Non-invasive intracranial pressure estimation in intracranial hypotension using magnetic resonance imaging

ClinicalTrials.gov ID # NCT03041441

12/16/2019

Research Summary

1. Protocol Title:

Non-invasive intracranial pressure estimation in intracranial hypotension using magnetic resonance imaging

2. Study Purpose:

The purpose of this study is to estimate the intracranial pressure (ICP) in subjects with intracranial hypotension (a condition caused by spinal cerebrospinal fluid (CSF) leakage, often associated with low CSF pressure) using non-invasive MRI techniques, and to determine whether changes in estimated ICP are seen after treatment of this condition.

3. Background & Significance:

Spontaneous intracranial hypotension (SIH) is a secondary cause of headache that has historically suffered from under-diagnosis but is becoming increasingly recognized. [1] Clinically, SIH is characterized by headaches that occur or worsen when sitting or standing and improve or resolve when lying down. In almost all cases, spinal cerebrospinal fluid (CSF) leaks are the causative etiology for the clinical syndrome.[2] As a result of CSF leakage, the CSF pressure is often low in this condition.[3]

Despite increasing recognition of the condition, there is still no single diagnostic test that can establish the diagnosis with a high degree of sensitivity. The most widely accepted criteria for the disease, the International Classification of Headache Disorders, Version 3 (ICHD-3), incorporates criteria derived from clinical presentation, anatomic brain imaging, spine imaging, and CSF pressure measurement, with the latter 2 tests typically involving invasive procedures. From the standpoint of diagnosis, it would clearly be advantageous to develop additional noninvasive diagnostic modalities that could help establish the diagnosis with a high degree of sensitivity.

Treatment can also be challenging in intracranial hypotension. The primary treatment modality, epidural blood patching, is not effective in all cases, and it is common for patients to require several epidural patching procedures before symptom relief is achieved. Furthermore, successful treatment may be complicated by inappropriate elevations of intracranial pressure, termed 'rebound intracranial hypertension,' that may mimic symptoms of low pressure.[4] Therefore, a non-invasive measurement of ICP would be useful for following post-treatment response and differentiating persistent intracranial hypotension form rebound intracranial hypertension.

Recently, MRI sequences have been developed that may be able to estimate ICP in a non-invasive fashion. The MRI-based method for measurement of ICP (MRICP method) is based on basic principles of the cranio-spinal CSF physiology: The mono-exponential relationship between intracranial volume and pressure leads to a linear relationship

between elastance (i.e., the derivative of pressure with respect to volume) and pressure. The MRI method utilizes well-established velocity encoding cine MR imaging to measure elastance from the ratio of volume and pressure changes during the cardiac cycle. The measurement of the momentary differences between the volumes of blood and CSF entering and leaving the cranium during the cardiac cycle provides an estimate of the intracranial volume change, and the pressure difference is estimated using the derivative of the CSF velocities. The method has been recently validated independently by a group in Munich by demonstrating significant correlation between shunt valve opening pressures and MRI derived ICP values in shunted patients with well-functioning shunts.

The MRI measurement is obtained using 3-cine phase contrast scan with a total scan time of about 10 minutes. Therefore the MRICP method is well suited as an add-on for a diagnostic MRI study. In this study the MRICP method will be utilized as a potential diagnostic tool diagnosis of intracranial hypotension, and as a tool to monitor treatment response.

In addition to estimation of ICP, the caliber and flow velocity through the dural venous sinuses will be studied. It is well established that there is a relationship between the caliber of the intracranial dural venous sinuses and disorders of CSF pressure. In particular, the caliber of the junction of the transverse and sigmoid sinuses has been found to be reduced in idiopathic intracranial hypotension (IIH) and increased in spontaneous intracranial hypotension, diseases characterized by high and low CSF pressures, respectively.[5-8] This portion of the sinus has been hypothesized to be distensible owing to its lack of fixed dural margins, and may serve as a 'barometer' of intracranial pressure.

As a secondary aim, therefore, we plan to study the caliber of the sinus and flow velocity through this portion of the sinus in subjects with SIH using non-contrast 3D phase-contrast MR venography, a well-established sequence in current clinical use. Our goals are to establish baseline measurements of cross sectional area and velocity, and to study how these parameters change following treatment of SIH with epidural blood patching.

4. Design & Procedures:

This is a prospective, single-arm proof-of-concept study with enrollment goal of 5 subjects.

4.1 Study summary

Subjects with known intracranial hypotension who are scheduled to undergo standard-of-care CSF pressure measurement using lumbar puncture prior to planned epidural patch treatment will first undergo a research MRI of the brain in order to estimate ICP. The imaging protocol is listed in Appendix 2. Approximate scan time per session will be 20-22 minutes.

Subjects will then undergo lumbar puncture according to the standard-of-care treatment plan. Estimated values of CSF pressure derived from MRI will be compared to values measured during lumbar puncture. Patients will then undergo standard-of-care epidural patching. A repeat research MRI after epidural patching will be performed to assess for differences in pre- and post-treatment scans.

4.2 Primary and secondary objectives

The primary objective is compare CSF pressure measured by lumbar puncture as part of standard-of-care testing to ICP measurements estimated by the MRICP technique.

Secondary objectives include: (1) assessment of change in estimated ICP prior to and following standard-of-care epidural patching and (2) evaluate changes in diameter and flow velocity through the transverse dural venous sinus prior to and following epidural blood patching.

4.3 Pre-registration procedures

Potential subjects will be identified from among patients referred to our department for evaluation/treatment of spontaneous intracranial hypotension. Currently, our department is one of the few referral centers for this condition in the country, ensuring an active practice with high volumes of new patients suffering from this condition.

Currently, our standard practice is to contact all patients by telephone for consultation prior to their visit to discuss the patient's history, prior testing, and expectation for their upcoming visit. This contract is made by one of 3 radiologists who perform epidural patching procedures, or the physician's assistant associated with our practice. Because many of our patients are referred from out of state, this provides an opportunity to establish a relationship with the provider, to determine what testing will be necessary, and to answer any patient questions about their trip. Patients typically arrive the day before the procedure, and are advised to stay locally1-2 days after their procedure.

At completion of the this telephone consultation, patients meeting eligibility criteria will be asked by their provider if they would be willing to speak to a research coordinator to learn more about this study. If they agree, they will be contacted separately by a trained clinical research coordinator to explain the study.

4.4. Enrollment procedures

If the patient decides to participate, the research coordinator will confirm eligibility and arrange for the research MRI to be performed within one day prior to the standard-of-care lumbar puncture (i.e. the same day as the procedure, prior to the scheduled procedure appointment, or the day before), and within one day following the epidural patch treatment. The lumbar puncture and the epidural patching are typically performed on

consecutive days. On the day of the pre-treatment MRI, the research coordinator will meet with the patient prior to the scan to have the patient sign consent for the study.

All subjects will undergo their scheduled medical procedures as planned regardless of their decision to participate or not participate in the study; no change to the medical care of the patient will be made as part of this study.

4.5 Study procedures

The main study procedures will consist of the pre-treatment MRI and post-treatment MRI. The study plan is presented in the schema in Appendix 1.

No intravenous contrast material is used in the research sequence.

The research MRI technologists will screen the subject for contraindications to MRI, according to established departmental protocol. Because completion of diagnostic brain MRI is required generally required by our service prior to referral of patients as part of standard-of-care procedure, and brain MRI imaging findings positive for intracranial hypotension serve as inclusion criteria (see section 5.1), it is anticipated that all patients will have undergone MRI scanning without complication prior to enrollment, and therefore few if any patients will be expected to have contraindications to MRI scanning.

5. Selection of Subjects:

5.1 Subjects and eligibility

Subjects will be identified and approached using the procedures describe in Section 4.3 and 4.4 above.

5.2 Inclusion & Exclusion criteria

Inclusion criteria will consist of the following:

- Known diagnosis of intracranial hypotension, established by the following criteria: the presence of orthostatic headache, and one or more of the following criteria: prior CSF opening pressure ≤6 cmH20, demonstration of an active spinal CSF leak on prior spine imaging, or cranial MRI changes of intracranial hypotension.[9]
- Ability to provide informed consent.
- Expected ability to complete standard-of-care procedures (lumbar puncture and epidural patching)

Exclusion criteria will consist of the following:

- Known contraindication to MRI (pacemaker, MRI incompatible hardware, etc.)

- Severe claustrophobia or other condition requiring the need for anxiolysis, sedation, or any other medication for MRI scanning
- Inability or expected inability to complete study interventions as scheduled
- Any known contraindication to standard-of-care procedures (e.g. coagulopathy, allergic reaction to required medication, lack of vascular access, etc.)

6. Subject Recruitment & Compensation:

There is no subject compensation in this study.

7. Consent Process:

Once patients have agreed to participate and arrive at Duke University Medical Center prior to their MRI scan, study personnel will approach eligible subjects in a location sufficient to provide for private and confidential discussion. Written informed consent will be obtained on the date of their procedure using standard IRB-approved consent processes.

The subject will be given time to read the consent and discuss alone or with family/friends present. The consent will be signed only after all questions are answered. There will be no time limit for potential subjects to consider participation. The study personnel will take as much time as needed to answer all questions and thoroughly review the consent form with potential subject. This will likely take between 5 and 15 minutes. Participants who do not read or are blind will have the consent form read to them in the presence of a witness. Subjects who withdraw consent or otherwise become ineligible for the study after enrollment may be withdrawn.

8. Subject's Capacity to Give Legally Effective Consent:

Subjects must be capable of providing informed consent to participate in this study.

9. Study Interventions :

The study intervention will consist of the pre-intervention and post-intervention MRI, as detailed above. Scans will be performed without the need for intravenous contrast.

10. Risk/ Benefit Assessment:

The risk to the subject from undergoing a non-contrast MRI study is minimal. The major risk is entering the magnetic field with an implanted non-MRI compatible device or hardware, or other ferromagnetic metallic object. This risk will be mitigated through the use of standard MRI screening techniques performed by the MRI technologist immediately prior to the scan. Again, because patients will have undergone MRI scanning of the brain as part of the standard diagnostic workup for intracranial hypotension, it is anticipated that few if any patients will have contraindicated hardware or metallic devices. Another risk is the risk of anxiety or claustrophobia associated with MRI scanning, which is screened for routinely by MRI technologists and will also be assessed by the research coordinator consenting patients for the study prior to enrollment.

Another potential risk associated with any research that involves data storage is the potential risk is loss of confidentiality. This will be minimized by adherence to the research data security plan (RDSP). Because this technique is investigational, no direct benefit to the subject can be promised.

11. Cost to the subject:

There will be no cost to the subjects

12. Data Analysis & Statistical Considerations:

As detailed above, the primary outcome measure is a comparison of ICP estimated with MR technique and the CSF pressure measured by lumbar puncture. Comparative statistics will be used for this analysis; the selection of appropriate statistical methods will depend on the normality of the data. It is anticipated that the main statistics will be descriptive and univariate comparisons. More advanced statistical techniques requiring support of a statistician are not anticipated, but if required by the data at the time of analysis, will be determined in consultation with the departmental statistician as necessary.

13. Data & Safety Monitoring:

Physical risks associated with the non-contrast MRI are minimal, as noted above. Any unexpected adverse events during the MRI will be addressed according to standard practice and departmental guidelines. Given the small number of subjects and exploratory nature of the data, no data monitoring committee will be used for this study. The risk of loss of confidentiality will be mitigated through the adherence to the RDSP.

14. Privacy, Data storage & Confidentiality:

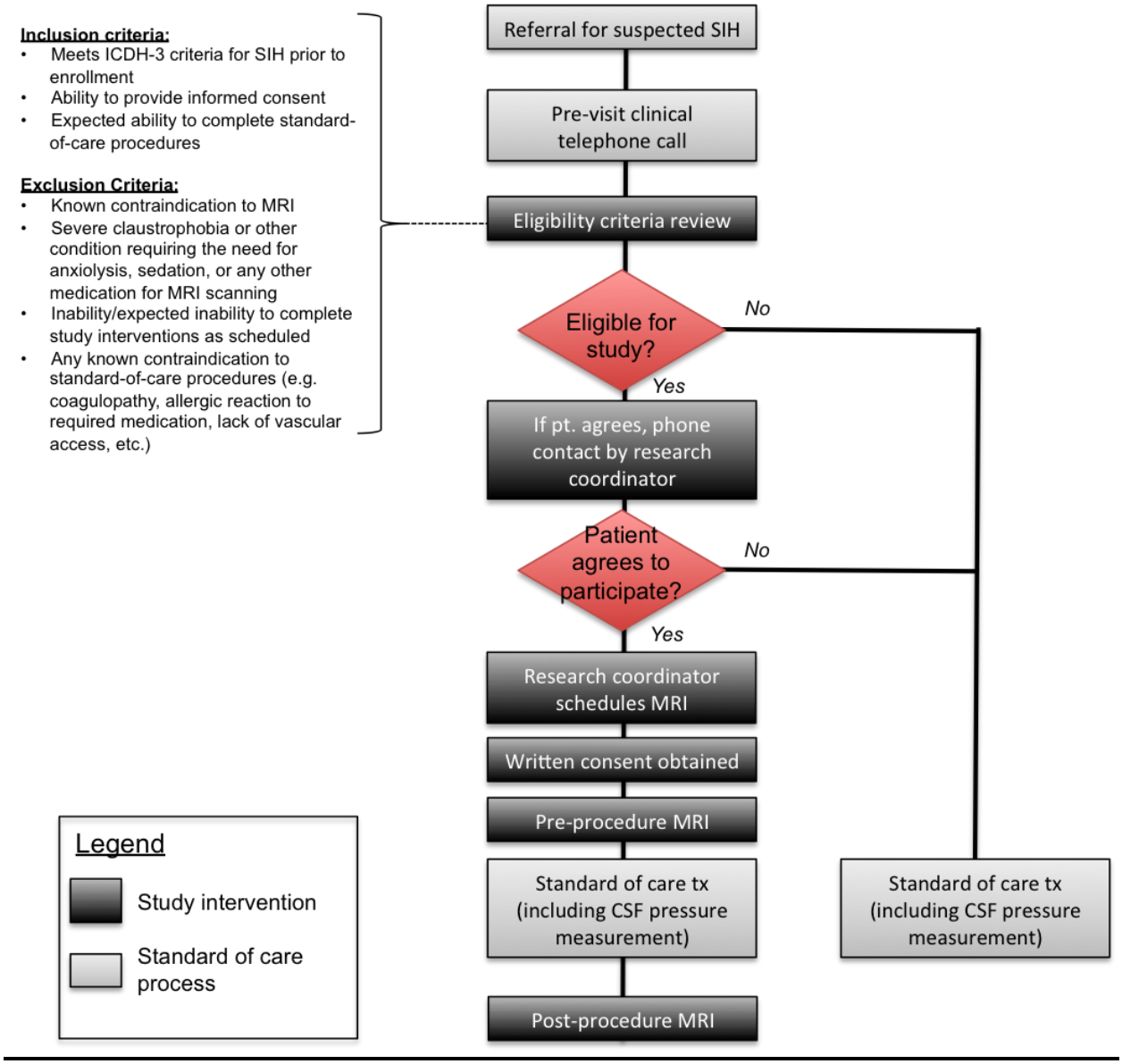
Every effort will be made to ensure confidentiality of the patients included in this study. Other data stored within Duke University Health System will be maintained in an IRB approved electronic storage format, as outlined in the RDSP.

Efforts will be made to protect the confidentiality of all medical records and other personal information to the extent required by law. However, we cannot guarantee absolute confidentiality. Patients will be advised in the consent process that the limited data set from their MRI will be sent to an outside institution for data analysis. Medical records of study participants are stored and kept according to legal requirements. They may be subject to inspection by the U.S Food and Drug administration and /or other regulatory authorities. A copy of this consent form will be put in the subject's medical record. All data will be considered confidential, and individuals will not be identified in any report or publication occurring as a result of this study.

15. References:

1. Mokri B, Posner JB. Spontaneous intracranial hypotension: the broadening clinical and imaging spectrum of CSF leaks. *Neurology* 2000;55:1771-1772
2. Kranz PG, Luetmer PH, Diehn FE, et al. Myelographic Techniques for the Detection of Spinal CSF Leaks in Spontaneous Intracranial Hypotension. *AJR Am J Roentgenol* 2016;206:8-19
3. Schievink WI. Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. *Jama* 2006;295:2286-2296
4. Kranz PG, Amrhein TJ, Gray L. Rebound Intracranial Hypertension: A Complication of Epidural Blood Patching for Intracranial Hypotension. *American Journal of Neuroradiology* 2014
5. Rohr A, Dorner L, Stingele R, et al. Reversibility of venous sinus obstruction in idiopathic intracranial hypertension. *AJNR Am J Neuroradiol* 2007;28:656-659
6. Simister R, Bowler JV, Wilson PL, et al. Transverse venous sinus stenosis and intracranial hypertension: evidence for which comes first. *J Neurol* 2008;255:601-603
7. Farb RI, Forghani R, Lee SK, et al. The venous distension sign: a diagnostic sign of intracranial hypotension at MR imaging of the brain. *AJNR Am J Neuroradiol* 2007;28:1489-1493
8. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension - The prevalence and morphology of sinovenous stenosis. *Neurology* 2003;60:1418-1424
9. Schievink WI, Dodick DW, Mokri B, et al. Diagnostic criteria for headache due to spontaneous intracranial hypotension: a perspective. *Headache* 2011;51:1442-1444

Appendix 1 – Schema


Inclusion criteria:
• Meets ICDH-3 criteria for SIH prior to enrollment
• Ability to provide informed consent
• Expected ability to complete standard-of-care procedures
Exclusion Criteria:
• Known contraindication to MRI
• Severe claustrophobia or other condition requiring the need for anxiolysis, sedation, or any other medication for MRI scanning
• Inability/expected inability to complete study interventions as scheduled
• Any known contraindication to standard-of-care procedures (e.g. coagulopathy, allergic reaction to required medication, lack of vascular access, etc.)
Referral for suspected SIH
Pre-visit clinical telephone call
Eligibility criteria review
Eligible for study?
No
Yes
If pt. agrees, phone contact by research coordinator
Patient agrees to participate?
No
Yes
Research coordinator schedules MRI
Written consent obtained
Pre-procedure MRI
Standard of care tx (including CSF pressure measurement)
Post-procedure MRI
Standard of care tx (including CSF pressure measurement)
Legend
Study intervention
Standard of care process

Appendix 2 – Summary of MRI brain protocol

Sequence	Approximate scan time
1. 3D T1 (for pre & post registration)	5min
2. sag FSE T2	3min
3. 3d phase-contrast MRV	4-5 min
4. MRICP protocol	8-10 min
	Total : 20-23 min

NB: all scans are performed without IV contrast administration.