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

NCT05141435

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Dear Madam/Sir:

We are considering inviting you and your baby to participate in a multicenter, randomized, controlled study: Noninvasive high frequency oscillatory ventilation (NHFOV) As Primary Support in Very Preterm Infants with RDS (Clinicalstudys.gov Identifier: 05141435). This study has been approved by the Ethics Committee of Children's Hospital of Chongqing Medical University.

Before agreeing to participate in the study, it is important that you understand the specific content of the study. Please read this document carefully and ask questions. Whether you and your baby participate in this study depends entirely on your personal wishes

1. Backgroud

Respiratory distress syndrome (RDS) is the main cause of respiratory failure in preterm neonates, its incidence varying from ≈80% to ≈25% depending on gestational age. Nasal continuous positive airway pressure (NCPAP) is a commonly established respiratory support used in preterm infants with RDS. However, the risk of failure while receiving initial NCPAP in very preterm infants was about 25% . As such, to minimize the risk of invasive mechanical ventilation (IMV), a relatively newer form of NIV that is emerging is nasal high-frequency oscillatory ventilation (NHFOV). NHFOV is an unconventional noninvasive ventilation mode that applies a bias flow to generate a continuous distending pressure with active oscillations that are superimposed on spontaneous tidal breathing. It matches together the advantages of high-frequency ventilation (no need for synchronisation, high efficacy in removing CO2) and nasal continuous positive airway pressure (NCPAP, non-invasive interface, increase in functional residual capacity allowing oxygenation to improve).

2. The aim of trial

The purpose of this larger multi center, randomized trial was to assess whether NHFOV as a primary mode of respiratory support as compared with NCPAP will reduce the need for intubation very in preterm infants with RDS.

3. The number participants and hospital

This trial will be conducted in Children's Hospital of Chongqing Medical University, Jiangxi Maternal and Child Health Hospital, Guiyang Maternity and Child Health Care Hospital,The Second Hospital of Shandong University, Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, Hunan Provincial Maternal and Child Health Care Hospital Zhangzhou Affiliated Hospital of Fujian Medical University, Women and Children's Health Hospital of Yulin, Chongqing Three Gorges Central Hospital, Gansu Provincial Maternal and Child Health Care Hospital The First People's Hospital of Yunnan, Chengdu Women's and Children's Central Hospital, Maternal and Children's Healthcare Hospital of Taian, People's Hospital of Xinjiang Uygur Autonomous Region, Quanzhou Children's Hospital, Chongqing West Hospital, Chongqing Medical Center for Women and Children, Xiamen Maternity & Child Care Hospital, Qujing Maternal and Child Health Hospital, Liuzhou Maternity and Child Healthcare Hospital and International Peace Maternity and Child Health Hospital.

We plan to recruit at least 360 preterm infants in this trial. The total time of this trial is 24 months, and the time of participation is estimated 12 months.

4. Inclusion of the trial

(1) gestational age between $24^{0/7}$ and $28^{6/7}$ weeks; (2) diagnosis of RDS and a fraction of inspired oxygen (FiO_2) greater than 0.25 for target saturation of peripheral oxygen (SpO_2) 89%–94%; (3) age<2hours

5. Exclusion of the trial

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

6. The procedure of trial

Preterm infants are eligible for the study if they present with RDS dignosed byclinical manifestations (tachypnea, nasal flaring and or grunting) and the typical X-ray picture of RDS. They will be randomly assigned to one of the treatment

groups to receive NCPAP or NHFOV according to a software-generated random number sequence posted on a dedicated and secure website available on a 24/7 basis.

Babies randomized to NCPAP will be initiated on a pressure of 6 cmH_2O, which could be raised to 10 cmH_2O. If this was not enough to maintain pre-ductal saturation (SpO_2) between 89 and 94%, the inspired oxygen fraction (FiO_2) was increased to 0.40.

Babies randomized 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); (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)

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

Caffeine (Caffeine Citrate Injection. Chiesi Pharmaceuticals, Parma, Italy) will be prophylactic administered. The initial loading dose is 20mg/kg, and the maintenance dose is 5mg/kg per day

Babies will be intubated if one of the following occurs: (1) severe respiratory acidosis (defined as PaCO2 >60mm Hg with pH<7.2) for at least 1hour; (2) hypoxia refractory to study intervention (defined as SpO2 <90%, with FiO2 =0.4and maximal pressures allowed in the study arm) for at least 1hour 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); (4) attending physician determined that urgent intubation is

necessary.

7. The potential discomforts and risks

Participants in this study may face complications of noninvasive ventilation: vomiting, feeding intolerance, abdominal distention, pneumothorax, nasal trauma, pain, etc.

8. The expected benefits

Your baby will be exempt from the cost of treatment and may have the opportunity to receive more advanced non-invasive ventilation mode to reduce the risk of invasive mechanical ventilation.

9. The alternative treatments and procedures that might also be beneficial

Your baby does not have to participate in this study to treat RDS. You can choose other treatments for your baby.

10. The compensation or medical treatments available if injury occurs

If your baby suffers from study-related damage in the course of participating in the study, we will provide you with emergency treatment free of charge. Damage compensation during the study period will beimplemented in accordance with the relevant laws of China

11. The protection of confidentiality and privacy

Investigators are responsible for following applicable data protection regulations to process data. However, such information can be accessed by ethics committees and inspections by administrative departments. The results may be published in medical journals/conferences, but personal information about you and your baby will not be made public.Your baby's health information is protected by relevant Chinese laws. After signing this informed consent, you agree to collect, use and share your baby's health information data with investigators. Your baby's name is abbreviated and a code assigned to the study data is now available to investigators. Your authorization to use your baby's health information will remain valid until the end of the study and the results of the study are available. At the end of the study and after the results are

obtained, we will delete your personal information and your baby's information from the study records.

12. The participation is voluntary

Participation in this study is entirely out of your personal desire to return your baby. Your baby can choose not to participate in this study, your baby can also withdraw at any time, any treatment and rights of your baby will not be affected, and will not be discriminated against by doctors.

13. Who to contact with questions about the study

Before you sign this agreement, all members of the study will answer all your questions. If you still have questions, suggestions or comments after signing the consent, you can also communicate with the investigators.You can keep abreast of the relevant information and study progress of this study.

Statement of Subject

I have read the above introduction to this study and have had the opportunity to ask my doctor questions about this study. All my questions have been satisfactorily answered.

I know there may be risks and benefits to participating in this study. I take part in the study on a voluntary basis.

I confirm that I have had enough time to consider this and I know that I can always consult my doctor for more information.

I can withdraw from this study at any time without discrimination or retaliation, and my rights and interests will not be affected.

I also know that if I drop out of the study, especially because of the acupuncture, it would be advantageous for me to report my changes to my doctor and complete the

check-related.

If I need to take any other medication as a result of my condition, I will consult my doctor in advance or tell my doctor truthfully afterwards.

I grant access to my research materials to research management, ethics committees or sponsors.

I will receive a signed and dated copy of the informed consent.

In the end, I decide to take part in the study and promise to follow my doctor's advice as much as possible.

Subject’s Signature:_____Date: _____Tel: _____

If signed by other than subject, indicate relationship:_____

Statement of doctor

I confirme that the patient have been explained in detail about the trial, including her rights and potential benefits and risks, and that I have given her a signed copy of the informed consent.

Doctort’s Signature:_____Date: _____Tel: _____