Project Title: Pilot Study Assessing the Effect of Osteopathic Manipulative Treatment (OMT) on Length of Stay in Infants with Neonatal Encephalopathy after Therapeutic Hypothermia

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Introduction:
Infants affected by neonatal encephalopathy (NE) have been shown to have better survival rates and improved long term neurodevelopment following treatment with therapeutic hypothermia[1]. However, a barrier to hospital discharge for these infants is a successful transition from gavage to either breast or bottle feeding. It is this transition that is the rate determining step to hospital discharge. Osteopathic manipulative treatment (OMT) helps to effectively stabilize and regulate the autonomic nervous system[2] as well as the cranial nerves important in the sucking and latching reflexes, which will in turn help to ease the transition to full oral feeding. It is therefore anticipated that for infants affected by neonatal encephalopathy, OMT will accelerate the transition to full oral feeds, thus decreasing their overall length of hospitalization.

Background: In the United States of America it is estimated that about 1-7 per 1000 births are affected by neonatal encephalopathy, a term that describes the abnormal features of a newborn neurological exam in an infant deprived of oxygen around the time of birth[3]. Prior to the advent of the therapeutic hypothermia, the combined rate of mortality and severe adverse developmental outcomes including cerebral palsy and epilepsy was near 50%. The current standard of care treatment for these infants is to initiate therapeutic hypothermia within the first six hours of life to increase chances of survival and preserve normal neurodevelopment. Hypothermia is achieved by placing the infant on a cooling blanket to allow them to reach temperature of 33.5°, which is maintained for 72 hours followed by a gradual period of rewarming over 12 hours. Once rewarming is complete, an MRI of the brain is performed to determine whether or not there were any areas of injury.

During the time infants are treated with therapeutic hypothermia, they are not fed enterally due to concern for decreased gut perfusion, a concern that lessens upon rewarming. For infants without injury to the brain, the hospital admission is often extended for an additional 7-10 days to allow the infant more time to develop the skills necessary to achieve full oral feeding prior to discharge. For infants with brain injury, the admission can be 4-6 weeks long and on occasion these infants require alternative surgically implanted feeding tubes as they are not able to learn the skills necessary to orally feed.

OMT helps to stabilize and regulate the autonomic nervous system as well as the cranial nerves important in the sucking and latching reflexes[4]. This in turn facilitates the acquisition of skills necessary for oral feeding. Previous studies have demonstrated that with OMT, premature infants improve their oral feeding skills and thus decrease their risk for gastrointestinal dysfunction, resulting in a length of hospital stay that is decreased by an average of six days[5]. Subjective experience with OMT at MMC has demonstrated similar improvements in ability to oral feed in term babies in the normal newborn nursery. It is therefore logical to hypothesize that term infants with feeding difficulties after hypothermia may similarly benefit. Ultimately if OMT shows an expedited and improved overall ability for these term

infants affected by NE to successfully transition to full oral feeds, then it is likely that OMT will be able to subsequently effect a reduction in the length of hospitalization in these infants.

In addition, it is important to further acknowledge the mechanism of labor in and of itself, as it can induce trauma to the craniosacral mechanism thus inducing somatic dysfunctions which can be palpated by skilled osteopathic hands. These traumas are manifested as various strain patterns specifically within the occipital bones, temporal bones, sacrum and at the sphenobasilar symphysis (SBS), and they can have direct effects on the symptoms which the infant may be expressing following delivery[4]. Previous osteopathic studies have demonstrated the significance of the relationship between craniosacral strain patterns and the associated symptomatology (poor latch, poor suck, vomiting, hyperactive peristalsis, tremor, hypertonicity and irritability) affecting primarily the nervous system but affecting the circulatory and respiratory systems as well (difficult or irregular respirations, excessive mucus, and marked cyanosis)[4]. In our proposed project we will also use qualitative data obtained from treatment notes to describe patterns of somatic dysfunction seen with osteopathic treatments, in the primary affected areas of the craniosacral mechanism including the occipital bones, temporal bones, sacrum, and at the SBS.

Preliminary data: In 2014-2015, a prospective safety study was undertaken at Maine Medical Center to assess vital sign stability and safety of OMT on term infant vital signs. Thirty term infants were treated with OMT using a combination of techniques including myofascial release, balanced ligamentous tension, and osteopathy in the cranial field. Pre- and post-vital signs were recorded including temperature, heart rate, respiratory rate and oxygen saturation. The infant temperature decreased during treatment by 0.1°C which although statistically significant, is not clinically significant. The heart rate also decreased after treatment by about 4 beats per minute and was also statistically significant, but not clinically significant. There were no significant changes in respiratory rate or oxygen saturation and most importantly no adverse events associated with the OMT intervention.

	Mean Pre-Vitals (SD)	Mean Post-Vitals (SD)	P-value
Temperature (℃)	36.9 (0.27)	36.8 (0.16)	0.02
Heart Rate (bpm)	136.8 (15.7)	132.5 (15.2)	0.05
Respiratory Rate (bpm)	44.3 (9.6)	43.6 (9.1)	0.55
Oxygen Saturation (%)	99.1 (1.7)	98.6 (1.6)	0.13

Hypothesis: Among term infants with NE following therapeutic hypothermia, use of OMT will improve clinical outcomes, as assessed by hospital length of stay, time to oral feeding and patterns of somatic dysfunction within the craniosacral mechanism.

Primary Aim:

- **Total hospital length of stay.** Assess the effect of OMT on total hospital length of stay. We will compare infants treated with OMT 1:3 with matched historical controls.

Secondary Aims:

1. **Number of days until full oral feeding is achieved.** Assess the effect of OMT on the number of days until full oral feeding is achieved.
2. **Patterns of somatic dysfunction.** We will perform an osteopathic structural exam before and after treatment while recording the specific somatic dysfunctions observed within the medical record. We will then use these notes to perform a qualitative analysis of patterns of somatic dysfunction specific to the craniosacral mechanism before and after OMT.

Significance: The results of this study have the potential to influence the use of OMT as a treatment modality for term infants with NE to help them to more effectively regulate their autonomic nervous system and in turn allow them to a more quick and efficient transition to full oral feeds following therapeutic hypothermia. A more rapid transition to full oral feeds will allow earlier discharge from the hospital.

Human Subjects: This will be a prospective clinical trial with matched historical controls. We will enroll 12 term (> 37 weeks at birth) infants who were born at Maine Medical Center, diagnosed with NE and treated with therapeutic hypothermia. After all data have been collected for these 12 cases, we will identify historical controls from the Neonatal Encephalopathy Therapeutic Hypothermia Database - [976245-1]. For each case we will identify three historical controls, which will be matched to the OMT treated case according to the following categories; gender, gestational age by completed week, severity of presenting encephalopathy as defined by Sarnat (mild, moderate, or severe), result of MRI (normal or abnormal), and an absence of seizures by EEG.

- **Population:** At Maine Medical Center (MMC), approximately 40 infants with NE are treated with therapeutic hypothermia annually. We aim to enroll 12 infants over a 6-month period from October 2017 to March 2018, during which time we anticipate there will be about 20 infants who require therapeutic hypothermia treatment. Based on prior experience with this population, we anticipate a high rate of recruitment (75%) and as such, we think that it is feasible to recruit 12 infants within this 6-month period. Recruitment will all occur at MMC in the private room where the infant receives treatment in the NICU.

- **Inclusion and exclusion criteria for infants treated with OMT:**
  Inclusion criteria:
  - Neonate ≥ 37 weeks gestational age at birth
  - Neonate been diagnosed with neonatal encephalopathy or hypoxic ischemic encephalopathy and treated with therapeutic hypothermia
  - Neonate with mild to moderate encephalopathy
  - EEG without seizure activity
  - Brain MRI without basal ganglia injury

  Exclusion criteria:
  - Neonate < 37 weeks gestational age at birth
  - Neonate with severe encephalopathy (as defined by Sarnat)
  - EEG demonstrated seizure activity or evidence of status epilepticus during therapeutic hypothermia treatment
  - Brain MRI demonstrating moderate or severe basal ganglia injury
  - Neonate affected by neonatal abstinence syndrome (NAS)
  - Neonate affected by intrauterine growth restriction (IUGR)
  - Neonate born with major congenital anomalies (i.e., cleft palate)

- Prenatal history of maternal insulin dependent gestational or type 1 diabetes
- Moribund status (i.e., infants unlikely to benefit from or are not responsive to aggressive life support)

- **Matched historical controls:** Three historical control infants will be matched per OMT treated case; these controls will be extracted from the database. The matching will be according to the following categories; gender, gestational age by completed week, severity of presenting encephalopathy as defined by Sarnat (mild, moderate, or severe), result of MRI (normal or abnormal), and an absence of seizures by EEG.

- **Enrollment and Informed Consent:** The parents of the neonate will be approached for recruitment into the study by Alexa Craig MD, the Principal Investigator (PI), who will be actively involved in the clinical care of all these patients. It is anticipated that the majority of the consenting will be done by Alexa Craig MD, and in a circumstance where Dr. Craig is not available, the consenting will be done by Kira Bendixen DO. The PI will track the EEG for presence or absence of seizures per usual clinical practice. If the infant has no seizures during the first 24 hours of life, the PI will approach the parents to inform them about the study. They will have 1-2 days to decide to participate, up until the completion of the therapeutic hypothermia treatment. The PI will review the study protocol and the informed consent document with the parents of the infant and obtain signatures for those who wish their neonate to participate.

- **Compensation:** The OMT will be provided at no charge to the patient, insurance, or any other third party payer. Participants will not be otherwise compensated for participation.

Study Procedures: Neonates who meet clinical criteria for NE will be treated per the current standard of care with therapeutic hypothermia according to existing clinical guidelines. The hypothermia treatment is NOT part of this investigation.

Neonates will remain NPO throughout therapeutic hypothermia, as is standard of care. The infant “oral readiness assessment tool” will be used clinically by nurses at the bedside after completion of the therapeutic hypothermia to assess when the infant is ready to trial oral feeding. This is also part of the standard of care and is applied to these babies to make the determination if trials for oral feeds may begin safely.

Infants whose parents consent to participate will receive two osteopathic manipulative treatments, between day of life 4 and day of life 7, following completion of the rewarming process. For those neonates remaining hospitalized for a longer duration, OMT will continue twice a week, every Tuesday and Friday, until the neonate is discharged from the hospital.

OMT Intervention:

- **OMT Technique:** Each neonate will have a structural exam completed assessing each body region (head, cervical, thoracic, lumbar, sacral, pelvic, rib cage, and abdominal regions) for underlying somatic dysfunctions prior to each treatment. The specific OMT techniques used will be left to the discretion of the treating physician and will not be based on a predetermined protocol. Treatment techniques will consist of myofascial release, balanced ligamentous tension, balanced membranous tension, and osteopathy in the cranial field. Total treatment time

will be 15 minutes. See Appendix A describing the features of the exam which will be recorded on paper by the treating physician at the time of the evaluation. The paper will be marked only with the research identifier.

APPENDIX A

Osteopathic Structural Exam: ● Patient Position: ● Head: ● Cervical: ● Thoracic: ● Lumbar: ● Sacrum: ● Pelvis: ● Rib cage:	Craniosacral Strain Patterns: ❑ Occipital ❑ Right compression ❑ Left compression ❑ Bilateral compression ❑ Free ❑ Temporal ❑ Right restriction ❑ Left restriction ❑ Bilateral restriction ❑ Free ❑ Sphenobasilar symphysis (SBS) ❑ Flexion ❑ Extension ❑ Torsion ❑ Side-bending rotation ❑ Vertical/lateral strain ❑ Compression ❑ Free ❑ Sacral ❑ Superior on left ❑ Superior on the right ❑ Flexion ❑ Extension ❑ Rotation between the ilia ❑ Free *(Simple check box for the qualitative collected data on the patterns of somatic dysfunction seen in the craniosacral mechanism that would have direct effects on the neurologic, cardiac and respiratory function of these infants.)*

- **Treatment Team:** MMC is uniquely partnered with the University of New England College of Osteopathic Medicine (UNECOM) and there is a long history of collaboration between the two institutions. MMC has a history of enthusiastic support of osteopathic training and promotion of the application of osteopathic treatment. As evidence of this, for the past 15 years, MMC has had a full time Hospital Manipulative Service with multiple providers who perform OMT on patients ranging across the spectrum of age. Bryan Beck DO, previously the Director of Osteopathic Medicine at the Osteopathic Hospital of Maine, is the founder of this OMT service. Dr. Beck has provided OMT to patients for more than 30 years and has been treating infants and children at MMC for at least 15 years.

OMT will be performed by one of four trained practitioners including, Dr. Bryan Beck, Dr. Kira Bendixen, Dr. Alexis Beinlich, and Dr. Nathan Rheault. All of these providers perform these techniques as part of routine medical care at Maine Medical Center.

Study Logistics:

- **Communication**: After the first 24 hours of hypothermia treatment, when the infant has met inclusion criteria, parents will be informed about the study and if they choose to participate, consent will be obtained from a parent. After consent is obtained, the consenter will communicate through personal communications to alert the OMT provider team that there is a new subject for the study. The Director of the Clinical Trials Office, Krista Garrison, is aware of the study and will insure that participants are flagged in EPIC and not charged for any OMT related activities unintentionally.

- **Scheduling**: Once a new infant has entered the study there will be a period of 2-3 days, during which the infant is completing the therapeutic hypothermia protocol, before OMT can be provided. During this time, the OMT provider team will determine who is available and able to treat at the predetermined times as specified by our study design.

Data Collection and Management: Data collection will occur after prospective OMT of the cases is complete and TH-associated clinical data have been entered into the existing REDCap database (Neonatal Encephalopathy Therapeutic Hypothermia Database - [976245-1], as per routine clinical protocol.

- **Historical data collection (controls):** For the historical controls, the data will be collected from the REDCap database (Neonatal Encephalopathy Therapeutic Hypothermia Database - [976245-1]). The parameters included in this database are demographic and clinical detailing the infant's presentation, maternal and delivery factors as well as infant outcomes both short and long term. Data collection tool attached as Appendix.

- **Prospective OMT data collection (cases):** For the OMT-treated cases, we will collect the same list of parameters from the Neonatal Encephalopathy Therapeutic Hypothermia Database as were collected for their historical controls (see Appendix B). In addition, we will collect the more comprehensive OMT provider notes outlining the osteopathic structural exam (see left column of Appendix A).

  In addition, we will use a paper document to collect the osteopathic structural findings pertaining to the craniosacral mechanism, which will be completed only prior to the first encounter for OMT and after the last encounter for OMT prior to discharge (see right column of Appendix A). Each paper will have the case ID number only. These papers will be kept in a locked drawer in the locked office of the PI once they have been completed.

- **Data management:** Following completion of the data collection for our prospective patients, the required data parameters (outlined for cases and controls in Appendix B) will be extracted electronically from the Neonatal Encephalopathy Therapeutic Hypothermia REDCap database and uploaded into the new, study-specific REDCap database. Additional data from EPIC (time to oral feeding, feeding method at discharge, OMT provider notes) and from the paper OMT

Structural Findings documents will then be manually entered directly into the new REDCap database.

Power Calculation: A two group t-test with a 0.05 two-sided significance levels will have 80% power to detect the difference between the group 1 mean Mu of 7.3 days and a group 2 mean Mu of 11.5 days. This is a difference in means of 4.2 days assuming that the common standard deviation is 4.4 when the sample sizes in the two groups are 12 and 36, respectively.

Data Analysis: Baseline differences between the OMT and historical controls will be compared using chi-square tests or Fisher's exact tests, as appropriate, for categorical variables and t-tests or their non-parametric equivalents, as appropriate, for continuous variables (with/without log transformation). The primary analysis will compare length of hospital stay for the OMT treated infants compared to the historical controls. In secondary analysis the number of days until full oral feeding is achieved will be similarly compared. Also in secondary analysis, there will be a descriptive comparison of the patterns of strain of treated infants before and after receiving OMT.

Data Security: Data for every infant treated with therapeutic hypothermia at MMC is stored in the Neonatal Encephalopathy Therapeutic Hypothermia Database [976245-1] which is encrypted.

Potential Problems: There is the potential that we will need to continue recruitment efforts for longer than six months if the percent who choose to participate is lower than anticipated. We have designed this study giving ourselves an extra six months buffer to achieve the goal of 15 infants between March 2018 and June 2018 when Dr. Bendixen and Dr. Beinlich are no longer available to work on this project. We have also recruited residents who are less senior to continue working on this project, should recruitment be prolonged.

We are aware of two significant sources of bias in this study design. The first is the bias associated with the use of historical controls. Use of historical controls, of course means we are not randomizing our sample. While this is a considerable methodological weakness, it is outweighed in this small study by the benefits of shortening the time to perform this study (we only have to recruit 12 rather than many more) and we are firmly convinced that participation will be better given that we are offering a treatment known to be harmless and beneficial (rather than offering treatment versus sham, which is harder to get parents to agree to). We intend to use historical controls only from the last three years of the database during which the time therapeutic hypothermia care has been standardized and is the same as the current delivery of care. In order to minimize potential selection bias in the choice of which infants are used as historical controls, we will complete the OMT study on our 12 infants and we will then use a third party to randomly match them to our collection of historical controls based on their matching criteria.

The second bias is the potential for performance bias in this study. Performance bias could occur due to the fact that our study is not blinded and nurses caring for the babies, who could have strong positive beliefs in the therapeutic effects of OMT, may be more persistent in their efforts to feed these babies, which may make it look like the OMT is more effective. We acknowledge this limitation, but with the current study design it is not possible to blind nurses to the treatment status as all enrolled neonates will be cases. A future randomized, double blind trial would need to be performed to confirm these findings. Pointing out this performance bias and creating a more cognizant treating environment with the nursing staff will hopefully reduce the potential for an over effect to be seen. There will be a

recruitment pool of historical controls from which a person not participating in the study will randomly select matching infants (after the 12 have been recruited and treated); the control data will not be affected by performance bias.

Timeline:

a. October 2017 - Submit IRB application with informed consent draft
b. October 2017 - Commence study enrollment.
c. March to April 2018 - Finish recruiting and begin data analysis
d. April to June 2018 - Submit paper for publication

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