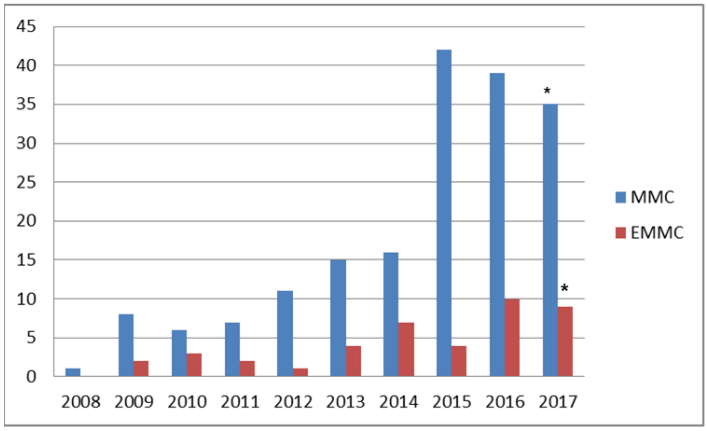
Title: Telemedicine to Improve Use of Therapeutic Hypothermia in Rural Settings
Clinicaltrials.gov #: NCT03706417

Background: Neonatal Encephalopathy (NE) is a clinical syndrome affecting between 2-5 per 1000 live births[1]. Abnormalities in the newborn neurological exam are the hallmark of NE which occurs due to the combined effects of lack of oxygen and blood flow to the brain around the time of birth. As many as 15-20% of infants with NE do not survive their brain injury and 25% of survivors experience substantial neuro-developmental deficits including intellectual disability, cerebral palsy, epilepsy and hearing or vision loss[2]. Until recently, infants suspected of having NE were treated with supportive care alone as there were no known therapeutic interventions. Approximately ten years ago, however, treatment options dramatically changed with the introduction of therapeutic hypothermia (TH), a novel neuroprotective therapy which involves deliberately decreasing the infant's body temperature to 33.5°C for 72 hours. The early safety studies of TH[3, 4] were published in the late 1990's and the positive results of the first efficacy trials in 2005[5, 6] moved this promising therapy into mainstream clinical practice. In a meta-analysis of 8 published clinical trials, TH was associated with a 25% decrease in the aggregated outcome of all-cause mortality and severe neurological abnormality and, as such, has become the standard of care for these critically ill infants[7].

Maine Medical Center (MMC), a tertiary care center with the only Neonatal Intensive Care unit (NICU) in the southern part of the state, employed TH for the first time in 2008. Eastern Maine Medical Center (EMMC) is the only tertiary care center in the northern part of the state and began using TH in 2009. In 2012, a Neonatal Neurology Program was started at MMC and this program was extended to EMMC through a unique and unprecedented collaboration in 2013. At both institutions, the number of infants treated with TH gradually increased with improved recognition of the mild to moderate forms of NE (Figure 1). While educational outreach efforts have successfully increased awareness of the symptoms of NE at both tertiary care centers in the state, infants who may benefit from TH are still not always recognized in a timely fashion. Missed

Figure1: Growth in use of Therapeutic Hypothermia (TH) at MMC and EMMC.



* Denotes partial year of data collection

opportunities for TH can occur when an infant's clinical presentation is less severe compared to those included in the original randomized controlled trials.

While TH must be initiated within the first 6 hours of life, there is solid evidence for improved outcomes in those for whom TH is initiated earlier. As a result of exceptional preclinical animal models of NE in the fetal lamb and piglet, there is a robust biochemical understanding of the temporal evolution of brain injury in neonates. TH must be initiated prior to 6 hours of life to intercede upon the second stage of injury with its features of excitotoxicity and associated cascade of inflammatory mediators that cause seizures and ultimately cell death[10]. Animal models have demonstrated lack of neuronal rescue if TH is initiated late (8.5 hours after ischemic insult)[11] and have also demonstrated improved neuronal rescue with earlier initiation of TH at less than 3 hours[12]. In a prospective cohort study, infants treated with TH prior to three hours of life were found to have improved motor function compared to those whose treatment was initiated after 3 hours[13]. In one of the first clinical trials of TH, the relative risk of death or severe abnormal neurological outcome was decreased in those for whom TH was started before 4 hours of life[14]. This combination of animal and human data suggests that mechanisms to improve the rapid initiation of TH, such as through a teleconsult, may lead to improved outcomes for infants with NE. In the proposed study, we hypothesize that use of telemedicine consults between a tertiary care center and a community hospital can improve the assessment, management, and short-term outcomes of infants with NE by decreasing delay in the initiation of TH through rapid and accurate assessment of NE.

Overview of the Study Design:

We propose to conduct a pilot intervention trial assessing the feasibility of decreasing the time to initiate TH for infants born in community hospitals who receive a Maine Neonatal Encephalopathy Teleconsult (Maine NET) compared 1:2 to with matched historical controls from the MMC database. We will also qualitatively assess provider experience of Maine NET (Appendix C) via zoom interviews and the parent perception of the process of having a telemedicine consult and participating in research in the setting of a critically ill newborn (Appendix D).

Study Goals:

The goals of this study are to:

1. Utilize telehealth for Neonatal Encephalopathy consults in community hospitals to determine if telemedicine can reduce time to initiation of TH treatment

2. Capture parent experience of telemedicine consult and remote consent process
3. Capture delivery hospital clinicians' (from community hospitals and tertiary care centers) experience of utilizing telemedicine for neonatal neurological exams to assist in decision making for therapeutic hypothermia
4. Identify themes from parent and clinician experiences to identify areas of improvement for future consultations
5. Publish research findings
6. Utilize data to improve future telehealth consultations

Human Subjects:

Recruitment sites: Multiple community hospitals in Maine have been offered the opportunity to participate in this feasibility study and all centers have provided letters indicating a strong desire for participation. See site list for recruiting community hospitals.

Inclusion criteria: Infants in need of Maine NET will be identified by the "Time is Brain" poster (see Appendix A) that was created and distributed across the state to all newborn nurseries at community hospitals in 2016. This poster is in routine clinical use and is intended to assist in the identification of infants with symptoms of NE. Rather than having inexperienced providers at community sites examine inclusion criteria for TH and make a determination of eligibility, this poster uses a color scheme in which the green designation denotes characteristics of low-risk infants who are not in need of consultation, the yellow designation denotes characteristics of moderate risk infants who should have consultation and who may need transfer, and the red designation denotes characteristics of high risk infants who are critically ill and will benefit from immediate consultation and transfer to a tertiary care center. Infants included in this study will be born at a community hospital, will be in either the yellow or red category on the "Time is Brain" poster, will be younger than 6 hours of age at the time of the consultation. Infants in the historical control group will be selected from the MMC database and matched according to gender, gestational age, severity of presenting encephalopathy (mild, moderate or severe) and community site at which the infant was born. Matching will occur after the 35 Maine NET subjects have been treated with TH. Infants assessed by Maine NET who are not treated with TH will not be compared to the control group. The control subjects will be chosen by an investigator blinded to the time to initiate TH and outcome of the infants from the database. Infants used for historical controls must have a time of TH initiation recorded in the MMC Therapeutic Hypothermia database. Any parent of any neonate, whether treated with hypothermia or not, will be eligible to participate in an interview about their telemedicine and research experience.

Exclusion criteria: Infants older than 6 hours at the time Maine NET is requested and infants for whom TH is not an appropriate therapy (e.g. due to premature birth or moribund status) will be excluded.

Number of subjects: We intend to recruit a total of 125 infants from the participating centers. Each center has referred between 0 and 6 infants for TH annually for the past 4 years and, by involving this number centers, it is likely that the targeted goal of 125 study subjects is achievable (Table 1). We have increased the number from 10 to 20 and then to 40 and then to 100 due to the fact that not all recruited infants will be treated with TH and to have an adequate sample size to make statistical comparisons with historical controls. We anticipate that by recruiting 125 infants we will be able to analyze data in the best way possible. We will recruit no more than 30 parents for the interviews.

Power calculation: With new funding from the COBRE grant, this study has expanded to recruit 125 subjects of whom we expect 30 to have been treated with hypothermia. 30 subjects in each group would yield 95% power to detect a 1hour difference in time to initiate TH.

Informed consent: Prior to the onset of any research related activities, informed consent for the main study will be obtained from one of the infant's parents through the telehealth interface. A paper copy of the informed consent document (ICF) will be provided to the parent and will be described in full detail by Dr. Craig who will answer all the parent's questions thoroughly. The parent will then sign and date and time the ICF document if they wish to have their infant participate. Parents will be asked to initial the informed consent document if they wish to be contacted about participation in the parent interview portion of the project. The physician at the participating hospital will witness the parent signature and also sign, date and time the ICF on the witness line. Dr. Craig will then sign a separate copy of the ICF and date and time it as well. The consent form that the parent signed will be transported with the baby to MMC or faxed to MMC by providers from the community hospital and will be conjoined with the copy signed by Dr. Craig and then uploaded into the infant's electronic medical record.

If a parent chooses not to participate, Dr. Craig will thank the family for considering and the standard of care consult will occur without employing telemedicine. The current standard of care for infants born in community hospitals is to have the provider attending the delivery (pediatrician or family medicine doctor) call the NICU at MMC to describe the cord gas parameters, the Apgar scores and the level of NE in the infant as well as any other clinically relevant data. The Neonatologist at MMC may suggest that the community provider "passively cool" the newborn per our standard guideline (see Appendix B) until the transport team arrives to make the actual determination of whether the infant will require TH treatment.

Compensation: Subjects will not be compensated for participation.

Follow-up plan: All subjects treated with TH will be offered routine neurological follow up at ages 3, 6 and 12 months per usual clinical routine after treatment with TH. These follow up visits are to insure maximization of early intervention services if they are needed. These follow up appointments are part of standard clinical care.

Primary Outcome: Hour of life in which TH is started. The “zero hour” for TH is recorded in the infant’s electronic medical record and refers to the time at which the infant starts the TH protocol.

Secondary Outcomes: Time at which passive cooling is initiated, temperatures recorded by the community hospital during passive cooling, in–hospital mortality, presence of seizures on electroencephalogram (EEG) and brain injury on MRI. The EEG is a routine part of the clinical care of an infant treated with TH and is applied for the 72 hours during TH. The PI is the person primarily responsible for interpreting the results of the EEG. The MRI is also part of the routine clinical care of infants treated with TH and is interpreted by a neuroradiologist who is unaware of the status of the infant regarding whether Maine NET was utilized.

Analysis: Baseline differences in selected characteristics between infants assessed by Maine NET versus historical controls will be compared using Fisher’s exact tests for categorical variables and t-tests, or their non-parametric equivalents for continuous variables. The primary analysis will compare differences in the time to achieve TH between infants assessed by Maine NET versus historical controls using a t-test. For secondary outcomes of mortality, seizures on EEG, and brain injury on MRI, chi-square or Fisher’s exact test will be used for analysis of the frequency of these adverse outcomes.

Potential limitations and contingencies: Maine NET has been successfully locally implemented at MMC with 11 successful teleconsults already performed. There are IT and other challenges involved in implementing Maine NET at outside hospitals, but, as should be evident from the enthusiastic letters of support, these institutions are more than eager to have this level of assistance and will work collaboratively to resolve challenges. If for some reason the Maine

NET cannot happen, providers will always default to the standard of care which is a phone call for assistance with decision making.

Potential Risks and Benefits: When working with PHI identifiers, there is always a risk of loss of confidentiality. This risk will be minimized in this study through use of a HIPAA compliant RedCap system, limited password-protected access, and use of a Master List, which will remove all PHI identifiers from the data that is used for analysis. Interview recordings will be stored on encrypted flash drives and within the MaineHealth Protected file share folder, which only the study team has access to. All identifiers will be removed from interview transcription for analysis.

Potential benefits for this study include determining if telemedicine can reduce time to initiation of TH treatment in community hospitals as well as documenting parent and provider experience in participation in telehealth consults for neonatal encephalopathy.

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