Evaluation of the efficacy of contrast enhanced ultrasound compared to MRI for differentiation of hepatic lesions

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Aim

In patients with hepatic lesions, to evaluate the efficacy of contrast enhanced ultrasound (CEUS) compared to MRI in differentiating focal nodular hyperplasia (FNH) and hepatic adenoma. Studies from Europe (Dietrich et al, Roche et al) have described different patterns of enhancement between FNH and hepatic adenoma. MRI is the current imaging modality of choice for making this determination, but has limitations. This pilot study aims to test the hypothesis that CEUS has similar ability to differentiate FNH and adenoma, using MRI as the gold standard.

Rationale

Hepatic imaging plays an important role in identifying and differentiating both benign and malignant neoplasms of the liver. One of the clinical and radiologic dilemmas facing hepatic medicine is the accurate differentiation of focal nodular hyperplasia (FNH) and hepatic adenoma (HA). This is a question of some import, as there are significant prognosis and treatment differences between these entities, as well as overlap in the patient populations in whom they occur.

FNH is the second most common benign neoplasm of the liver, with a strong female predilection. These lesions are usually asymptomatic and incidentally discovered, and carry only a small risk of complication such as bleeding. There is no malignant potential. Hepatic adenomas (HAs) are more rare benign neoplasms that also have a female predilection. However, these lesions are more likely to be symptomatic, and carry a higher bleeding risk especially as they grow over 4 cm. In addition, they harbor a small risk of malignant transformation to hepatocellular carcinoma (HCC). Of note, patients may present with both types of lesion concurrently.

Currently, MRI with hepatobiliary contrast agents is the standard for differentiation of these lesions. These agents (such as gadoxetate disodium, or Eovist) are actively transported into hepatocytes, which are present in FNH and only in very rare cases with HA. Previous research (such as from Grazioli et al.) has shown that hepatobiliary agents can differentiate these lesions with excellent accuracy. However, there is still overlap between these lesions on imaging, and for certain patients MRI may be difficult or impossible.

FDA approval of contrast enhanced ultrasound (CEUS) agents in 2016 has opened a new avenue for abdominal imaging. CEUS utilizes gas containing lipid microbubbles to provide pure intravascular contrast, allowing for evaluation of vascular and solid organ perfusion. It has an excellent safety profile and is not excreted by the kidneys, allowing for use in patients with acute and chronic renal disease. It has been used for some time outside of the US for liver lesion evaluation, and the enhancement patterns of both FNH and HA have been described in the literature as having different appearances. CEUS can be especially useful for focal liver lesion

imaging for patients who cannot or will not undergo MRI, and it has the advantages of flexibility, increased temporal resolution, and decreased cost. This study aims to compare the utility of CEUS for differentiating FNH and HA with the current standard of hepatobiliary contrast MRI.

Performance site

University Hospital
Methodist Hospital

Patient selection

Inclusion criteria

1. Males and females
2. Age 18 years or greater
3. Recently have undergone (within 365 days) or are scheduled to undergo abdominal MRI with contrast at a performance site for evaluation of a hepatic lesion(s).

Exclusion criteria

1. History of acute cardiac ischemia
2. History of hypersensitivity reaction to Lumason
3. Pregnancy

Methods

Potential subjects will be identified by three methods.

1) From the MRI schedule at the performance site, a radiology investigator will prospectively identify patients who are to undergo abdominal MRI with hepatobiliary contrast and who otherwise meet entry criteria. Exclusion criteria will be evaluated by consulting the medical record. At the time of MRI scanning, a radiology investigator will meet with the potential subject, confirm that exclusion criteria are not met, explain the study, answer any questions, and seek written informed consent. If consent is granted, CEUS of the liver will be scheduled.
2) From the surgery/hepatology clinic schedule, a surgery or hepatology investigator will identify patients who meet entry criteria. The investigator will explain the study to the patient; if he/she expresses interest, the investigator will give a copy of the informed consent to the potential subject, and contact radiology and have the patient scheduled for CEUS of the liver. At the time of CEUS, a radiology investigator will meet with the potential subject, confirm that exclusion criteria are not met, explain the study, answer any questions, and seek written informed consent.
3) The principle investigator will retroactively review the radiology database, DORIS, for patients who have had a recent MRI with hepatobiliary contrast and who otherwise meet entry criteria that may have been missed by the previous methods mentioned. A study

radiology investigator will reach out to the patient's hepatologist about enrolling them in the trial and obtain best contact information. A study coordinator will contact the patient by email or phone, with IRB approved script, to seek consent to contact for recruitment purposes.

The subjects will be scanned in the University or Methodist Hospital ultrasound department by technicians trained in use of CEUS, under supervision of one of the study's key personnel. The contrast agent used will be Lumason (sulfur hexafluoride lipid-type A microspheres) distributed by Bracco Diagnostics Inc. Previous MRI images will be reviewed, and up to two of the largest lesions will be evaluated. Each lesion will be interrogated with a single intravenous dose of contrast (2.5 mL). If there is a single lesion, a second 2.5 mL injection may be used as needed to improve lesion visualization. If there are two lesions, each will be evaluated with one injection. Since the intention to treat includes all lesions chosen from MRI, if the injection(s) do not provide adequate images, the lesion in question will not be excluded from the study.

Once the study is closed to enrollment and all subjects have completed the research CEUS scan. The obtained CEUS images will then be reviewed in consensus by two radiologist investigators, blinded to clinical information and MRI findings. Each lesion assessed will be given a presumed diagnosis of FNH, HA, or indeterminate. At the completion of the study, the CEUS data will be compared to the official reports from the MRIs dictated by IUH radiologists to assess concurrence between the two imaging modalities.

The PI and another investigator will quarterly review data quality, subject recruitment, accrual, outcome and adverse event data; assess scientific reports or therapeutic development, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects.

We will compile descriptive statistics comparing the sensitivity, specificity, and accuracy of CEUS for differentiating FNH and hepatic adenoma, compared with MRI results as the gold standard.

Enrollment

As this study explores a new method of diagnosing hepatic lesions and there is little published data on the subject, we do not have sufficient knowledge to do power and sample size calculations to demonstrate the number of patients needed to show equivalence between the two imaging methods. The proposed enrollment of 40 patients reflects the availability of both Lumason and the approximate number of qualifying patients who would undergo MRI for evaluation of these lesions in one year.

Resources/Budget

At the performance site, patients with suspected FNH or HA typically undergo MRI of the liver as part of standard of care, and the patient or insurer will be billed for the examination and radiologic interpretation. CEUS is not routinely performed in this population. The cost

associated with CEUS and the time of the investigators will be the responsibility of the Department of Radiology and Imaging Sciences.

Subjects will be compensated for their time and effort with a $50.00 gift card upon completion of research imaging.

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