Comparison of efficacy of less invasive surfactant treatment under nasal CPAP and nasal IPPV in premature babies: CURLISPAP STUDY

NCT NUMBER: NCT04698473

Primary Investigator
Hilal Ozkan, MD
Bursa Uludag University Faculty of Medicine, Division of Neonatology
Bursa Uludag University Campus of Görükle 16059 Nilüfer/BURSA
Phone: (224) 2950427
Fax: (224) 294-06291000

Sponsor
Bursa Uludag University
Phone: (224) 294-0600
Fax: (224) 294-06291000

STUDY SUMMARY

Title	Comparison of efficacy of less invasive surfactant treatment under nasal CPAP and nasal IPPV in premature babies: CURLISPAP STUDY
Methodology	Randomized, controlled trial
Study Duration	Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study) is approximately 2.0 years
Study Center(s)	Multi-center (Uludag University Hospital Marmara University Hospital, Gazi University Hospital, Ankara University Hospital Başakşehir Çam ve Sakura City Hospital and Dokuz Eylul University Hospital)
Objectives	**Primary Objective:** To compare the effectiveness of nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (CPAP) in preterm infants with respiratory distress syndrome (RDS). **Secondary Objectives:** To evaluate short and long term neonatal outcomes such as bronchopulmonary dysplasia, duration of mechanical ventilation, retinopathy of premature and intraventricular hemorrhage.
Number of Subjects	170 randomized patients in two arms; NCPAP and NIPPV group
Diagnosis and Main Inclusion Criteria	**Inclusion Criteria** • Gestational age 24 -29 week • Clinical and radiological diagnosis of RDS • Born in a hospital with a study center • Spontaneous breathing • Within the first 6 hours • Non-invasive ventilation and FiO2 requirement >0.30 • Parental concent **Exclusion Criteria** • Major congenital malformations • Need of mechanical ventilation • Need of entubation in delivery room • Air weak syndrome • No parental concent
Study Product, Dose, Route, Regimen	• **NCPAP Group:** Will receive standard NCPAP protocol • **NIPPV Group:** Will receive standard NIPPV protocol • **SURFACTANT:** As a surfactant preparation, Curosurf® will

	be applied in all patients with a standard dose of 200 mg / kg and a special catheter Lisacath® as a standard in all of patients.

PURPOSE

To evaluate the effectiveness of nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (CPAP) in preterm infants with respiratory distress syndrome (RDS).

BACKGROUND

Respiratory distress syndrome (RDS) is the leading cause of respiratory failure in preterm infants. The incidence and severity of RDS are inversely related to the gestational age of the newborn. Despite recent improvements in neonatal care, RDS still remains as major cause of morbidity and mortality in preterm infants. Exogenous surfactant treatment is known to reduce mortality and morbidity in premature infants with RDS.

Surfactant therapy should be performed by health care-givers who are experienced in intubation and MV of the newborn. Most premature infants can tolerate extubation after application of surfactant and continue with CPAP or nasal intermittent positive pressure ventilation (NIPPV) so INSURE (INtubate, SURfactant, Extubate) can be preferred as the surfactant application method. Researchers have thus been looking for less invasive ways to administer surfactant without the need for intubation. A method, called LISA (less invasive surfactant administration) in which a soft flexible catheter instead of an endotracheal tube is placed in the trachea under direct laryngoscopy using Magill forceps and the surfactant is applied. The method, non invasive ventilation (NIV) continues during the surfactant application. All meta-analyses reviewing LISA methods showed that LISA reduced the need for MV in the first 72 hours of life. LISA method can be used with NCPAP or NIPPV.

GOALS OF THE STUDY

1. To compare the effectiveness of NIPPV versus NCPAP in preterm infants with RDS.
2. To evaluate the development of apnea, bradycardia, desaturation and surfactant reflux
3. To evaluate need of repeat surfactant dose
4. To evaluate need of mechanical ventilation within 72 hours following surfactant treatment
5. To evaluate duration of non invasive and invasive ventilation
6. To evaluate long term outcomes such as bronchopulmonary dysplasia, retinopathy of premature, intraventricular hemorrhage, necrotizing enterocolitis.

DURATION OF THE STUDY

Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study) is approximately 2.0 years

PRODUCT DESCRIPTION

As a surfactant preparation, Curosurf® will be applied in all patients with a standard dose of 200 mg / kg and a special catheter Lisacath® as a standard.

STUDY ARMS

1. **NCPAP Group:** Will receive standard NCPAP protocol
    a. Ventilator-derived NCPAP will be administered using binasal prongs. Standard Devices or infant flow-driver device. Initial NCPAP settings are: PEEP:6 cmH2O and FiO2: adjusted to keep preductal sPO2 between %90-94. Failure is defined as FiO2 requirement of >%50, capillary blood gas obtained at the 4th hour of therapy showing pH<7.20 or pCO2>60 cmH2O.

2. **NIPPV Group:** Will receive standard NIPPV protocol
    a. Ventilator-derived NIPPV will be administered using binasal prongs. Standard Devices or infant flow-driver device. Initial NIPPV settings are: PEEP:6 cmH2O, PIP: 15 cmH2O, Rate: 30-40/ bpm and FiO2: adjusted to keep preductal sPO2 between %90-94. Failure is defined as FiO2 requirement of >%50, capillary blood gas obtained at the 4th hour of therapy showing pH<7.20 or pCO2>60 cmH2O.

POTENTIAL BENEFITS AND RISKS TO PATIENTS

The study includes routine treatment protocols. LISA is one of the standard surfactant treatment applications. Possible complications during surfactant treatment such as apnea, bradycardia, desaturation and surfactant reflux will be followed.

METHODS

Study Design.

The prospective, multi-center, randomized, controlled study involving one hundred and seventy (170) premature with RDS.

Study population and selection criteria

Premature babies who have spontaneous breathing between $24^{1/7}$- $29^{6/7}$ weeks and who have FiO2>0.3 required to reach target saturation (90-94%), who are indicated for surfactant treatment and who are within the first 6 hours of life.

Inclusion Criteria

- Gestational age $24^{1/7}$- $29^{6/7}$ week
- Clinical and radiological diagnosis of RDS
- Born in a hospital with a study center
- Spontaneous breathing
- Within the first 6 hours
- Non-invasive ventilation and FiO2 requirement >0.30
- Parental concent

Exclusion Criteria

- Major congenital malformations
- Need of mechanical ventilation
- Need of entubation in delivery room
- Air weak syndrome
- No parental concent

Study centers and collaborators

1. Uludag University Faculty of Medicine, Division of Neonatology
    - Hilal Ozkan (Coordinator, Principal investigator, Neonatolog)
    - Nilgun Koksal (Co-investigator, Neonataolog)
    - Fatma Kocael (Co-investigator, Fellow of Neonatology)
2. Marmara University Faculty of Medicine, Division of Neonatology
    - Eren Özek (Principal investigator, Neonataolog)
    - Hülya Özdemir (Co-investigator, Neonataolog)
    - Sinem Gülcan Kesrin (Co-investigator, Fellow of Neonatology)
3. Gazi University Faculty of Medicine, Division of Neonatology
    - Esin Koç (Principal investigator, Neonataolog)
    - Canan Türkyılmaz (Co-investigator, Neonataolog)
    - İbrahim Hirfanoğlu (Co-investigator, Neonataolog)
4. Ankara University Faculty of Medicine, Division of Neonatology
    - Saadet Arsan (Principal investigator, Neonataolog)
    - Ömer Erdeve (Co-investigator, Neonataolog)
    - Emel Okullu (Co-investigator, Neonataolog)
5. Başakşehir Çam-Sakura City Hospital, Neonatology
    - Merih Çetinkaya (Principal investigator, Neonataolog)
    - Beril Yaşa (Co-investigator, Neonataolog)
    - İlker Gönen (Co-investigator, Fellow of Neonatology)
6. Dokuz Eylul University Faculty of Medicine, Division of Neonatology
    - Hasan Ozkan (Principal investigator, Neonataolog)
    - Nuray Duman (Co-investigator, Neonataolog)
    - Funda Tuzun (Co-investigator, Neonataolog)

Recruitment methods

Subjects will be identified through of investigators in study centers. The Primary Investigators and their partners (co-investigators) will be performing the study groups treatment.

Data collection and reporting

Patient data will be collected electronically through the "Turkish Neonatal Society Trials Network" operating system. Data from the study will be maintained for two (2) years after the date the investigation is completed, terminated or until the records are no longer required to support the protocol, whichever date is later.

Expected outcomes

The study objective is to compare the effectiveness of nasal NIPPV versus CPAP in preterm infants with RDS. It is thought that the surfactant treatment by LISA with both methods will be effective.

Adverse reactions

There is no expectation of any adverse outcomes. It has been shown that surfactant administration can be performed safety with the LISA method. No risk is expected in the study, and benefits are expected in both groups.

REASONS FOR WITHDRAWAL OR TERMINATION

Parents may be discontinued from the study at any time, for any reason, specified or unspecified, and without prejudice
The following is a list of possible reasons for study treatment discontinuation:

• Screening Failure
• Parents withdrawal of consent
• Lost to follow-up
• Subject death before 36 week gesatational age

METHODS AND STUDY SCHEDULE

Subjects eligible for the study will review and undergo informed consent. Once consented, subjects will be randomly assigned on a 1:1 basis to undergo:

- NCPAP Group: Will receive standard NCPAP protocol
- NIPPV Group: Will receive standard NIPPV protocol

Randomization

- Patients who are hospitalized in the neonatal intensive care unit (NICU) due to RDS within the first 6 hours of life, and who are indicated for non-invasive

surfactant administration (LISA) due to their spontaneous breathing, will randomized as **NCPAP or NIPPV**.

- Randomization will be done automatically over the Turkish Neonatal Society Trials Network system, without being user dependent.
- When entered into the system, each patient will be given a number, and each center will be able to enter their own patient's data.

Standard procedures after randomization

- Patients in the NCPAP group will start CPAP with an initial pressure of 6 cm H_2O, while patients in the NIPPV group will be applied 6 cm H2O pressure, 15-20 cm H_2O peak inspiratory pressure, and NIPPV at a rate of 20-30 per minute.
- In both groups, the surfactant will be administered at a dose of 200 mg / kg / dose through a special catheter named Lisacath, by visualizing the vocal cords by the responsible and experienced physician in each center.
- In cases with fractional inspired oxygen FiO_2 >0.3, the second dose of surfactant will be administered within the first 12 hours at least 6 hours after the first dose.
- "Study Algorithm" is presented.
- Data such as possible adverse effects, complications related to the procedure, prenatal, natal and postnatal demographic characteristics, need for repeat dose surfactant, intubation requirement and time, follow-up NCPAP / NIPPV settings will be recorded.

Baseline/Screening Visit 1 (-14 to -1 days from day 0)

The following procedures will be performed at the Baseline/Screening visit:

- Review the study with the subject and obtain written informed consent
- Review and record antenatal and postnatal medical history to determine eligibility based on inclusion/exclusion criteria
- Record demographics
  - Maternal
    - Maternal age
    - Preeclampsia
    - Diabetes
    - Antenatal steroid
    - Drugs
    - Chorioamnionitis
    - Premature rupture of membranes
    - Caesarian or normal vaginal delivery
    - Multipl pregnancy
  - Neonatal

  - Gestational age (week)
  - Birth weight (gram)
  - Apgar scores
  - Gender
- Perform physical examination
- Record settings of ventilation
  - NCPAP group: Positive end expiratory pressure (PEEP), FiO_2
  - NIPPV group: Peak inspiratory pressure (PIP), PEEP, FiO_2 , rate, flow.
- Record blood gas analysis

Surfactant treatment

- Surfactant preparation, standard Curosurf® will be applied at a dose of 200 mg / kg and a special catheter Lisacath® as standard
- Surfactant application with the LISA method, which is routinely used in the world and in our country, was well tolerated in most cases. Although sudden decreases in heart rate for less than 10 seconds can be seen in approximately half of the cases during surfactant administration by LISA method, such short-term changes in heart rate are not considered harmful for the baby. In current studies, problems such as airway damage or damage to the vocal cords have not been encountered. The treatment team will apply treatments that will reduce pain and eliminate possible discomfort when necessary.
- Surfactant reflux may occur during less invasive surfactant application.
- Surfactant reflux will be scored according to the status of reflux in the catheter, in the mouth and in the nose.

Visit 2: (1st hours after surfactant treatment)

- Record settings of ventilation
  - NCPAP group: PEEP, FiO2
  - NIPPV group: PIP, PEEP, FiO2 , rate, flow.
- Record blood gas analysis

Visit 3: (4st hours after surfactant treatment)

- Record settings of ventilation
  - NCPAP group: PEEP, FiO2
  - NIPPV group: PIP, PEEP, FiO2 , rate, flow.
- Record blood gas analysis

Visit 4: (7nd days)

- **Neonatal outcomes 1**
  - Need of mechanical ventilation and entubation, time of entubation
  - Need of repeat surfactant treatment

Visit 5: (Postnatal 36 gestational week))

- Type of respiratory support
  - NCPAP
  - NIPPV
  - Mechanical ventilation
  - Head box oxygen
  - No resiratory support

Visit 6: (discharge date)

- **Neonatal outcomes 2**
  - Duration of total NCPAP, NIPPV, entubation and oxygen
  - Intraventricular hemorrhage
  - Bronchopulmonary dysplasia
  - Necrotizing enterocolitis
  - Retinopathy of prematurity
  - Sepsis
  - Advers events

Unscheduled Visit

The following procedures will be performed if the subject presents to the clinic at any other time point not specified above

- Assess for adverse events
- Assess for complications following treatments

RANDOMIZATION

- Patients who are hospitalized in the neonatal intensive care unit (NICU) due to RDS within the first 6 hours of life, and who are indicated for non-invasive surfactant administration (LISA) due to their spontaneous breathing, will randomized as **NCPAP or NIPPV**.
- Randomization will be done automatically over the Turkish Neonatal Society Trials Network system, without being user dependent.

- When entered into the system, each patient will be given a number, and each center will be able to enter their own patient's data.

SAMPLE SİZE JUSTIFICATION

With the power analysis performed for the study, the number of samples required to determine a 15% difference in terms of going to mechanical ventilation between both groups was calculated as 170, with a power of 80% for each group. In the study, 15% of the difference in babies 26 weeks and younger; Under the assumption that the difference will be 10% for babies older than 26 weeks, it is planned to have babies aged 26 weeks and younger than 26 weeks equally in each group.

STATISTICAL ANALYSIS PLAN

Primary Endpoint

Need of mechanical ventilation first 72 hours in life

Secondary Endpoints

Development of bronchopulmonary dysplasia and other prematurity-related morbidity

All analyses will be performed using per-protocol population as well as intention-to-treat population.

ASSESSMENT OF SAFETY

Adverse events (AE) will be monitored and collected by the study team For each AE, a detailed explanation will be obtained from the subject and subject's medical record. All AEs will be recorded on the CRFs.

Definition of Severe Adverse Event (SAE)

An AE is defined as any unanticipated medical occurrence regardless to relationship of the investigative arm of the trial.

- Death
- Prolong hospitalisation

Relationship to Study Products

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical

judgment. The degree of certainty about causality will be graded using the categories below.

Definitely: The relationship of the AE and the study device or the study procedure can definitely be established.

Probably: While a clear relationship to the study device or to the study procedure cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.

Possibly: There is no clear relationship between the AE and the study device or study procedure; however, one cannot definitely conclude that there is no relationship.

Unrelated: There is no relationship between the AE and the study device or study procedure.

SAE Reporting

In the case of a SAE, the Investigator must notify the Sponsor within 1 working day after the Investigator first learns of the event.

DATA MONITORING

Study data will be collected electronically via “Turkish Neonatal Society Trials Network System”. The Principal Investigator will be responsible to ensure the study is conducted in accordance with the protocol, applicable regulatory requirements, and that the data recorded is valid. To achieve this objective, the study will be continuously monitored and reviewed on a monthly basis by the study team.

DATA HANDLING AND RECORD KEEPING

Study data will be collected electronically via “Turkish Neonatal Society Trials Network System”. Only study personnel will collect data. Data will be exported into Excel file format (password protected), which will then be used for data analysis. Only de-identified data will be used for data analysis. All documents will be shredded within five years after completion of the study upon Sponsor approval

CONSENT PROCESS

Each potential issue must provide written consent with complete information on the procedures involved. the informed consent must be fully disclosed by the Researcher or study staff, including the purposes, methods, benefits, and risks of the trial, and signed by the subject prior to participation in the study. Potential issues will be informed that participation in the study is optional and can be withdrawn at any time. The parents will be told that choosing to participate will not affect the care received for treatment. Parents will be informed that they will allow research staff to access confidential medical records. The subject will be given sufficient time to read the confirmation and ask any questions. Once the informed consent has been signed, the parentswill be given a copy of the document.

LAWS AND REGULATIONS

This study was approved by the “Uludag University Faculty of Medicine Clinical Research Ethics Committee” and Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency. This clinical study will be conducted in compliance with all national laws and regulations as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

PUBLICATION AND DATA SHARING POLICY

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions.

STUDY PERSONNEL AND ROLES

Hilal Ozkan, MD	Uludag University	Study Coordinator, Principal investigator	Responsible for all study related issues Data collection; screen, consent, randomize, and follow up with subjects
Nilgun Koksal, MD	Uludag University	Co-investigator	Data collection; screen, consent, and follow up with subjects
Fatma Kocael	Uludag University	Co-investigator	Data collection; screen, consent, and follow up with subjects
Eren Ozek, MD	Marmara University	Principal investigator	Data collection; screen, consent, randomize, and follow up with subjects
Hülya Ozdemir, MD	Marmara University	Co-investigator	Data collection; screen, consent, and follow up with subjects
Sinem Gulcan Kesrin	Marmara University	Co-investigator	Data collection; screen, consent, and follow up with subjects
Esin Koç, MD	Gazi University	Principal investigator	Data collection; screen, consent, randomize, and follow up with subjects

Canan Turkyılmaz, MD	Gazi University	Co-investigator	Data collection; screen, consent, and follow up with subjects
İbrahim Hirfanoğlu, MD	Gazi University	Co-investigator	Data collection; screen, consent, and follow up with subjects
Saadet Arsan, MD	Ankara University	Principal investigator	Data collection; screen, consent, randomize, and follow up with subjects
Omer Erdeve, MD	Ankara University	Co-investigator,	Data collection; screen, consent, and follow up with subjects
Emel Okullu, MD	Ankara University	Co-investigator,	Data collection; screen, consent, and follow up with subjects
Merih Cetinkaya, MD, PHD	Başakşehir Çam-Sakura City Hospital	Principal investigator	Data collection; screen, consent, randomize, and follow up with subjects
Beril Yaşa, MD	Başakşehir Çam-Sakura City Hospital	Co-investigator	Data collection; screen, consent, and follow up with subjects
İlker Gönen	Başakşehir Çam-Sakura City Hospital	Co-investigator	Data collection; screen, consent, and follow up with subjects

CONFLICTS OF INTEREST

No conflicts of interest have been reported.

APPENDIX

Visit	**Screening/Baseline -14 to -1 day from 0 day**	**Treatment hour 0**	**Treatment hour 1**	**Treatment hour 4**	**Postnatal 7 day**	**Postnatal 36 GW**	**Discharged**	**Unscheduled Visit**
Informed Consent								
Assign subject ID								
Medical History								
Concomitant Meds Physical Exam								
Inclusion/ exclusion criteria								
Randomization								
Bloog gas analysis								
AE /complication								