A Introduction

A1 Study Abstract:

This study will use non-invasive MR scanning to help answer questions related to brain function and development in children suffering from craniosynostosis. Craniosynostosis affects roughly 1 in 2000 children. Primary indication for operative treatment for patients with craniosynostosis is to prevent or treat increased Intra-Cranial Pressure (ICP) and avoid neurological impairment. Increased ICP is thought to result from restricted space for brain growth caused by the abnormal cranial vault. However, the literature on the relationship between craniosynostosis and ICP is limited. Due to the invasiveness of the test, preoperative ICP monitoring is not routinely performed to decide if operative repair is required. Other indirect signs of elevated ICP have been described but are not reliable.

While it is not currently feasible to measure ICP directly, we may be able to indirectly determine ICP in children via magnetic resonance imaging (MRI). We aim to compare the assessment of ICP with the conventional, invasive intraventricular shunt to an indirect assessment of ICP via MRI.

Ten children with an intraventricular shunt will be enrolled in this pilot study over a one-year period. We will obtain indirect measures of ICP. The results will be compared to ICP measures obtained via the shunt.

Ultimately the assessment of ICP using MRI in patients with craniosynostosis may revise surgical indications and timing of surgery, potentially changing the standard of care for patients with craniosynostosis. Additionally, this approach might be used for patients with other diagnoses which impact ICP.

A2 Primary Hypothesis

Indirect (via MRI) and direct measures of ICP will have a significant positive correlation.

A3 Purpose of the Study Protocol

The purpose of this study is to evaluate the use of magnetic resonance imaging (MRI) to determine intra-cranial pressure in young children.

B Background

B1 Prior Literature and Studies

Literature is limited on the relationship between craniosynostosis and ICP. The most widely reported study is by Renier and colleagues.[1] In 75 patients preoperative ICP monitoring was performed using an epidural sensor. They identified ICP to be normal in one-third of the cases, obviously elevated in one-third, and borderline in one-third. When counseling patients, practitioners report a 13% rate of increased ICP for single suture synostosis and 42% for multiple suture synostosis. However, the authors used adult normative values for ICP (normal less than 10mmHg and elevated greater than 15mmHg). Normal ICP in children and infants has been identified to be closer to 6 mmHg.[2]

B2 Rationale for this Study

Currently all patients with craniosynostosis are treated surgically due to concern that the abnormal cranium restricts the brain, causing increased ICP. However, due to the invasiveness and potential harm of the current approach, ICP is rarely measured in patients with craniosynostosis. Accurate measures of ICP using MRI in patients with craniosynostosis may revise surgical indications and timing of surgery, potentially changing the standard of care for patients with craniosynostosis. This would allow family members of patients with craniosynostosis to be more informed as to the indication for operative repair, i.e., decreased brain metabolic activity and/or cosmetic.

Our research may ultimately provide a tool for practitioners to not only identify which patients need to be treated, but also show adequate surgical therapy with resolution of ICP. Some patients, particularly those with syndromic craniosynostosis, require a secondary operation at an older age to expand cranial volume. The decision to perform a secondary operation is based on clinical signs and symptoms. Development of non-invasive techniques to identify ICP will also inform this process and allow for early and correct identification of patients who need surgical treatment.

C Study Objectives

C1 Primary Aim

To evaluate ICP through the use of magnetic resonance (MR) imaging techniques in patients under the age of eight years old.

C2 Rationale for the Selection of Outcome Measures

Although multiple tests have been suggested to assess ICP in patients with craniosynostosis, including papilledema and copper beaten appearance of the skull on plain film, none have been shown to be reliable measures or markers of ICP. Recent advances in MRI suggest that ICP can be indirectly measured with this modality non-invasively and with minimal patient risk.

D Investigational Agent

D1 Clinical Data to Date

The MR sequences for this study have been used in studies of traumatic brain injury. To our knowledge these sequences have not yet been used for patients with craniosynostosis.

D2 Dose Rationale and Risk/Benefits

The main risk of the MR scan in this population is the feeling of being closed in or discomfort from lying still. This is an acceptable risk given the benefit of obtaining hard evidence of brain stress in subjects with synostosis. The time patients are in the scanner (approximately 45 minutes) has been adequate to obtain useful data in populations of minors post traumatic brain injury and normal controls. These tests were performed by Drs. Jose Pineda and Dustin Ragan.[7]

E Study Design

E1 Overview or Design Summary

Up to 12 patients with craniosynostosis will be enrolled in this pilot study. Various measures of cerebral metabolism and perfusion will be taken during a single visit via MR scanning.
The results may also be compared to age and gender matched normative data. These controls will be recruited in the plastic surgery clinic and/or deidentified data from normal subjects from another study will be used. Participation in this research study consists of one to two parts. First, all patients will be asked to extend a clinical visit for MRI. During this time the intra-cranial pressure MRI testing will be done, lasting approximately 10 minutes. The scan will be performed in the radiology center on the 1st floor of Children's Hospital. The clinical scan will be done under sedation. Secondly, during the same visit, a transducer will be attached to the participant's intraventricular catheter if it is not already in place. The patients ICP will be measured directly with this transducer. Subjects have no further commitment once the scan (and ICP measurement) is complete.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- Subjects presenting to the Plastic Surgery clinic with unrepaired single-suture craniosynostosis.
- Age-matched controls

Exclusion Criteria

- Implants (e.g. pacemakers) that might rule out use of MR scanning.

- History of other abnormalities known to affect brain topology or function.
- Control subjects must have no history of craniofacial abnormality or head trauma.

2.b Subject Recruitment Plans and Consent Process

Subjects will be recruited through the Plastic Surgery clinic.

2.c Risks and Benefits

Risks: the risk of discomfort of claustrophobia during the MR scan

Benefits: Future patients with craniosynostosis might benefit from this study because it may lead to a revision of surgical indications and timing of surgery, potentially changing the standard of care for patients with craniosynostosis.

2.d Early Withdrawal of Subjects

Subjects may withdraw at any time before or during the study.

2.e When and How to Withdraw Subjects

Subjects or their parents/guardians may withdraw verbally.

2.f Data Collection and Follow-up for Withdrawn Subjects

There will be no follow-up data collection

F Study Procedures

F1 Screening for Eligibility

Craniosynostosis will be diagnosed via computed tomography performed as part of standard care

F2 Schedule of Measurements

There will be a single visit consisting of the MR scan, performed in the Center for Clinical Imaging Research.

F3 Safety and Adverse Events

3.a Medical Monitoring

Prior to MR scanning, subject’s parent or guardian will complete an MRI safety questionnaire. The subject's heart rate and blood pressure will be continuously monitored and recorded every 15 minutes during the MR scan.

3.b Definitions of Adverse Events

Typical adverse events during MR scans are claustrophobia and issues relating to metallic implants.

3.c Data Collection Procedures for Adverse Events

Any adverse events will be duly recorded and noted by the investigators

3.d Reporting Procedures

A summary of any adverse events will be included in continuing review forms sent to the IRB.

3.e Adverse Event Reporting Period

Annually (in the continuing review forms)

F4 Study Outcome Measurements and Ascertainment

MR spectroscopy (MRS) will be used to obtain concentrations of N-acetyl aspartate (NAA) and lactate. NAA is a highly sensitive marker of brain injury and the presence of lactate can indicate compromised metabolism. We will measure whole-brain oxygen extraction (OEF) using a magnetic field mapping approach. Elevated OEF is a key indicator of compromised perfusion. Cerebral blood flow (CBF) will be measured using an arterial spin labeling (ASL) sequence, which will allow direct measurement of perfusion deficiencies. We will also obtain functional connectivity data using an rfcMRI sequence, which is sensitive to developmental delay. The analysis for OEF and ASL data will be performed by Dr. Dustin Ragan. The MRI images will be read by Dr. Robert McKinstry, Chief of Radiology at Saint Louis Children's Hospital. Measures will include location and severity of metabolic effects, size of the optic nerve sheath, and cerebral perfusion.

G Statistical Plan

G1 Sample Size Determination and Power

As this is a pilot study there is no relevant data to determine the power of this study. The data collected here will be used as a guide for sample size determination of future studies.

G2 Interim Monitoring and Early Stopping

N/A

G3 Analysis Plan

The data obtained from the pilot study will be evaluated for patterns in the data between the subjects with craniosynostosis and the matched controls.

G4 Statistical Methods

Various graphical and image analysis approaches will be applied to tease out potential patterns between cases and controls and between the affected and unaffected sides of patients with unilateral craniosynostosis.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Privacy during the recruitment and consent process will be protected by performing these procedures in private patient rooms in the hospital or clinic setting.
The MRI will be performed in the Center for Clinical Imaging Research (CCIR).
No unnecessary PHI will be collected. Data will be a coded.

H2 Training

All members of the research team will be familiar with this protocol and the standard prosecution of clinical trials.

H3 Records Retention

Patient records will be stored behind a double lock system in the craniofacial laboratory in the division of Plastic Surgery.

I Study Administration

I1 Organization and Participating Centers

Division of Plastic Surgery in cooperation with the Department of Radiology

I2 Funding Source and Conflicts of Interest

None at this time.

I3 Subject Stipends or Payments

None.

I4 Study Timetable

We anticipate obtaining all pilot data within a year of IRB approval.

J Publication Plan

Within one year of final data collection the results of this pilot study are to be submitted for presentation at a national craniofacial or neurosurgical conference. Similarly, the results will be submitted for publication in a peer-reviewed journal within the same time frame.

K Attachments

K1 Informed consent documents

Included in the IRB submission.

L References

The following publications are related either to ICP in patients with craniosynostosis or to the non-invasive, MR-based methods of determining cranial metabolism.

1. Renier D, Sainte-Rose C, Marchac D, Hirsch JF. Intracranial pressure in craniostenosis. Journal of neurosurgery 1982;57:370-7.
2. Minns RA. Intracranial pressure monitoring. Archives of Disease in Childhood 1984;59:486-8.
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4. Jain V, Langham MC, Wehrli FW. MRI estimation of global brain oxygen consumption rate. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2010;30:1598-607.
5. Wu WC, Fernandez-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2007;58:1020-7.
6. Ragan DK, McKinstry R, Benzinger T, Leonard JR, Pineda JA. Alterations in cerebral oxygen metabolism after traumatic brain injury in children. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2012.
7. Ragan DK, McKinstry R, Benzinger T, Leonard J, Pineda JA. Depression of whole-brain oxygen extraction fraction is associated with poor outcome in pediatric traumatic brain injury. Pediatric research 2012;71:199-204.