Rapid MRI for Acute Pediatric Head Trauma

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1. **Protocol Title:** QuickBrain MRI for Pediatric Head Trauma: A Pilot Study

2. **Objectives:**
   A. Develop a feasible protocol for obtaining QbMRI for children presenting to the emergency department with acute head injury.
   B. Prospectively test the diagnostic accuracy of qbMRI for detection of acute pediatric TBI in the emergency care setting compared to head CT as the reference standard.
   C. Evaluate the feasibility of obtaining QbMRI in the emergency department to assess acute pediatric brain injury, including need for sedative medications, time to imaging, and provider satisfaction.

3. **Background:**

Pediatric head trauma remains a frequent reason for children to visit the emergency department (ED).[1] The current standard of care is to identify clinically important traumatic brain injury (ciTBI) which is defined as injuries that require surgical intervention, hospital length of stay greater than 2 days, intubation or result in death. This standard is used rather than "radiographic injuries" as this identifies lesions that require clinical intervention and observation rather than things that may be imaging artifact or so small that they are not clinically relevant. A majority of children with head injuries present to the ED with mild symptoms and Glasgow Coma Scale (GCS) scores of 14 or 15 resulting in a relatively low risk of a ciTBI that require neuroimaging.[2] However, due to the potential consequences of missed intracranial injury, CT imaging is frequently employed to further evaluate these patients. This concern is part of the cause for the dramatic increase in the rate of CT imaging over the last 10-20 years.[3] A recent Pediatric Emergency Care Applied Research Network (PECARN) study addressed this issue and developed a highly sensitive clinical decision rule that identified children at low risk of ciTBI that may not need head imaging.[1] In many clinical scenarios, this rule has the potential to substantially reduce CT use. However even when this rule is applied, the majority of CT scans obtained are negative, exposing children unnecessarily to ionizing radiation.

Magnetic Resonance Imaging (MRI) does not use ionizing radiation and has been shown to be accurate for detecting traumatic brain injury.[4,5] However, MR imaging takes longer to obtain than CT and requires patients to hold still for an extended period of time, often requiring sedation and limiting its use in acute injuries among pediatric patients. An abbreviated "Quick" brain MRI (QbMRI) protocol includes single-shot T2 weighted ultrafast spin echo images acquired in the axial, sagittal, and coronal planes. Images can be obtained in approximately 1-3 minutes. QbMRI has been previously studied for evaluating ventriculoperitioneal shunt failure in children with hydrocephalus and was found to be equally accurate to CT with approximately 4% of patients needing anxiolysis/sedation in both CT and MRI groups.[6] In a recent survey of institutions with a pediatric neurosurgeon on staff, approximately 80% have QbMRI capabilities, but its clinical utility remains uncertain as over 97% of these institutions still use CT for pediatric head trauma.[7–9] However, the effectiveness of QbMRI to diagnose ciTBI in the acute setting is unknown and has not been studied in a prospective manner. This subject is very important to improve the care we provide as pediatrics makes up the majority of acute head injuries seen in

emergency departments in combination with the increased radiosensitivity of their tissue and risk for malignancy.[10,11]

Preliminary Data:

Our initial retrospective study suggests that QbMRI has adequate sensitivity to detect acute ciTBIs in children. The study was presented at 2 national conferences in the spring of 2016 (Society for Academic Emergency Medicine and Pediatric Academic Society) with a manuscript currently under review.[12] This preliminary study included all pediatric trauma patients presenting to OHSU from 2/2010 through 12/2013 who had both a head CT and QbMRI. The current standard of care in the pediatric ICU at OHSU is for patients admitted with an acute head injury to undergo routine QbMRI follow up to assess status of the injury rather than a repeat head CT. Our study team collected clinical data on these patients that included clinical interventions and then de-identified all head CT and QbMRI images for this cohort. The images were then independently reviewed by 2 neuroradiology fellows at OHSU (Please refer to **Figure 1**). The sensitivity of QbMRI to detect any radiographic injury was 85% (95% CI: 73, 93), but increased when evaluating clinically important TBIs to 100% (95% CI: 89, 100). The largest limitation of this study was the variable and often long time interval between acquisition of the head CT and QbMRI. The average length of time between the initial head CT and QbMRI was 27.5 hours with only 41% receiving both imaging tests within 12 hours of each other. Also, our preliminary data was collected by retrospective review. As such, it is very promising that our initial study had high sensitivity, but further prospective pilot data with a shorter interval between the index and reference test is needed to assess the discrepancy between the two types of lesions (radiographic vs clinically important) and feasibility of obtaining qbMRI in the setting of acute pediatric head trauma. While our study did not miss any clinically important TBIs, on further review of radiographic "missed lesions", the study pediatric neurosurgeon noted signs of a healing bleed. This may suggest that they were "missed" because they were healed rather than present and not seen. All patients that did not have a lesion identified on QbMRI did not require significant clinical interventions and only underwent periods of observation in the hospital. However, this raises the need for a prospective trial to obtain QbMRI imaging within the same time frame sequentially after the initial head CT. The current proposed pilot study will provide further data to guide a larger, future multicenter study.

Specific Aims:

There are 3 specific aims for this study during the grant period:

D. Develop a feasible protocol for obtaining QbMRI for children presenting to the emergency department with acute head injury.
E. Prospectively test the diagnostic accuracy of qbMRI for detection of acute pediatric TBI in the emergency care setting compared to head CT as the reference standard.
F. Evaluate the feasibility of obtaining QbMRI in the emergency department to assess acute pediatric brain injury, including need for sedative medications, time to imaging, and provider satisfaction.

Outcomes:

1. Primary Outcome: Test characteristics of QbMRI to detect acute pediatric TBIs, including sensitivity, specificity, positive/negative predictive value and positive/negative likelihood ratios.

2. Secondary Outcomes: Develop formal protocol to be employed for further clinical evaluation and trials on QbMRI in pediatric head trauma; assess feasibility of obtaining QbMRI in the emergency department to include need for anxiolysis/sedation, time to imaging and provider satisfaction.

Hypothesis:
We hypothesize there is no significant difference of sensitivity and specificity of QbMRI for detection of clinically important traumatic brain injuries as compared to non-contrast head CT in patients less than 15 years presenting with head trauma. We hypothesize that it will be feasible to obtain QbMRI in the emergency department without increased use of anxiolysis/sedation or prolonged time to obtain imaging

4. Study Design:
Overview: The study will be a prospective cohort study of diagnostic accuracy comparing QbMRI (index test) to non-contrast head CT (reference test). Children being evaluated for acute TBI with head CT will then undergo QbMRI in the emergency department**.** Only subjects who the attending physician has decided to obtain neuroimaging in will be enrolled; therefore subjects will not undergo imaging just for the study. The results of the QbMRI will not be used for clinical care. All images will be de-identified prior to review by the neuroradiologist including patient name, hospital and date.

5. Study Population:
Inclusion criteria:

1. The patient presents to the pediatric emergency department or trauma system at OHSU or is a trauma system transfer patient to OHSU
2. Age 0-14 years.
3. Being evaluated for a traumatic head injury and attending physician decides to obtain a head CT.
4. Clinically stable for additional testing: provider deems it safe to obtain a QbMRI in the ED without deep sedation

Exclusion criteria:

1. Subject is from outside hospital and head CT was performed greater than 6 hours prior
2. Subject is from outside hospital and initial head CT is not in our imaging system for review
3. History of intracranial surgery
4. History of metallic implants making MRI contraindicated
5. Decompressive surgery prior to QbMRI

Study Procedure:

The Clinical Research Investigative Study Program (CRISP) volunteers who are on duty in the emergency department between the hours of 7 am and 11 pm will screen all ED patients for eligibility including pediatric trauma system entries. They will identify possible subjects based on suggestive chief complaints (e.g. head injury, trauma, fall, etc.) and approach the attending physician about whether the subject is being evaluated for possible acute head injury and will be receiving neuroimaging. If so, they will approach the family and review the consent forms with them for participation. After subjects are found to be eligible (see above inclusion/exclusion criteria) and consented, the physician will order the study QbMRI to be done after the head CT. QbMRIs are available to our pediatric ED at all hours as it is standard of care for other indications as described previously. Subjects will only be enrolled in the study if the attending physician feels they warrant neuroimaging with a head CT. After undergoing a QbMRI, their clinical care will be the same whether they are in the study or not. A copy of the images will then be de-identified and placed in separate review folders in the electronic radiology system so they cannot be linked (ie. One folder for head CTs and one folder for QbMRIs) for review by an attending neuroradiologist. Clinical data including length of stay, procedures performed and disposition will be collected directly from EPIC.

QbMRIs will be obtained in the MRI scanner at OHSU available to the ED. The protocol will consist of a QbMRI protocol modified to include a blood-sensitive T2* sequence. No intravenous contrast will be administered. It is not anticipated that any sedation or anti-anxiety drugs will be administered to patients. However, this is reflected in the consent that a small portion of children will need for any type of neuroimaging. For this reason, parents may decline participation. No deep sedation drugs will be administered as that will fall under the definition of clinically unstable in the exclusion criteria. The protocol consists of:
-Coronal single-shot T2 weighted ultrafast spin echo
-Sagittal single-shot T2 weighted ultrafast spin echo
-Axial T2* weighted gradient recall echo
After a subject undergoes their imaging in the MRI suite, their further disposition will be selected by the attending physician as what they feel is necessary including admission to the hospital, observation or discharge.

Traumatic Brain Injury on neuroimaging will be defined as previously published[1] to include:

- Intracranial hemorrhage or contusion
- Cerebral edema
- Traumatic infarction
- Diffuse axonal injury
- Shearing injury
- Midline shift of intracranial contents of signs of brain herniation
- Skull fracture depressed by at least the width of the table of the skull
- Pneumocephalus

Number of Subjects:

A total of 100 subjects will be enrolled in this pilot study. To generate an approximate study timeframe and potential patient sample, EPIC was accessed to identify all patients less than 19 years of age who were seen in the OHSU emergency department in 2015 and had a "CT Head WO contrast (CPT code 70450)" performed while in the ED. This resulted 363 patients. As a large referral center, OHSU receives many transfers from outside hospitals. In our retrospective data of trauma system activations, the majority were transfer patients with head injuries. These numbers would not be included in the 363 most likely as their neuroimaging was done at an outside hospital. A review of the trauma registry at OHSU for the year of 2015 and patient less than 19 years of age resulted 221 patients who had head and neck injuries. There is most likely overlap between these 2 data points as some trauma registry patients were not transfers and underwent head CT in our department. However, we would conservatively expect that 400 patients may be eligible for this study during a 12 month period.

To assess the adequacy of this proposed pilot sample, we calculated the number of positive head CTs obtained in our department. Our rate of positive findings were better than the previous study mentioned rate of 2.5% positive head CTs of all ordered. At OHSU 10% of CTs in patients less than 19 years of age were positive for an acute intracranial injury. This was generated by applying the above search criteria in EPIC and associated an intracranial injury final diagnosis code including epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intracranial bleed, skull fracture and cerebral contusion. This is a very conservative estimate as the majority of transfer patients through the trauma system will have positive neuroimaging as the reason for transfer and further pediatric subspecialty care. With these numbers we would expect to enroll the 100 patients within 1 year and have at least 10-20% with a positive acute TBI when taking into account the positive imaging rate in the OHSU emergency department and transfer patients with positive imaging.

Vulnerable Populations

This study, by design, is focused on pediatric patients. It may include other vulnerable populations such as pregnant women and minorities, though they are not the focus of the study

and are not included in screening criteria. No pregnant women will be given an MRI knowingly. Prisoners will not be included in this study.

Setting

The Doernbecher Children's Hospital emergency department

Consent Process

All parents will be consented on presentation to the emergency department by a member of the study team including the CRISP team. Please find attached consent form. All children ages 7-14 will be asked to signed the assent form as well.

We are requesting a consent/HIPAA waiver for a select group of patients. Any patient who is excluded from the study after initial screening for any reason other than the LAR refusing to be included will be reviewed by the principal investigator. If the clinical team, without any input from the research team, has obtained the same imaging test this study is evaluating, QuickBrain MRI, the study team will use the imaging and data as in the rest of the protocol under a waiver. It is not possible to obtain consent due to the short time window of being in the ED. Due to the acute nature of the injuries they do not have follow up in the ED either to allow consent.

For patients who are excluded after the parent/LAR refuses the study, all charts will be reviewed. If the patient underwent the same imaging test this study is evaluating, QuickBrain MRI, by the clinical without any input from the research team, the patient family will be contacted by the study Principal Investigator as participation is generally declined in the trauma bay due to family stress. Unless at time of consent, study team noted reason for declining participation would be such that they would not be amenable to re-contact. The principal investigator will only discuss the study once with parents/LAR via phone number in EHR and detail that their child underwent the same imaging test we are studying. At that time, the principal investigator will ask for consent to include the patient in the study as nothing is needed in addition or further follow up. A telephone script has been uploaded to further detail this consent process.

Data Analysis:

All data will be entered into a RedCap database maintained on the OHSU network server requiring a username and password. Clinical data will consist of descriptive statistics. The primary outcome of whether a lesion was seen on QbMRI will be presented as sensitivity, specificity, negative predictive value and positive predictive value with 95% confidence intervals. The secondary outcome of whether patients need anxiolysis will be compared between head CT and QbMRI with an independent t-test. The QbMRI protocol will be described with language to describe the imaging.

Clearance of perivascular waist in the brain is critical for recovery after traumatic brain injury. Some of these clearance happens through a network of perivascular spaces surrounding the brain

vessels called the glymphatic system. When the glymphatic system becomes dysfunctional, enlarged perivascular spaces (ePVS) can be seen on MRI. The third outcome of this study is to evaluate the presence of ePVS in patients with concussion receiving an MRI during their emergency department evaluation. We hypothesize that changes in perivascular spaces happen over time, and therefore ePVS should not be present in these early studies.

Three blinded researchers (Juan Piantino, Erin Boespflug and Daniel Schwartz) will count ePVS on single axial MRI slices containing the basal ganglia and centrum semiovale regions using established visual rating scales based on anatomical landmarks. Inter-rater agreement will be calculated. In addition, ePVS will be calculated automatically using an imaging software and the counts will be compared to human raters. The size and number of ePVS will be compared to a large database of normal children.

Sharing of Results with Subjects: results of this study will not be shared with patients as it is not impacting clinical care. In addition, the gold standard for this study and clinical care currently, head CT, will be performed and direct care. The results of the head CT will be discussed with families as that is what is dictating their medical care.

Data and Specimen Banking: Records will be destroyed at termination of the study

Privacy, Confidentiality and Data Security

The primary ethical consideration is maintenance of privacy as all data being collected is already part of the medical record other than the Quickbrain MRI. The access to study data and key linking subjects will be restricted to PI and study staff. The Quickbrain MRI is stored within the OHSU imaging system (IMPAX) which requires user authentication and network login. These imaging tests will only be reviewed by members of the study team.
All records detailing clinical data will be entered into a RedCap Database with limited access requiring an OHSU network username and password. The records will then be coded prior to analysis with study ID numbers that do not contain any HIPAA identifiers. A list of medical record numbers that are associated with each study ID number will be kept on the OHSU network server in a separate Microsoft excel file that is password protected. This will only be used to identify a study ID medical record in cases of data discrepancy or if clinical outcome data is further needed. The study data will remain on this secure server with coded study ID numbers until all academic activity is completed (ie, published article, presentation, etc). At which time, the study database will be deleted/destroyed from the server. With these safeguards, we are confident that we can adequately protect patient confidentiality.

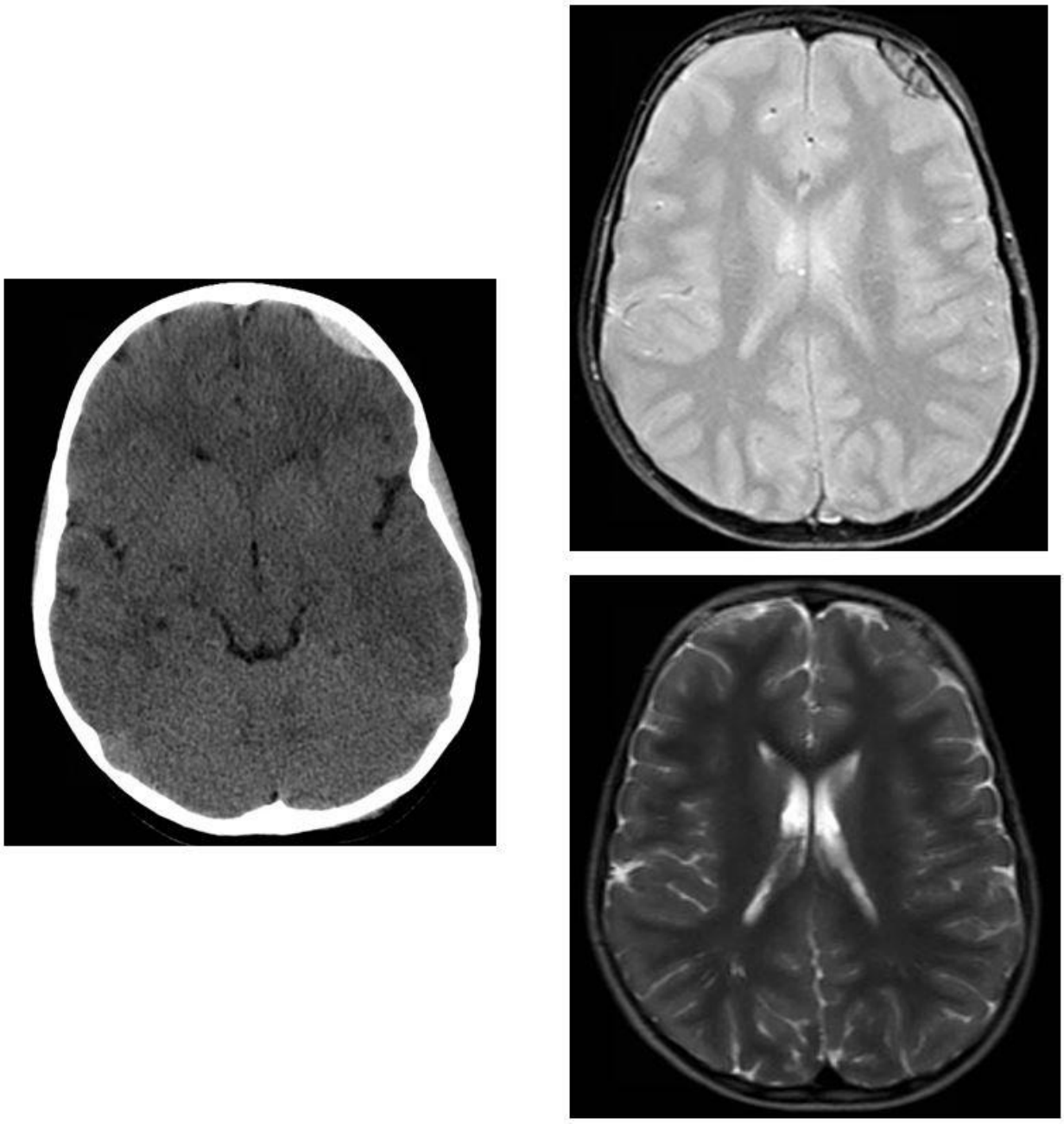
Risks and Benefits

a) Risks to Subjects: There is a small risk of loss of confidentiality, however, safeguards are being taken to code the data and protect all confidential information as described in the

protocol. There is no risk associated with Quickbrain MRI as it is without any radiation, pain or adverse effects which is why we are studying it.

b) Potential Benefits to Subjects: There is no potential benefit in this study for patients directly but can change the standard of care for future patients.

Figure 1. Image Comparisons



The image on the left is from a non-contrast head CT of patient with an acute epidural hematoma (annotate image). The top right (T2*) and bottom right (single-shot T2) were acquired as part of a QbMRI and show the same hematoma.