NHFOV vs nCPAP in Very Preterm Infants With Respiratory Distress Syndrome: A Multi-center, Prospective, Randomized, Controlled Clinical Superior Trial

NCT05141435

DATE: August 1, 2022

NHFOV vs nCPAP in Very Preterm Infants With Respiratory Distress Syndrome: A Multi-center, Prospective, Randomized, Controlled Clinical Superior Trial

Trial Design

This will be a multicentre, randomised controlled, superiority trial conducted in 20 tertiary NICUs in China from August 2022 to August 2024. We preform this trial to compare the need for invasive mechanical ventilation (IMV) in very preterm infants with respiratory distress syndrome (RDS) randomized to Noninvasive high-Frequency oscillatory ventilation (NHFOV) versus nasal continuous positive airway pressure (NCPAP).

Inclusion criteria:

i. GA between $24^{0/7}$ and $28^{6/7}$ weeks
ii. Diagnosis of RDS. The diagnosis of RDS will be based on clinical mani festations (tachypnea, nasal flaring and or grunting) and a fraction of inspired oxygen (FiO_2) greater than 0.25 for target saturation of peripheral oxygen (SpO_2) 89%–94%
iii. Age <2hours
iv. Informed parental consent has been obtained

Exclusion criteria

i. Intubated for any reasons at birth

ii. major congen ital malformations or known complex congenital heart disease

iii. transferred out of the NICU before randomisation

Randomization

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

Trial intervention

Delivery room

In the delivery room, all eligible infants with spon taneously breathing shoud be supported by NCPAP(pressure: 6–8cm H_2O) 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 cmH2 O and can be raised in steps of 1 cmH2 O up to 10 cmH2 O. 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, Loweinstein Med LEONI+). Infants assigned to NHFOV will be started with the following boundaries: (1) mean airway pressure (MAP) of 6 cmH_2O (can be changed in steps of 1 cmH_2O within the range range 6–10 cmH_2O); 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 FiO_2 ≤25% to 30%.12 (2) frequency of 10Hz (can be changed in steps of 1Hz within the range 8–12Hz). (3) Inspiratory time 50% (1:1). (4) amplitude 15 cmH_2O (can be changed in steps of 5 cmH_2O within the range 15–30 cmH_2O). In case of hypoxaemia, MAP and FiO_2 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, binasal 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; 200mg/kg) will be administered if infants have FiO_2 >30%to maintain the target SpO_2 89%–94% by less invasive surfactant administration.

Caffeine treatment

Caffeine (Caffeine Citrate Injection. Chiesi Pharmaceu ticals, Parma, Italy) will be prophylactic administered. The initial loading dose is 20mg/kg, and the mainte nance dose is 5mg/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 3days 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/nutri tional 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…).

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 consid ered if one of the following occurs: (1) severe respiratory acidosis (defined as $PaCO_2$ >60mm Hg with pH<7.2) for at least 1hour; (2) hypoxia refractory to study interven tion (defined as SpO_2 <90%, with FiO_2 =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 pneumomediasti num) occurred during treatment of RDS.

(2)BPD, defined according to the NICHD definition.

(3) Haemodynamically significant PDA, defined accord ing to local NICU protocols.

(4) Retinopathy of prematurity (ROP) >2nd stage.

(5) Necrotising enterocolitis (NEC) ≥2nd stage.

(6) Intracranial haemorrhage (IVH) ≥3rd grade.

(7) In-hospital mortality.

(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 con sent 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)

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 enrollment

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

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 7days, 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 secre tions causing an airway obstruction, nasal trauma.ictitious data before the actual enrolment.

Sample size calculation

According to the results of our last multicentre study, the risk of failure while receiving NCPAP for very preterm infants with RDS was 30%, and a reduction of 20% for babies receiving NHFOV. 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.

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 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 $\chi 2$ test. P values < 0.05 were considered statistically significant.

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 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 regula tions 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