SHARP Mary Birch Hospital for Women & Newborns

INFORMED CONSENT

A Multicenter, Randomized Trial of Preterm Infants receiving **Ca**ffeine and **L**ess **I**nvasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

IRB #
1911902

Consent Date
06Aug2020 v1.2

Principal Investigator

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SHARP Mary Birch Hospital for Women and Newborns
3003 Health Center Drive, San Diego, CA 92123

Research Grant

Chiesi Farmaceutici S.p.A.

If you are serving as a legally authorized representative, a guardian or are providing parental permission for a child in this study, the terms "you" and "your" refer to the person for whom you are providing consent or parental permission.

CALIFORNIA EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in an experimental procedure. Before you decide whether you want to participate in the experimental procedure, you have a right to:

1. Be informed of the nature and purpose of the experiment;

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;

3. Be given a description of any discomforts and risks reasonably to be expected from your participation in the experiment;

4. Be given an explanation of any benefits reasonably to be expected from your participation in the experiment;

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to you, and their relative risks and benefits;

6. Be informed of the avenues of medical treatment, if any, available to you after the experimental procedure if complications arise;

7. Be given an opportunity to ask any questions concerning the medical experiment or the procedures involved;

8. Be instructed that consent to participate in the experimental procedure may be withdrawn at any time and that you may discontinue participation in the medical experiment without prejudice;

9. Be given a copy of this form and the signed and dated written consent form; and

10. Be given the opportunity to decide to consent or not to consent to the medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on your decision.

I have carefully read the information contained above and I understand fully my rights as a potential subject in a medical experiment involving people as subjects.

Signature of Parent or Legally Authorized Representative	Printed Name	Date

Sharp HealthCare Institutional Review Board
APPROVED
12Aug2020

PARTICIPATION IN A RESEARCH STUDY

This is a research study. The purpose of a research study is to answer scientific questions. We are asking for your permission to have your baby participate in a research study so that we can learn new information that may help others in the future. Research is not the same as routine treatment or medical care.

Your participation is voluntary. You do not have to allow your baby to be in this study. You are free to say yes or no, or to allow your baby to drop out after joining. If you decide not to participate there is no penalty or loss of benefits. Whatever you decide, your baby's regular medical care will not change.

This process is known as the informed consent process. It is important that you read this consent form and ask the study doctor any questions you may have. Please take your time to make your choice. Discuss it with your friends and family.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

Your baby has been chosen because he/she may be born prematurely with immature lungs and a lack of natural lung surfactant, a fluid that coats the lungs and help them remain open. Due to this condition, your baby may not breathe well at birth or in the first days after birth and may benefit from receiving surfactant medicine or continuous airway pressure to help your baby's lungs remain open and improve oxygenation. Both Surfactant administration and continuous positive airway pressure (CPAP) are currently standard treatments for premature infants that need respiratory support after delivery.

Surfactant administration traditionally involves inserting a breathing tube in your baby's airway (intubation) and placing them on a breathing machine for respiratory support. Continuing on a breathing machine for a long period of time increases your baby's chance of developing bronchopulmonary dysplasia (BPD), a chronic lung disease of the neonate. Delivery room resuscitation of very premature infants has evolved dramatically over the past decades. Optimizing the care of these newborns now involves early continuous positive airway pressure (CPAP) and the avoidance of mechanical ventilation. However, mechanical ventilation is still often used when administering surfactant as the need arises.

The LISA method (Less Invasive Surfactant Administration) is another method that involves using a small catheter to administer surfactant directly into a baby's lungs. It also involves administering a precautionary dose of surfactant, compared to the traditional method which only administers doses of surfactant as needed using the breathing tube. A recent study in Europe showed that the Less Invasive Surfactant Administration (LISA) method had the lowest risk for the development of bronchopulmonary dysplasia (BPD) when compared to mechanical ventilation. Despite these results showing it decreased the need for mechanical ventilation compared to CPAP alone, there have been no studies done in the United States and the use of the LISA method is still not widely accepted.

We are conducting this study to find out if infants that receive surfactant by the LISA method (study method) compared to early CPAP and mechanical ventilation (standard method) require less intubation and less days on respiratory support.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 180 babies will take part in the study. We will enroll 120 babies at Sharp Mary Birch Hospital for Women & Newborns, 30 babies at Loma Linda University Medical Center, and 30 babies at University of California Irvine Medical Center.

HOW LONG WILL YOU BE IN THE STUDY?

Your baby will be in this study from birth through 2 years of age. We will also collect information about your baby from the 2-year follow-up visit described below.

WHAT IS INVOLVED IN THIS STUDY?

We are asking for your permission to have your baby be in a research study so that we can learn new information that may help other babies.

If you decide to let your baby take part in the current research study and your baby needs support with breathing, your baby will be given CPAP through the nose. If your baby's breathing remains stable, he/she will be randomized (meaning based on chance, like flipping a coin) to either continuing on CPAP or being given a medicine called surfactant. The surfactant medicine is a small volume of liquid that will be placed directly into your baby's lungs using a small catheter (a small flexible tube). This is called the LISA method. This medication helps keep your baby's lung inflated and improves oxygenation.

Your baby will have a 50/50 chance of being placed in either group (CPAP or LISA). After your baby is placed on CPAP or given surfactant, he/she will be carefully monitored.

In either case if your baby needs more help with breathing, your baby's doctor will decide the best way to help support your baby's breathing which may include placement of an endotracheal tube into your baby's airway.

In some cases, your baby may require additional surfactant, if they are not breathing well or continue to need increased support such as additional oxygen. If your baby is in the CPAP group and becomes unwell in this study, your baby's doctor may decide to provide an initial dose of surfactant, and maybe more doses, as needed. This would require insertion of a regular endotracheal breathing tube (if not already placed), which is the current standard practice for providing surfactant.

If your baby is in the LISA group and becomes unwell in this study, your baby's doctor may decide to provide additional doses of surfactant as needed. This will be done by insertion of a regular endotracheal tube.

The procedures of the study are described below. The decision for treatment will be made at the first 5 minutes after your baby's birth.

- The doctor will evaluate your baby's condition at birth. If your doctor determines that your baby needs immediate placement of an endotracheal tube to assist breathing, your baby will not be in the study. Babies who are intubated at birth will not be in the study.

- If your baby is stable and breathing on his/her own with CPAP, he/she will be randomized to either the LISA group with CPAP or CPAP alone. This is done by selecting an envelope which contains a card telling the team which treatment the baby will receive.

During the NICU hospitalization, your baby will be continuously monitored to check the health of your baby's heart, brain and lungs and overall condition. This is normally part of the standard care for preterm babies.

OUTPATIENT FOLLOW-UP

All premature babies are evaluated periodically (at 6 months, then once a year) as part of routine care at the Nemeth NICU Follow-up Clinic during the first 2 years of life. At these visits, the doctors and nurses who work at the clinic will check your baby's health and development. At every visit, they will ask questions about your living arrangements and your baby's medical condition. They will evaluate your baby's development using toys and items that are part of a developmental test. They will do a physical exam and check your baby's muscle strength and reflexes (neurologic exam).

WHAT IS THE RESEARCH PART OF OUTPATIENT FOLLOW-UP?

The research visit is between 22-26 months corrected age (2 years from your baby's original due date). At this visit, the doctors and nurses will do everything listed above that is routine for your infant given their prematurity. The results of the routine evaluation will be obtained as part of our data collection. We will use a study number, not your child's name to ensure confidentiality and anonymity of your medical information.

After that, your baby's involvement will be completed and there are no further study requirements for your baby.

WHAT ARE THE RISKS OF THE STUDY?

Both methods of administering surfactant either by the LISA method or the endotracheal tube are practiced in our NICU. The surfactant used in this trial is our current standard surfactant.

You should note:

- Infants randomized to the LISA group could receive an extra dose of surfactant when they otherwise might not have if they were not part of the study.
- Infants randomized to the CPAP group may receive mechanical ventilation that they otherwise might not have if they were not part of the study
- The catheter used in the LISA method is being used off-label, meaning it is used in a way that is different from the FDA's approved packaging label. It is used intratracheally (into the trachea) rather than intravenously (into the vein).

Risks of surfactant include:

- Low blood oxygen level
- Slow heart rate
- Low blood pressure

Risks of Intra-tracheal catheter:

- There may be risks that are unknown at this time

Risks of mechanical ventilation include:

- Volutrauma- over expansion of the lungs by delivery of too much gas
- Pneumothorax- is a collapsed lung
- Pneumonia- lung infection
- Development of Bronchopulmonary Dysplasia (BPD)- a chronic lung disease that affects premature infants

Based on the current literature to date, there are no increased risks with less invasive administration of surfactant with a small catheter (i.e. the LISA method) compared to endotracheal administration of surfactant in several large European trials. All risks with conducting this study are associated with prematurity including severe IVH, death, retinopathy of prematurity, chronic lung disease and other lung problems such as possible air leaks. There should be no more risks for babies in this study than are possible for any Extreme Low Birth Weight (ELBW) baby needing surfactant therapy. However, as with all research, there may be risks that are unknown at this time.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There may or may not be direct benefits to your baby for participating in this study. We hope the information we learn will help babies with respiratory distress syndrome in the future.

WHAT OTHER OPTIONS ARE THERE?

Your baby's alternative is to not participate in this study and receive treatment of Respiratory Distress Syndrome as prescribed by your personal physician. Your doctor will discuss these alternative treatments with you as well as their benefits and risks.

WILL YOU OR YOUR CHILD BE PAID TO BE IN THIS STUDY?

You and your child will not be paid to be in this study. No additional compensation is available for participation in this study.

WHAT ARE THE COSTS?

The study drug, Curosurf, will be provided for you at no cost by the study sponsor.

There are no additional costs to be in this study. You and/or your health plan/insurance company are responsible for the cost of your baby's hospitalization and standard clinical care provided. You will be responsible for co-pays and deductibles in the same way as outside of a clinical trial.

For more information about your costs, please discuss with the hospital's billing department, or call your health plan/insurance company to find out your financial responsibility for this trial.

RESEARCH-RELATED INJURY

If your baby gets sick or injured in this study, please tell your study doctor. Your baby will be treated or referred for medical treatment. You or your insurance will be responsible for the cost of treatment.

Sharp HealthCare will not provide any compensation for treatment of research related injury or illness.

PAYMENT TO STUDY SITE

CHIESI has provided a grant to Sharp Mary Birch Hospital for Women & Newborns to reimburse the study site for expenses related to the conduct of this study. This includes providing the Surfactant medication your baby may receive while in the study.

NEW INFORMATION

You will be told if any important new information is found during the course of this study that may affect your wanting to continue. If you decide to continue in the study, your study doctor may ask you to sign an updated consent form.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Organizations or individuals that may inspect and/or copy your medical and/or research records for quality assurance and data analysis include groups such as:

- Study Doctor and Research Staff at the Neonatal Research Institute
- Sharp HealthCare Institutional Review Board (IRB, a group of people who review the research to protect your rights)
- The Food & Drug Administration (FDA)

Your information will be coded and stored anonymously in a database with information about other people in this study. Access to this database is limited to the research staff.
Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

As part of this research study you will be asked to sign an additional document, Authorization to use Protected Health Information (PHI). This authorization will explain in further detail how your and your baby's PHI will be used and shared in the study, who will have access to it, what information will be obtained, and how long Sharp HealthCare will use your information. It will also explain what to do if you decide you no longer want to share your PHI, and your rights regarding your ability to see and copy your research information.

If the results of this study are published or presented at meetings, your identity will remain confidential.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Participating in this study is entirely voluntary. You may refuse to allow your baby to participate or withdraw your baby at any time without penalty or loss of benefits to which you or your baby are entitled. If you decide that you no longer want your baby to continue in this study, we encourage you to talk to the study doctor. Please contact Dr. Katheria to tell him you no longer want to participate:

Dr. Anup Katheria
(858) 939-4170
Anup.katheria@sharp.com

If you decide to remove your baby from the study, the study team may ask your permission to keep your baby's test results and information that has already been collected.

WHOM DO YOU CALL IF YOU HAVE ANY PROBLEMS, COMPLAINTS, CONCERNS, OR QUESTIONS?

If you have problems, complaints, concerns, or questions about this study, you may talk to your study doctor anytime.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	858-939-4170 Dr. Anup Katheria 858-939-6307 Neonatal Research Institute
If you get sick or hurt in this study	858-939-4170 Dr. Anup Katheria
Your rights as a research participant and: • Discuss problems, concerns, and questions • Obtain information	Sharp HealthCare Institutional Review Board 7930 Frost Street, Suite 300 San Diego, CA 92123 (858) 939-7195

WHERE CAN YOU GET MORE INFORMATION?

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you or other participants. At most, the web site will include a summary of the results. You can search the web site at any time. The registration identifier for this study is NCT#04209946.

STATEMENT OF CONSENT

Your signature below means that you have read the above information about this study and have had a chance to ask questions to help you carefully consider whether you agree to have your child take part in this study and how your and your child's information will be used.

You can change your mind later if you want to. You will be given a copy of this consent form including a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

You agree to participate in this research study.

_____

Printed Name of Participant (Baby)

_____

SIGNATURE OF PARENT OR LEGALLY AUTHORIZED REPRESENTATIVE **PRINTED NAME** **DATE**

_____

AUTHORITY OF SIGNEE OR RELATIONSHIP TO PARTICIPANT

_____

SIGNATURE OF PRINCIPAL INVESTIGATOR/DESIGNEE **PRINTED NAME** **DATE**

---------- **USE THE FOLLOWING ONLY IF APPLICABLE** ----------

If this consent form is read to the participant because the participant is unable to read the form, an impartial witness not affiliated with the research or study doctor must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant. The participant freely consented to be in the research study.

_____

PRINTED NAME OF IMPARTIAL WITNESS

_____ _____

SIGNATURE OF IMPARTIAL WITNESS **DATE** **TIME**

NOTE: *This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling participants who do not speak English.*

Authorization to Use your Protected Health Information (PHI)

Study Title: A Multicenter, Randomized Trial of Preterm Infants receiving **Ca**ffeine and **L**ess **I**nvasive Surfactant Administration Compared to Caffeine and Early Continuous Positive Airway Pressure (CaLI Trial)

Investigator: Anup Katheria, MD
Neonatal Research Institute
Sharp Mary Birch Hospital for Women & Newborns

Research Grant: Chiesi Farmaceutici S.p.A

Protected Health Information, or PHI, is any personal health information through which you or your baby can be identified. We are asking for your permission to use your baby's PHI in this research study. The information we may use includes maternal (prenatal) data from your baby's record, your baby's present health information, information that can be used to contact you, and results of your and your baby's medical tests. Maternal data will be collected from your baby's medical record; your medical record will be accessed for study purposes. The specific items of information that will be used and disclosed include:

- Maternal (prenatal) information related to the health of your baby, including:
    - Information about mother's pregnancy
    - Fetal History
    - Pregnancy complications
    - Medications for mother
    - Delivery record
- Information from your baby's medical record, including:
    - Medications for baby
    - Results of lab tests
    - Blood gases
    - Respiratory management

- Vital signs
- Diagnoses

The following people will access and use your baby's PHI for the purpose of this research:

- Dr. Anup Katheria, Primary Investigator, Sharp Mary Birch Hospital for Women & Newborns
- Sharp Mary Birch Hospital Neonatologists
- Research Staff at Sharp Mary Birch Hospital for Women & Newborns

Who may see your PHI?

Certain offices and people other than the researchers may look at your medical charts and study records. There may be times when federal or state law requires the sharing of such records. This is very unlikely, but if sharing the information is ever required, Sharp Mary Birch Hospital for Women & Newborns will take steps allowable by law to protect the confidentiality of personal information. If this information is shared with outside reviewers for audit purposes, it may be further shared by them and may not be covered by the federal privacy laws.

Representatives that may review your study records:

- the Sharp HealthCare Institutional Review Board (IRB; a group of people that review the research to protect the rights of research participants)
- the US Food and Drug Administration

How long will the Neonatal Research Institute use your information, and what will it be used for?

- Your and your baby's PHI may be used and shared until December 31, 2044.

The groups above will use your health information:

- To complete this research
- To evaluate the results of the study
- To check that the study is being done properly

What if you change your mind and want to withdraw your authorization for the use and disclosure of your PHI for this study?

You must write to the study doctor and tell him that you no longer want to share your child's information at: Anup Katheria, MD. Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, 3003 Health Center Drive, San Diego, CA 92123.

- Your baby will no longer be a part of the research study because the study doctor, and the research staff will not be able to use any new information about your baby.
- The research team can continue to use any of the PHI that was already collected.
- You and your baby will still get the same medical care that you have always had from Sharp Mary Birch Hospital for Women & Newborns.

Do you have the right to see and receive a copy of your research information?

You can see your research information if:

- It is also being used for your and your baby's current treatment, or
- At the end of the study.

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Authorization:

If you agree to share your and your baby's PHI, you must sign this form below. If you do not sign this form, you and your baby will not be able to participate in this research study. You will be given a copy of this form.

_____

Printed Names of Mother and Baby

_____

Signature of Mother or Legally Authorized Representative | Printed Name | Date

_____

Signature of Father | Printed Name | Date

_____

Authority of Signee or Relationship to Participant