary and non-pulmonary outcomes in very low birth weight infants. Various modes of non-invasive respiratory support are being increasingly used to decrease the incidence of bronchopulmonary dysplasia (BPD). The aim of this trial is to compare the effect of noninvasive high-frequency oscillatory ventilation (NHFOV) and nasal continuous positive airway pressure (NCPAP) in preterm infants with respiratory distress syndrome (RDS) as a primary noninvasive ventilation support mode.

Methods/Design: In this multicenter, randomized, controlled trial, 300 preterm infants born at gestational age (GA) less than 34 weeks with a diagnosis of RDS will be randomized to NHFOV or NCPAP as a primary mode of noninvasive respiratory support. Study will be conducted in 18 tertiary neonatal intensive care units in China. The primary outcome is the need for invasive mechanical ventilation (IMV) during the first 7 days after enrollment in preterm infants randomized to the two groups. The

prespecified secondary outcomes include days of hospitalization, days on noninvasive respiratory support, days on IMV, days on supplemental oxygen, mortality, need for surfactant, severe retinopathy of prematurity(ROP) requiring laser or surgery, patent ductus arteriosus needing ligation, bronchopulmonary dysplasia(BPD), occurrence of abdominal distention, air leaksyndromes, intraventricular hemorrhage (IVH \geq grade 3), necrotizing enterocolitis (NEC \geq II stage) and nasal trauma. Other secondary outcomes include Bayley Scales of Infant Development at 18-24 months of corrected age.

Trial registration: ClinicalTrials.gov Identifier: NCT03099694.

Key words: Noninvasive high-frequency oscillatory ventilation; nasal continuous positive airway pressure; respiratory distress syndrome; preterm infants; surfactant; invasive mechanical ventilation

Background

Respiratory distress syndrome (RDS) due to surfactant deficiency is the leading cause of respiratory failure in preterm infants [1]. Early noninvasive positive pressure ventilation has become a recommended strategy for respiratory management of preterm infants with RDS [2]. In addition to nasal continuous positive airway pressure (NCPAP), various types of noninvasive ventilation (NIV) modes have been used in the treatment of RDS including heated, humidified, high-flow nasal cannula (HHFNC), biphasic NCPAP (BP-NCPAP) and nasal intermittent positive airway pressure (NIPPV) [3]. However, clinical trials have shown that 25 to 67% of very low birth weight preterm infants fail these NIV modes and require IMV [4-5]. To minimize the need of IMV, noninvasive high-frequency oscillatory ventilation (NHFOV) has been studied as a rescue treatment after failure of other NIV modes or following extubation from IMV during weaning phase [6]. However, to date, no studies have been published on the efficacy of NHFOV as a primary mode of respiratory support in preterm infants. In the present trial, we aim to compare the effect of NHFOV and NCPAP in preterm infants with RDS as a primary NIV mode. Our main hypothesis is that NHFOV is more effective in the treatment of preterm infants with RDS than NCPAP when used as a primary NIV mode.

Trial Design

Aim

The primary aim of this trial is to compare the need for IMV during the first 7 days of life in infants randomized to NHFOV versus NCPAP.

Study design

This will be a multi-center, prospective, randomized controlled trial conducted in 18 tertiary neonatal intensive care units (NICUs) in China. The trial will be performed in accordance with prospective trial flow (Fig.1).

Inclusion criteria:

(1) Gestational age (GA) is from 26 weeks 0 days (26⁺⁰weeks) to 33 weeks 6 days(33⁺⁰weeks) (estimated on the postmenstrual date and early gestation ultrasonographic findings); (2) diagnosis of RDS. The diagnosis of RDS will be based on clinical manifestations(tachypnea, nasal flaring and or grunting) and the typical X-ray picture of RDS (grain shadow, air bronchogram or white lung)-see appendix; (3) RDS Silverman score>5; (4) Age <12 hours; (5) informed parental consent has been obtained.

Exclusion criteria

(1) Resuscitation requiring early intubation according to the American Academy of Pediatrics guidelines for neonatal resuscitation [8]; (2)major congenital malformations or known complex congenital heart disease; (3)pulmonary hemorrhage or pneumothorax; (4) congenital lung diseases or malformations or pulmonary hypoplasia;

Setting

We plan to enroll preterm infants born between 26 and 34 weeks of gestational age from 18 tertiary NICUs in China. These 18 tertiary NICUs have more than 800 NICU beds and annual admissions of nearly 8,000 preterm infants with RDS each year. The first (XZ) and last authors (RR) take responsibility for the accuracy and completeness

of the trial.

Randomization

To avoid the chance of having more infants in one group than another, block randomization will be applied, with a block size of 4. The envelopes are sealed, shuffled, and then numbered in sequential order from 1 to 4. A clinician who is not in the trial group will open the envelope and randomize patients. This procedure will be repeated for each group of four infants. Infants will be stratified according to 26^{0/7}-27^{6/7} weeks, 28^{0/7}-29^{6/7} weeks, 30^{0/7}-31^{6/7} weeks and 32^{0/7}-33^{6/7} weeks. Infants born from multiple gestations will be assigned by individual randomization. Infants randomized to one arm cannot crossover to the other or vice-versa during the study.

Trial intervention

Ventilators

CPAP: CPAP will be provided by continuous flow devices (CNO Medin, Germany or Carefusion, USA) Bubble CPAP devices will not be used.

NHFOV: NHFOV will be provided by two ventilators (CNO, Medin, Germany or SLE 5000, UK). The Medin CNC ventilator produces high-frequency oscillations by flow interruption with cyclic opening-closure of the end expiratory valve. Otherwise, The SLE 5000 ventilator is a time-cycled, pressure-limited and continuous-flow neonatal ventilator.

Before the beginning of the study all ventilators will be checked to ensure that there is no malfunction.

Interfaces

CPAP and NHFOV will be all administered through short, low-resistance binasal prongs,

since these are supposed to be the best in terms of resistive charge, leaks and/of comfort. 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. Particular care (e.g.: pacifiers, positioning, nursing) will be applied to reduce leaks and improve patients' comfort. These matters will be evaluated through a dedicated 30 min observation period when study intervention will be instigated.

Ventilatory management

The two different respiratory supports will be managed as follows:

CPAP: Neonates assigned to the CPAP group were initiated on a pressure of 5 cmH₂O. CPAP can be raised in steps of 1 cmH₂O up to 10 cmH₂O. If this is not enough to maintain target oxygen saturation (SpO₂) from 89% to 92% in preterm infants <30 weeks GA and 90-94% in infants ≥30 weeks GA by pulse oximeter, FiO₂ will be added up to 0.40.

NHFOV: For Medin CNO, the initial NHFOV settings will be: mean airway pressure (MAP) of 6cmH₂O (range 6-10cmH₂O), frequency of 10 Hz (range 6-12), The Medin CNO has ten grades of amplitude. grade 7th amplitude will be to start with (grade range 7th-10th). For SLE 5000, The initial settings will be: MAP of 6 cm H₂O (range 6-10cmH₂O); frequency of 10Hz (range 6-12), inspiratory time 50% (1:1), oscillations of amplitude of 20 cm H₂O (range 20-35 cm H₂O). It is not strictly necessary to have visible chest oscillations, as most of the CO₂ elimination during NHFOV will occur in the upper airway dead space. Maximal allowed FiO₂ will be 0.40 and SpO₂ from 89% to 93% in

preterm infants <30 weeks GA and 90-94% in infants \geq 30 weeks GA by pulse oximeter.

Surfactant Therapy

Surfactant (Poractant alfa, Chiesi Pharmaceuticals, Parma, Italy) at dose of 200 mg/kg will be administered via INSURE method if infant presents with the following: infants \leq 26 week's gestation when FiO_2 requirement >0.30 and infants >26 week's gestation when FiO_2 requirement >0.40 [2]. Additional doses of surfactant may be given using INSURE technique at the discretion of the clinician.

Caffeine Therapy

Caffeine (Caffeine Citrate Injection, Chiesi Pharmaceuticals, Parma, Italy) will be administered when infants present with moderate apnea (defined as 3 or more episodes in 24 hours or a single episode requiring resuscitation and bag-mask ventilation). The initial loading dose is 20mg/kg, and the maintenance dose is 5mg/kg per day.

Weaning from study interventions

The criteria for weaning noninvasive respiratory will be: (1) minimal or no signs of respiratory distress (RDS Silverman score < 5) ; (2) NHFOV MAP or NCPAP pressure <6 cmH₂O and (3) $FiO_2 < 0.25$ to achieve target SpO₂.

Criteria for intubation and IMV

These will be as follows [10-11]: (1)severe respiratory acidosis ($P_aCO_2 > 65$ mmHg with $pH < 7.20$);(2)severe apnea and bradycardia (defined as recurrent apnea with >3 episodes per hour associated with heart rate < 100 /min, a single episode of apnea that

requires bag and mask ventilation); (3) hypoxia ($FiO_2 > 0.5$ with $PaO_2 < 50$ mmHg), severe respiratory distress (RDS Silverman score > 7); (4) pulmonary hemorrhage; (5) pneumothorax; (6) cardiopulmonary arrest needing chest compressions.

Training

Since not all clinicians are well versed in all respiratory techniques and, particularly, NHFOV is a relatively new technique, the training is capital for the trial success. The protocol will be diffused between participating centers at least 3 months before the study begins. One investigator (YS) will explain the study protocol in an in-person meeting with all investigators. During the two months' period, clinicians will familiarize with the protocol and the respiratory techniques and the two co-principal investigators will be available to solve any doubt. A dedicated social media chat has been set to facilitate these exchanges. The trial is supposed to actually start in July 2017.

Outcomes

The primary outcome of this trial will be to determine the need for IMV in the first 7 days of life in preterm infants randomized to the two groups. Secondary outcomes include days of hospitalization, days on noninvasive ventilation, days on supplemental oxygen, pre-discharge mortality, surfactant doses, incidence of stage III ROP and BPD, occurrences of abdominal distention, air leaks, IVH \geq grade 3 and NEC. Secondary outcomes also include Bayley Scales of Infant Development at 18-24 months of corrected age. BPD will be defined according to the National Institutes of Health consensus definition as mild, moderate and severe BPD [12], IVH classification according to Papile et al [13] and for NEC, Bell staging will be used [14].

Data collection

Patient demographic data include: sex, birth weight, gestational age, Apgar scores, mode of

delivery, prenatal corticosteroid use, premature rupture of the membrane, RDS Silverman score and critical risk index for babies-II (CRIB-II) score. More details see in the appendix Clinical data :Including the need for IMV, days of hospitalization, days on noninvasive respiratory support, days on supplemental oxygen, mortality, the need for surfactant, occurrences of abdominal distention, air leaks, IVH \geq grade and NEC \geq stage II. More details see in the appendix Follow-up data: The incidence of BPD and ROP at a post-menstrual age of 36 weeks or at discharge, and Bayley Scales of Infant Development at 18-24 months of corrected age.

Sample size calculation

It is difficult to calculate a sample size for such a study, since it is the first to investigate NHFOV vs CPAP in primary support phase in preterm infants with RDS. There is only one preliminary study available about the primary outcome “need for IMV”. This pilot study conducted by Zhu et al provides data about the primary outcome “need for IMV”. This trial showed the need for IMV was significantly lower in the NHFOV compared with the NCPAP group (24.3% vs. 56.4%, $P < 0.01$). Considering an α -error of 0.05 and a power of 90%, 150 neonates should be enrolled in each arm (with a 1:1 design) to detect the same difference.

Statistical methods

Data will be analyzed using SPSS version 19 software. The statistical analyses include Student's t-test for continuous data and compared proportions using Chi-squared test, and Fisher's exact test for categorical data. Predefined four subgroups are 26^{0/7}-27^{6/7} weeks, 28^{0/7}-29^{6/7} weeks, 30^{0/7}-31^{6/7} weeks and 32^{0/7}-33^{6/7} weeks, and subgroup analyses will be conducted for the primary outcome in the preterm infants. To further evaluate the effect of NHFOV on intubation within

subgroup, the test of treatment-by-gestational age subgroup interaction will also be done using the paired binary logistic regression. For the preterm infants lost to follow-up, the missing values of the primary and secondary outcomes are replaced using multiple imputation. A P -value < 0.05 will be regarded as statistically significant.

Data Safety Monitoring Board (DSMB): Dr. Kris Sekar, Professor of Pediatrics, Oklahoma University Medical Center, Oklahoma, Dr. Jatinder Bhatia, Professor of Pediatrics, Medical College of Georgia, Georgia Health Sciences University, Augusta, Georgia, and Dr. Rowena Cayabyab, MD., MPH (Biostatistics and Epidemiology) Assistant Professor of Pediatrics, Keck School of Medicine of the University of Southern California, Los Angeles, California will serve as DSMB members. Dr. Cayabyab will also serve as consultant for statistical analysis.

Registration number

The trial has been approved by the centralized ethics committee (The Ethics Committee of Daping Hospital, Research Institute of Surgery, Third Military Medical University) and registered at <http://www.clinicaltrials.gov>(ID: NCT03099694).

Discussion

In the past decades, several clinical trials have compared the effects between NHFOV and NCPAP in neonates as a rescue mode or during weaning from IMV. These trials demonstrated that NHFOV applied with nasopharyngeal tube are more beneficial than NCPAP in reducing CO₂ levels [16-19]. Recently, two retrospective case series also reported NHFOV could be applied in preterm infants as a rescue treatment after the

failure of other noninvasive ventilation modes[15,20].However, there are some limitations in these trials: 1) small sample size; 2) lack of a prospective, randomized trial design; and 3) wide range of NHFOV parameters used in these trials. Given these limitations, a multi-center, prospective, randomized, controlled trial is necessary for better evaluation of NHFOV as a primary mode of noninvasive support. To our knowledge, this will be the first multi-center prospective randomized controlled trial for evaluation of NHFOV as a primary noninvasive mode in preterm infants with RDS in China or any other part of the world. Our trial may help contribute to establish guidelines for NHFOV in preterm infants with RDS to minimize the need for IMV, and to decrease significant pulmonary and non pulmonary morbidities associated with IMV.

Funding

The trial is initiated and planned by the researchers and funded by Scientific Research Projects unit of Chongqing (Project- cstc2016shms-ztxx13001)

Acknowledgement

The authors would like to thank all families whose infants will participate in this trial, and staff providing patient care in all the participating sites.

Conflict of Interest

None of the authors have declared conflicts of interests to participate in this trial.

APPENDIX

A1. Diagnosis of RDS:

Respiratory distress appearing within the first 24 h of life, with complete, sustained, and prompt response to surfactant or lung recruitment or both; additional non-mandatory criteria are

lung imaging (chest X-rays or ultrasound, according to local policies) supporting the diagnosis or lamellar body counts $\leq 30\,000/\text{mm}^3$, or both

A2. CLARIFICATIONS FOR EXCLUSION CRITERIA

Some exclusion criteria are represented by congenital disorders: when a patient is affected by these disorders his biology and physiology are significantly changed and are not eligible for the study and will not be randomized. If the condition has been discovered/suspected after the randomization but before the study inclusion (that is, before extubation), they will not receive the study intervention and will not entry in the study. If one of these conditions is diagnosed after the inclusion in the study, the neonate will be excluded *a posteriori*. This is the case of neonates with major congenital anomalies, chromosomal abnormalities, neuromuscular diseases, congenital upper respiratory tract abnormalities and congenital lung diseases or malformations or hypoplasia. Examples of these conditions are: genetic syndromes, surfactant protein defects, congenital adenomatous pulmonary malformations, congenital diaphragmatic hernia or sequestration, congenital hypoventilation syndrome, pulmonary hypoplasia or any metabolic disease.

A3. LIST OF STUDY DEFINITION

- **Gestational age (GA).** GA is determined based on sure dates of last menstrual period or early ultrasound scan (within the first trimester). If a discrepancy of more than 2 weeks exists, the early ultrasound scan will be chosen.
- **INSURE.** Intubation-Surfactant-Extubation
- **Antenatal steroids.** Antenatal steroid prophylaxis will be considered complete if two 12 mg doses of betamethasone 24h apart and between 1 day and 7 days before the delivery had been given.
- **Clinical Risk Index for Babies (CRIB-II) score.**⁴² This is an estimator of the clinical severity at the NICU admission. CRIB-II score considers 4 variables: *birth weight, GA, base excess within the 1st hour of life and temperature at*

theadmission(see below). An online calculator is available at

www.sfar.org/scores2/crib22.php

Birthweight (g) and gestation (weeks):

The maximum (worst) score for birthweight and gestation is 15, which is obtained for a 22 week male infant of less than 501 g birthweight

Male infants																Female infants																
Birthweight (g)	2751 to 3000																															0
	2501 to 2750																															1
	2251 to 2500																															3
	2001 to 2250																															2
	1751 to 2000																															3
	1501 to 1750																															6
	1251 to 1500																															5
	1001 to 1250																															3
	751 to 1000	12	10	9	8	8	7	6	5	4	3	3	2	1	0	0	11	10	8	7	6	5	4	3	3	3	3	2	1	1		
	501 to 750	14	13	12	11	10	9	8	8	8	8	8	6	6	6	13	12	11	10	9	8	7	6	5	5	5	5	5	5			
251 to 500	15	14	13	12	11	10	10								14	13	12	11	10	10												
Gestation (weeks)																Gestation (weeks)																

Temperature at admission (°C)

≤29.6	5
29.7 to 31.2	4
31.3 to 32.8	3
32.9 to 34.4	2
34.5 to 36	1
36.1 to 37.5	0
37.6 to 39.1	1
39.2 to 40.7	2
≥40.8	3

Base excess (mmol/L):

<-26	7
-26 to -23	6
-22 to -18	5
-17 to -13	4
-12 to -8	3
-7 to -3	2
-2 to 2	1
≥3	0

Sex, birthweight (g) and gestation (weeks):	_____
Temperature at admission (°C):	_____
Base excess (mmol/L):	_____
Total CRIB II Score	_____

The logistic regression equation relating CRIB II to mortality (CRIB II algorithm) is:
 Log odds of mortality = $G + 6.47 + 0.450 \times \text{CRIB II}$
 Probability of mortality = $\exp(G) / (1 + \exp(G))$
 The range of possible CRIB II scores is 0 to 27

Clinical risk index for babies II (CRIB II) score

- **Premature rupture of the membrane.** Premature rupture of the membrane will be considered complete if more than 18 hours.
- **Abdominal distension.** Abdominal circumference (cm) at 48h and 96h after study intervention.

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