UTHealth Houston

Bilirubin Neurotoxicity (BN) and Neurodevelopmental Impairment (NDI) in Extremely Preterm (EP) Infants: Avoidable by Reducing the Usual Intravenous Lipid (UL) Administration?

NCT04584983

Version Date: 07/28/2023

PARENTAL PERMISSION TO TAKE PART IN RESEARCH

Simple Study Title: Reduced versus Usual Lipid Study for Small Premature Infants

Full Study Title: Bilirubin Neurotoxicity (**BN**) and Neurodevelopmental Impairment (**NDI**) in Extremely Preterm (**EP**) Infants: Avoidable by Reducing the Usual Intravenous Lipid (**UL**) Administration?

Principal Investigator: Lindsay Holzapfel, MD, MS
Department of Pediatrics, Division of Neonatology, UTHealth Houston

Study Contact: Lindsay Holzapfel, MD, MS Principle Investigator [redacted]
Research Nurse Team [redacted]

The purpose of this study is to determine if the usual nutrition given to premature newborns might cause a problem that has not been recognized or appreciated. Specifically, it may be that the usual amount of intravenous ("IV") fat (lipid) results in higher levels of a substance (unbound bilirubin) that injures the brain if toxic levels are reached. This study compares blood levels of fat and unbound bilirubin and weight gain in premature newborns who either get the usual amount of IV fat or get a reduced amount of IV fat during the first 2 weeks after birth. If you choose to allow your child to take part in this study, your child will be assigned randomly (like a coin flip) to the usual IV fat or reduced IV fat group, and provide up to a maximum of 2 ml of blood (less than ½ teaspoon) over 1-2 weeks that will be collected during routine blood draws. There will be a painless hearing screen called at BAER prior to discharge and a developmental evaluation at 2 years of age.

There are potential risks involved with this study that are described in this document. Some known risks include potential slower weight gain and loss of confidentiality. There may be potential benefits to your child such as lower level of unbound bilirubin with reduced risk of brain injury and contributing to improvement in babies' health in the future.

The alternative to taking part in this research study is not participating in this study and receiving usual amounts of IV fat as part of usual care.

Participation in this research study is voluntary. You may choose not to allow your child to take part in this research study or may choose to leave the research study at any time. Your decision will not affect the clinical care your child receives at the University of Texas Health Science Center at Houston (UTHealth Houston) or Memorial Hermann Health System.

If you are interested in participating, please continue to read below.

What is the purpose of this research study?
Very small and premature babies have limited energy reserves and are unable to eat by mouth like a term baby. Because of this, very small and premature babies are given a concentrated diet through an IV. This diet contains protein, carbohydrate, and fat to help babies grow. Lipids

UTHealth Houston
IRB NUMBER: HSC-MS-20-0916
IRB APPROVAL DATE: 07/28/2023

(IV fat source), like the name brand Intralipid, are recommended in babies born before 28 weeks and are widely used. More fat helps you grow faster, but doctors are concerned that a higher fat diet may cause more serious and lasting problems. Doctors are worried that higher fat diets in very small and premature babies may lead to higher levels of a toxic substance called unbound bilirubin that can cause brain damage if the levels become too high. When fat breaks down in the body, it divides into small building blocks called free fatty acids. These free fatty acids are carried by a protein called albumin, which is the same protein that carries the bilirubin. Bilirubin is harmless when it is attached (bound) to the albumin protein, but potentially toxic when it is free (unbound). When there is too much fat in the diet, this increases the free fatty acids which can push bilirubin off the albumin protein, causing unbound (free) bilirubin levels to rise, potentially to dangerous levels.

The purpose of this study is to see how well reduced amounts of IV fat works at providing premature infants less than 28 weeks gestational age with appropriate nutrition for growth while reducing the risk for high levels of toxic unbound bilirubin. This study will test the safety of a reduced dosing of Intralipid (brand name for the IV lipid used in this study). This dosing is within the normal range of practice for premature infants' nutritional needs.

A description of this clinical trial (NCT 04584983) will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This will not include information that can identify your child. After the study has ended, website will include a summary of the results. You can search this website at any time.

Who is being asked to take part in this study?
You are being asked to allow your child to take part in this research study because your child is less than 27 weeks' gestation by best obstetric estimate or less than 751 grams birth weight and is enrolled in the NRN Cycled Phototherapy Trial. This study is being conducted at UT Health, Texas currently, with plans to expand to multiple sites in California and Alabama. About 80 babies will take part in the study worldwide including up to 175 babies at UTHealth Houston, Memorial Health System.

What will happen if your child takes part in this study?
As part of normal care for small babies, Intralipid will be started for your baby around 24 hours after birth. If you agree to have your baby take part in the study, he/she will receive Intralipid in one of two ways: 1) usual dose as if he/she were not part of the study, or 2) a reduced dose, which is half the usual dose. Doctors do not know which method is best. Which way your baby receives Intralipid during the study is based on chance (like a flip of the coin).

As part of your baby's usual care, the bilirubin levels in your baby's blood are tested each day for his/her first 7 days of life (days 1 to 7) and when needed during the next 7 days (days 8 to 14). If your baby is given Intralipid and the level rises more than expected, your baby's doctor will decrease or stop Intralipid until the level falls. Research nurses will record the daily bilirubin level and Intralipid dose.

When your baby is about a month before his/her due date or is close to going home, your baby will have a special test similar to the routine hearing screen all premature babies get. However, this test is more detailed, and it decides if the speed that your baby's brain responds to sound is affected by the phototherapy treatment or the bilirubin level in the blood. This test will be done when your baby is asleep or quiet. Three sensors like the heart rate sensors that

are on your baby's chest will be placed on your baby's head. Earphones will be placed over your baby's ears. Your baby will hear clicking sounds, and a machine will record your baby's brainwave responses to the sounds. This hearing test is not painful.

By agreeing to take part in this study you consent to the use of information from medical records from the hospital and from UT-Houston outpatient clinic visits. Information collected from the medical record to include maternal pregnancy-related information, infant delivery information, infant nutrition, infant outcomes, and hospital course. Also, we will use information from UT-Houston outpatient clinic visits, including information recorded to evaluate the mental and physical health of children born prematurely, in this study. This information will be pooled (mixed) with other patients' information such that individual patient anonymity (privacy, confidentiality) will be protected. (See Confidentiality section, below).

If you allow your child to take part in this study your child will be randomized (similar to flipping a coin) to receive reduced Intralipid dose or usual Intralipid dose. It is not known whether a reduced dose of Intralipid will be of benefit. For this reason, some study participants must receive a placebo. This will allow a careful comparison to study the benefits and side effects of the different dosing of Intralipid on bilirubin levels. There is a 50% chance your child will receive reduced dose and a 50% chance that your child will receive the usual dose of Intralipid. Neither you, your child nor your doctor will know if your child is receiving reduced or usual dose Intralipid dose, as both will look the same.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your child's safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

Your child will have less than 1/10th of a teaspoon of blood drawn from a vein in his or her arm for 6 times. The total amount of blood withdrawn during your child's participation will be about 4/10th of a teaspoon for the entire study duration.

How long will your child be in the study?

If you agree to take part in this study, your baby will be followed throughout their time in hospital until discharge. The hearing test at 36 weeks corrected age (approximately 4 weeks prior to your full-term due date), will take about 30 to 60 minutes. If your baby is fussy or wakes up in the middle of the test, then it might need to be repeated on another day.

There is no time commitment after going home from the NICU that is specific to this study. However, because information taken during scheduled visits to UT-Houston outpatient clinics will be used in this study, members of our research team may contact you to remind you of scheduled appointments. Some of these clinic visits might include developmental testing that takes 2-4 hours.

What choices does your child have, other than this study?

This study is voluntary. If you choose not to have your baby take part in the study, he/she will continue to receive routine care. Usual dose Intralipids are likely to be included in routine care to provide energy for your baby and routine monitoring of bilirubin levels.

What are the risks of taking part in this study?
There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

If you choose to allow your child to take part in this study, there is a risk that the reduced Intralipid dose may not be as good as the usual Intralipid dose in reduction of toxic bilirubin levels.

Some of the most common side effects that the study doctors know about are:
- Poor weight gain
- Loss of confidentiality

Some of the less common side effects that the study doctors know about are:
- Discomfort from blood sample collection

There may be some risks that the study doctors do not yet know about.

What are the benefits to taking part in this study?
There may be no benefit to your baby from taking part in this study. If your baby receives Intralipid at usual dosing, he/she would receive the same care he/she would if he/she were not in the study. There are no direct benefits from being in the optional study; however, your baby taking part may benefit other babies in the future.

Can you stop taking part in this study?
Your decision to take part in this study is completely voluntary. You have the right to choose not to take part or to withdraw your baby from the study at any point in this study without affecting your baby's future health care or other services to which you are entitled. You may withdraw by calling Dr. Lindsay Holzapfel at [redacted].

Although unlikely, your baby's doctor or the PI may remove your baby from the study without your permission if your baby's doctor or one of the investigators decides that taking part in the study could be harmful to your baby or for some other unforeseen reason.

What happens if your child is injured during the study?
We hope this study increases the safety of the Intralipid and bilirubin monitoring your baby receives. You, all members of the members of the research team, and the Committee for the Protection of Human Subjects will be told if your baby unexpectedly suffers an injury as a result of taking part in this research study. Please know that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment, and professional services will be available to your baby, just as they are to the community in general. If you are concerned that your baby has been injured by taking part in the study, you should call Dr. Lindsay Holzapfel at [redacted] and to the Committee for the Protection of Human Subjects at [redacted].

What are the costs of taking part in this study?
It will not cost you anything for your baby to be in this study. You and/or your health care provider will be responsible for covering your baby's hospital costs, doctor's fees, and medicine. This study will not refund you for these routine medical care costs. If you get a bill that you

believe is related to taking part in this research study, please call Dr. Lindsay Holzapfel at [redacted].

How will privacy and confidentiality be protected?
Your child's privacy is important and your child's participation in this study will be kept confidential. However, absolute confidentiality cannot be guaranteed.

Information about what the doctors learn from this study may be published or given to other people doing research, but neither your name nor your baby's name will be used. Information gathered on your baby as part of this study will be part of his/her medical record and will otherwise be confidential to the extent permitted by law. The Fluoresprobe Laboratory in San Diego, California will only have access to the study number assigned to the baby and the bilirubin test results. The University of Texas at Houston McGovern Medical School and Stanford Medical School have secure databases and computers order to reduce the risk of loss of confidentiality.

People who receive your child's health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect your child' health information and may share your child's information with others without your permission, if permitted by laws governing them. Your child will not be personally identified in any reports or publications that may result from this study. If all information that does or can identify your child is removed from your child's health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

Representatives of the organizations listed below will see your child's name and other personal identifiers when they review your child's research records and medical records for the purposes of verifying study data:

- Representatives of UTHealth Houston and Memorial Hermann Health System
- Members of the research team reviewing the data in this study to make sure the participants are safe and the research data is reliable.

Unidentified study data (information without name or date of birth) may be shared with researchers inside and outside the University according to the NIH public access policy. NIH's public access policy requires scientists to submit final peer-reviewed journal manuscripts arising from NIH funding to be placed on PubMed immediately upon acceptance for publication.

Please note that you do not have to sign this Authorization, but if you do not, your child may not participate in this research study. UTHealth Houston and Memorial Hermann Health System may not withhold treatment or refuse treating your child if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about your child as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must contact Dr. Lindsay Holzapfel at [redacted].

This Authorization will expire 15 years after the end of the study.

New Information
You will be informed of any new information that may change your mind about participating in this study. The results of this study will be available after the research article is published. You can get those results from Dr. Lindsay Holzapfel at [redacted].

Whom can you contact if you have questions about the study?
If you have questions at any time about this research study, please feel free to contact the Dr. Lindsay Holzapfel (Principle Investigator) at [redacted], or study coordinator and research nurses at [redacted] as they will be glad to answer your questions. You can contact the study team to discuss problems, report injuries, voice concerns, obtain information in addition to asking questions about the research.

The Committee for Protection of Human Subjects at the University of Texas Health Science Center has reviewed this research study. You may contact them for any questions about your rights as a research subject, and to discuss any concerns, comments, or complaints about taking part in a research study at [redacted].

Contact after registration
To contact you after your baby's hospital stay, we will ask for your contact information, including your home address, home and cell phone numbers, email address, and permission to use the pages. search engines and public Internet social networks (such as contacting you on Facebook or getting your current address from the county tax office). The 24-month age-adjusted visit is the end point of the study; However, we would like your permission to remain in contact with you and your baby beyond this time in case the study analysis shows a need / opportunity for additional follow-up.

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to allow your child to take part in this research study. Make sure that all your questions have been answered. If you decide to allow your child to take part in this research study, a copy of this signed consent form will be given to you.

_____
Name of Child

Name of Parent/ Guardian	Relationship to Child	Signature	Date

Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

Contact: Lindsay Holzapfel, MD
Telephone: [redacted]