Permission to Take Part in a Human Research Study

Study Title: Topiramate for infants receiving whole body cooling in neonatal encephalopathy

NCT01765218

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Title of research study: Topiramate for infants receiving whole body cooling in neonatal encephalopathy

Participants in medical experiments have specific rights. The following are your rights as a Parents if agree to have your baby join this study:

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits your baby might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications. Whether or not your baby takes part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose to have your baby not take part.
- You can agree to have your baby take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to all your baby to take part, you will be given a signed and dated copy of this document**.**

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Title of research study: Topiramate for infants receiving whole body cooling in neonatal encephalopathy

Investigator(s): MD, Kristin Hoffman MD, Catherine Rottkamp MD, PhD, Jaskiran Ranu MD, Lida Zeinali MD, Pranav Garlapati MD, Jessica Vaughn MD, Shoshana Newman-Lindsay MD,Peggy Chen MD, Ziad Al-Hassen MD

Study Contact Information

Medical emergency	Call 911		
Questions, complaints, possible injury or harm – during business hours (specify, e.g. Monday to Friday, 8 am to 5 pm)	Research team: Ranu, Hoffman, Rottkamp, Neonatal Fellows	Phone#: 9167033050	Email: jkranu@ucdavis.edu
Questions, complaints, possible injury or harm – after business hours, on weekends and holidays	UCDHS Operator	(916) 734-2011	Ask for: Neonatal ICU and to speak with a Neonatology Fellow in House
Question about your rights or if you want to speak to someone who is not part of the research team	Institutional Review Board (IRB)*	(916) 703-9151	HS-IRBEducation@ucdavis.edu

**The IRB is a group of people who oversee research involving humans as participants.*

You are being asked to take part in this study because you have a newborn child with perinatal depression or neonatal encephalopathy who will receive whole body cooling upon admission to our NICU.

We hope to learn more about perinatal depression, epilepsy and neonatal encephalopathy. Perinatal depression is a sign of poor brain function in the newborn shortly after birth that can be caused by many things one of which is neonatal encephalopathy. Neonatal encephalopathy is reduced blood and oxygen supply to the brain of a baby and can appear as over-activity, startling easily, floppiness, extreme sleepiness, coma, abnormal movements, reflexes or seizures. These are very serious problems for newborn babies and can lead to handicap and/or even death.

We know that whole body cooling helps these babies; this procedure is used at UC Davis and nationwide. However, many babies still have problems and do poorly. Many of these infants develop seizures and a third of the surviving infants develop moderate or severe neurological disabilities.

This study examines whether administration of an antiepileptic drug called topiramate helps babies with neonatal encephalopathy who receive whole body cooling. Topiramate is a drug that might limit damage to the brain while still letting the brain develop normally. However, it is not known whether it will really help babies with perinatal depression or neonatal encephalopathy.

The purpose of this research study is to find out whether topiramate will help babies with perinatal depression or neonatal encephalopathy, and whether it will reduce seizures (convulsions), quicken the recovery from perinatal depression/ neonatal encephalopathy, or improve long-term development. We also want to see whether a urine test called S100ß (marker for brain cell damage in the urine) and a blood test of UCHL1 (marker for brain cell damage in the blood) will help us identify babies who are at more risk of seizures or poor development. S100ß and UCHL1 are released from damaged brain cells and may let us see which babies might be at highest risk in the future.

General information about this research:

- Participants will be in this study as long as the following:
    - You as Parents will be asked to have your baby participate for a period of 5 days in which the study drug/Topiramate or placebo is administered. You and your baby are also expected to come to our clinic for 1 hour follow up neurodevelopmental test when your baby is 9, 18 and 27 months old. Participation in this study will not change the period of admission to our NICU and follow ups because infants with neonatal encephalopathy are usually in the hospital for several weeks and are all eligible for follow outpatient clinic visits.
- The main risks of participation include the following:
    - Every baby taking part in the study will be watched carefully for any side effects. However, the Researcher may not know all the side effects or risks. Side effects may be mild or very serious. The Researchers may give the baby medicines to help lessen side effects. Many side effects go away soon after the baby stops taking the drug. In some cases, side effects can be serious, long lasting, or may never go away.
    - Side Effects:
        1. Increased risk of infection- viral infection, upper respiratory infection, bronchitis, pharyngitis, rhinitis, otitis media
        2. Cough
        3. Bronchospasm
        4. Fever
        5. Diarrhea
        6. Vomiting
        7. Weight decrease
        8. Renal Issues- increased creatinine (measure of kidney function), BUN (measure of kidney function), and decreasd potassium (electrolyte)
        9. Metabolic Acidosis (also a side of effect of whole body cooling)
    - Risks and side effects related to the minimum clinical dose of topiramate administered in this study are minimal. Topiramate may cause changes in the acid level in your baby's blood. However, these are checked for very carefully in all babies getting whole body cooling whether or not they are getting topiramate. If these changes happen, they are relatively easy to treat and many babies getting whole body cooling need these types of treatment whether or not they are getting topiramate. The extra amount of blood to be taken (less than 3 teaspoons) is small and much less than is needed to be taken for routine tests. It should not affect your baby. The urine collection involves using a cotton ball to collect the urine from the diaper area. It is safe, and should not affect your baby.

- There may also be risks to your privacy. The Researchers will store study records and other information about you in a secure location and will grant access only to those who need to know and are involved in this research study. However, just like with other personal information kept by your health care providers, your banks, and others, even these safeguards cannot guarantee absolute protection of the data. If private information gets into the wrong hands, it can cause harm. Although rare, there are reported cases of breaches that have resulted in discrimination in insurance or employment.
- For more information about risks and side effects please ask the Researcher.

- You will not receive results of the procedures and tests performed on you as part of this research.
- You will not be compensated for participating in this research.
- Participation in this research is voluntary.
- During the study, we will tell you about any new information that may affect the baby's health, welfare or the Parent's choice to stay in the research.
- We cannot promise any benefits to your baby or others from your taking part in this research. However, the information from this study may help children with this condition in future.

The following are the drugs you may receive during this research:

If you as Parents allow your baby to be in this study, your baby may receive topiramate an anti-epileptic medication or a placebo.

Topiramate is considered investigational in this study because the U.S. Food and Drug Administration (FDA) has not been approved this drug for use in patients with perinatal depression or neonatal encephalopathy. Topiramate is approved for use in patients with epilepsy. Topiramate will be given 5mg/kg daily enterally for a total of 5 doses. Parents or your baby's insurance company will not be charged for the test drug.

The risks of the drug described can be found above.

How your baby will be assigned to either receive the study drug vs the placebo:

The treatment the baby will get will be chosen by chance, like flipping a coin or drawing a number out of hat. Your baby has a 50/50 chance of getting each treatment. The study team and you will not and cannot choose which treatment you will get. The study doctor and you will not know which treatment your baby is receiving.

The following procedures will be done for this research:

If your baby takes part in this study, you as Parents will be asked to read and agree with the following: Parts of this study involve standard medical care. Standard care being what is normally done to prevent, diagnose, or treat a certain condition or illness. Other parts of this study involve the study drug or placebo.

The following procedures are part of standard of care and will be done if whether or not your baby qualifies for the study.	**The following procedures WILL ONLY BE DONE IF YOUR BABY JOINS THE STUDY:**
• Whole body cooling - your baby will be looked after on a cooling blanket that will lower their temperature to 33.5°C (92.3 degrees Fahrenheit) for 72h. After this your baby will be slowly rewarmed back to a normal temperature • Continuous monitoring of your baby's brain wave activity to look for seizures (aEEG/cEEG) for 3-5 days by electrodes placed externally on the head • Vital signs - will be measured constantly for at least the first 4 days • Blood gases - will be measured every 6h (unless your Doctor thinks more or less frequent measurements are needed) • Blood chemistry- will be measured every 24h (unless your Doctor thinks more or less frequent measurements are needed) • Blood glucose - will be measured every 6h (unless your Doctor thinks more or less frequent measurements are needed) • Blood calcium - will be measured every 6h (unless your Doctor thinks more or less frequent measurements are needed) • Blood count (Hemoglobin etc)- will be measured every 24h (unless your Doctor thinks more or less frequent measurements are needed) • Blood clotting - will be measured every 24h (unless your Doctor thinks more or less frequent measurements are needed) • Brain scan - an MRI will be carried out at 5-7 days of age to look for signs of	• Your baby will be randomized to get a solution orally once a day for five days. The solution will either be topiramate or placebo. • A small amount of extra blood (about 1/2 teaspoon) will be taken three times to measure a special protein (UCHL1) that may detect brain injury. This blood will be taken at the same time as your baby needs a routine blood test. • A small amount of extra blood (less than 1⁄2 teaspoon) will be taken three times to measure the level of topiramate in your baby's blood. This blood will be taken at the same time as your baby needs a routine blood test. • A small amount of urine (1 to 3 teaspoons) will be collected from a cotton ball in your baby's diaper to measure a special protein (S100B) three times during the study.

damage to the brain Developmental assessment - your baby will get his/her development check at 9, 18 and 27 months of age to see how they are doing.	

You or your health plan will be billed for the costs of routine medical care you receive during the study. These costs may include operating room fees, pharmacy charges, treatments, hospitalization, scans, etc. You will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered. Only the costs of research or experimental procedures will be paid by the study.

Alternatives to joining this research include:

Instead of being in this research study, your choice as Parents will be to have your baby undergo our standard protocol for perinatal depression or neonatal encephalopathy – whole body cooling without the drug or placebo being given.

Information about the confidentiality of the information collected:

Information will be collected about your baby for purposes of this research. The research records and the baby's medical records may be looked at by the sponsor of this study and agents of the sponsor, the FDA, other government agencies and other groups associated with this study. More information about who will have access to your baby's records is found in Appendix 2 and 3.

Federal law provides protections of your baby's medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/compliance/pdf/notice.pdf).

Reasons your baby may be removed from this research.

Your baby will be ineligible if they have major medical conditions from birth. If the baby had a proven (i.e. electrically confirmed seizure) prior to enrollment they would not be eligible for the study. If a seizure occurred after enrollment/ randomization but before the first dose of study medication the protocol would continue based on the intention to treat.

Treatment of seizures will be guided by our Pediatric Neurologists (who will be unaware of treatment assignment). Currently we do not use study drug topiramate as first-line treatment for seizures, and do not intend to change our management of seizures in the foreseeable future.

If your baby develops seizures during the study he or she would receive our current standard of care, but will continue to be in the study. If your baby develops any issues with their kidneys or liver they will not be eligible for the study.

Participation in research is voluntary

You as Parents may decide not to have your baby take part in this research or you can leave the research at any time and you will not be penalized or lose benefits that your baby is entitled to receive. You should contact the research team to discuss how your baby can safely leave the study. If you leave the study, data that

has already been collected about your baby will remain in the research database. The research team may ask you if they can continue to collect data from your baby's routine medical record.

Signature Block for Research Involving Children Requiring Parental Consent

Do not sign this document until you have read the consent document and any appendixes (or the document and appendixes have been read to you) and your questions have been answered. Your signature documents your permission for the named child to take part in this research.

Note: Investigators are to ensure that individuals who are not parents can demonstrate their legal authority to consent to the child's general medical care. Contact legal counsel if any questions arise.

Printed name of child

Signature of parent or individual legally authorized to consent to the child's general medical care

Date

- ❑ Parent
- ❑ Individual legally authorized to consent to the child's general medical care and to authorize the release of Personal Health Information (See note below)

Printed name of parent or individual legally authorized to consent to the child's general medical care

Signature of parent

Date

Printed name of parent

If signature of second parent not obtained, indicate why: (select one)

- ❑ The IRB determined that the permission of one parent is sufficient.
- ❑ Second parent is deceased
- ❑ Second parent is unknown
- ❑ Second parent is incompetent
- ❑ Second parent is not reasonably available
- ❑ Only one parent has legal responsibility for the care and custody of the child

Assent

- ❑ Obtained
- ❑ Not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.
- ❑ Waived by the IRB because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.

Signature of person obtaining consent and assent

Date

Printed name of person obtaining consent

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Appendix 1 – Risks of Drugs used in this study

Please see risks of the study drug/Topiramate listed on Page 3-4

Appendix 2 - Additional Information about Confidentiality

ClinicalTrials.Gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify your baby. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Appendix 3 – Data and Biospecimens

During this research private identifiable information may be obtained from records or collected as your baby completes study procedures. In addition, biospecimens may be collected from your baby, including blood and tissue.

You will not receive the results, including your baby's individual results, of this study. Yet if you wish to know data results during your baby's treatment protocol you can always ask the providers.