Using Ultrasound Elastography to Predict Development of Sinusoidal Obstruction Syndrome

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1. STUDY OBJECTIVES/HYPOTHESIS

Primary Objective

Hepatic sinusoidal obstruction syndrome (SOS) or hepatic veno-occlusive disease (VOD) is a complication of hemopoetic stem-cell transplantation that results from injury to the venous endothelium causing hepatic venous outflow obstruction at the level of the venules and sinusoids. Other causes of SOS include liver transplant, radiation therapy, chemotherapy and alkaloid ingestion. Clinically, it is characterized by hepatomegaly, jaundice, right upper quadrant pain and ascites. Traditional ultrasound imaging criteria for the diagnosis of SOS have been shown to have poor sensitivity and specificity. Our hypothesis is that quantitative shear wave ultrasound elastography will be more accurate in detecting this disease compared with conventional ultrasound parameters.

Secondary Objective

Our secondary hypothesis is that to quantitative shear wave ultrasound elastography will be more accurate in determining that SOS/VOD is severe (See Table 2 for grading) compared with conventional ultrasound parameters.

2. BACKGROUND

Sinusoidal obstruction syndrome (SOS) is a potentially fatal hepatic veno-occlusive disease-affecting children following bone marrow transplantation (BMT). SOS most likely develops secondary to sinusoidal endothelial damage and subsequent obstruction. The disease can be separated into mild, moderate, and severe forms; almost all patients diagnosed with severe SOS will die from this disease [1]. Children with severe SOS suffer from multi-organ failure with signs and symptoms of portal hypertension (ascites, varices, edema), renal and respiratory failure [1,2]. Although these children may be few and far between, the mere severity of the disease process and awful prognosis factors are valid reasons for more medical attention. SOS is usually diagnosed via clinical criteria and, despite available prophylaxis and treatment, children continue to die from this devastating disease. There have been a few retrospective and prospective studies examining ultrasound in adults BMT patients, which have showed limited effectiveness of traditional ultrasound parameters to detect SOS [3-7].

Quantitative shear wave ultrasound elastography with acoustic force radiation imaging is an emerging technology that uses ultrasound pressure waves to provide an estimate of tissue stiffness[8-11]. This technique is promising for pediatric imaging because it is portable, quick to perform, relatively low cost and involves no ionizing radiation. Acoustic force radiation imaging and ultrasound elastography does not have any increased risks over conventional ultrasound imaging[8-13]. It has been studied in pediatric liver imaging[14-16], placental imaging[13], thyroid imaging[17,18] and musculoskeletal imaging[19].

Table 1. A table to show the clinical criteria for veno-occlusive disease

Modified Seattle Criteria	***Baltimore Criteria***

Two of the following criteria must be present with in 20 days of SCT	Bilirubin must be ≥ 2mg/dL before 21 days SCT and two of the following criteria must be present
Bilirubin ≥ 2mg/dL	Ascites (Physical exam or radiographic)
Hepatomegaly increased over baseline	Weight gain ≥ 5 %above baseline weight *
Ascites (Physical exam or radiographic) and /or Weight gain ≥ 5 %above baseline weight	Hepatomegaly increased over baseline

Table 2. Staging of VOD/SOS [20]

Mild : Resolved without interventions
Moderate : Requires treatment • Bilirubin > 6 mg/dl • AST > 5 times upper limit of normal • Weight gain > 5 % • Ascites
Severe : Progression to Multi-organ dysfunction syndrome • Respiratory failure (O2 saturation < 90 %) • Hepato renal syndrome • Encephalopathy • Severe renal failure (creatinine > x 2) • Bilirubin > 20 mg/ dl

3. RATIONALE

SOS is a disease with a low incidence but high mortality rate once diagnosed. There are treatments available for this disease if diagnosed early. Currently, no good imaging prognostic factors are known. Some imaging criteria for SOS are available but all detect the disease after it has been clinically confirmed.

If we can discover an imaging modality that can more accurately diagnose SOS and determine prognosis at the time of imaging, then we can guide how aggressive to be with the available interventions that can slow progression or stop the disease.

4. STUDY DESIGN

This is a single site prospective cohort study that will compare ultrasound elastography to traditional ultrasound parameters in bone marrow transplant patients who are at risk for development of SOS.

5. TARGET STUDY POPLUATION SPECIFICS

Inclusion Criteria

All patients Age < 21 years who are undergoing allogenic or autologous myeloablative stem cell transplant.

Exclusion Criteria

- Any patient who is undergoing reduced intensity conditioning regimen for stem cell transplant.
- Any other medical or social condition that in the opinion of the investigator would make them unsuitable to participate.

6. DATA COLLECTION

Data Collection Procedures

- Candidates for the study will be identified by the Hematology Oncology service when they are admitted for bone marrow transplant.
- A member of the study team will consent that patient and/or their parents once the patient has been identified.
- If the patient consents to the study, three limited abdominal Doppler ultrasound (US) and shear wave elastography will be performed. The initial US and elastography will be performed within a week from receiving condition regimen, second US and elastography on Day +3 to Day + 7 of transplant (preferably on day + 5 of transplant) and lastly, on Day +12 to Day +16 (preferably on Day +14)
- Demographic, laboratory and clinical variables will be collected from CIBMTR research registry database (IRB# 11120281) as well as from the EMR from the time of initial ultrasound and through day 100 post-transplant.

  For subjects whom consented to take part in the CIBMTR database, a data request from CIBMTR will be requested using the assigned CRID number for each subject.

  Subjects that did not consent for CIBMTR database will have demographic, laboratory and clinical variables collected out of EMR into REDCap.

  Data will provided from CIBMTR in the form of a spreadsheet and will be password protected and sent to CMH only for data analysis.

Clinical and outcome data, including DOB, dates of service, exams, lab values and clinical timepoints will be evaluated.

- Multiple shear wave elastography measurements of the liver will be obtained during any post-transplant clinical abdominal ultrasounds.

Table 3. Timeline for obtaining the limited abdominal Ultrasound and Elastography

First Ultrasound Exam	Within a week prior to receiving conditioning regimen
Second Ultrasound Exam	Day +4 to Day + 7 of transplant (Preferably on day + 5 of transplant)
Third Ultrasound Exam	Day +12 to Day +16 of transplant (Preferable on Day +14 of transplant)
Further Ultrasound Exam	Performed based on clinical necessity. Elastography will be performed with every ultrasound.

Records to be kept

Protected health information (PHI) to be collected for the purpose of this study alone will include; age, gender, race, MRN, date of transplant, dates of ultrasound exams. This information will be documented in RedCap and CIBMTR password protected spreadsheet. Within RedCap, there will be two separate files. One file will exclude PHI and contain study data according to an assigned study ID number. The second file, will contain a master list of subjects linking the subject PHI with the assigned study ID #. The research record generated will consist of an excel spreadsheet from the data dictionary within RedCap. Security measures include: storage of the data on a password protected computer in a restricted assess departmental folder limited to only identified study personnel.

Secure Storage of Data

CIBMTR data will be stored on the hospital server and REDCap data will be manually entered and stored on the hospital server. Development of data entry record will occur in collaboration with Medical Information Technology to ensure compliance and completeness. The Children's Mercy Hospital (CMH) Windows-based network is configured with the security of an individualized log in on a server that is backed up daily. Resources provide full support for electronic data collection, storage, analysis and exchange. The network is maintained by the Hospital Information Services professional staff. CMH has two firewall protected Internet connections that allow transmission of large data and graphics files between CMH investigators and collaborators with I-2 connections. CMH has secure transport appliances that use SSH, SFTP, and FTPS protocols to allow researchers to transmit and receive large datasets manually or automatically.

Study data points will be entered into the RedCap research record, according to assigned study ID#. A master list linking only subject medical record number with assigned study number will be maintained in a separate, RedCap data file.

7. STUDY DURATION/STUDY TIMELINE

Stage 1, patient accrual and data collection (2015-2017)
Stage 2, data analysis (2017-2018)
Stage 3, presentation and publication (2018)
Projected start date: Novemeber 1, 2015
Total length of time: two years
Approximate end date of the study: June 1, 2018

8. STATISTICAL CONSIDERATIONS

Measures

- Primary measure: presence or absence of SOS (clinical determination from provider, will refer to Cerner chart)
- Secondary measure: severity of SOS (Cerner chart)

General Design Issues

- Primary objective: compare sensitivity and specificity of traditional ultrasound parameters and ultrasound elastography of the liver for detecting SOS in BMT patients.
- Secondary objectives: 1. compare sensitivity and specificity of traditional ultrasound parameters and ultrasound elastography of the liver for identifying severe SOS in BMT patients.

Sample size determination

Previous articles showed that patients with SOS had velocities of 2.75 and 2.58 m/s versus velocities of 1.08 m/s in normal controls[20,21]. The incidence of SOS in our BMT patient is estimated to be around 10% and about 40 patients undergo transplant here in 1 year. So assuming a two year interval, we would have 8 patients with BMT and SOS and 72 patients with BMT and no SOS. Based on a mean velocity of 2.66 m/s in SOS patients and 1.08 m/s in non-SOS patients and a standard deviation of 1 m/s in both populations, a two-sided t-test would have a power of 0.987 for detecting a statistically significant ($p<0.05$) difference between the means

Data Analyses

We will perform two-sided t-tests and nonparametric tests for categorical and continuous data, respectively. Additionally, we will perform a multivariate regression to determine which variables are significantly correlated to severe SOS (table 2) and calculate an odds ratio for each of these variables. If a patient is missing any imaging or clinical data, then this patient will be excluded from those parts of the data analysis, but the rest of their data will still be included in the study.

HUMAN SUBJECTS

Institutional Review Board (IRB) Review and Informed Consent

Potential subjects will be identified by the Hematology/Oncology service once they are scheduled for BMT. Once potential subjects are identified and general eligibility is determined, a member of the study team will approach the patient and their family and present the study to them. If the parent(s)/legal guardian deny an interest in the study, they are thanked for their time and are not subsequently contacted again.

Subject Confidentiality

Each subject's medical record will be reviewed by research staff and data entered into the research record. A master linking list will be maintained in the REDCap database and this list will only be visible to study personnel.

Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the OHRP, the FDA or other Government agencies as part of their duties to ensure that research subjects are protected.

9. PUBLICATION OF RESEARCH FINDINGS

Results are intended to be presented at the Society of Pediatric Radiology 2017 annual meeting.
Results are intended to be published in the radiology or hematology trade journals in 2017.

10. REFERENCES

1. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med.* 1993;118(4):255-267.
2. Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. *Blood.* 1998;92(10):3599-3604.
3. Hommeyer SC, Teefey SA, Jacobson AF, et al. Venocclusive disease of the liver: prospective study of US evaluation. *Radiology.* 1992;184(3):683-686.
4. Teefey SA, Brink JA, Borson RA, Middleton WD. Diagnosis of venoocclusive disease of the liver after bone marrow transplantation: value of duplex sonography. *AJR Am J Roentgenol.* 1995;164(6):1397-1401.
5. Garcia-Criado A, Gilabert R, Salmeron JM, et al. Significance of and contributing factors for a high resistive index on Doppler sonography of the hepatic artery

immediately after surgery: prognostic implications for liver transplant recipients. *AJR Am J Roentgenol.* 2003;181(3):831-838.
6. Nicolau C, Bru C, Carreras E, et al. Sonographic diagnosis and hemodynamic correlation in veno-occlusive disease of the liver. *J Ultrasound Med.* 1993;12(8):437-440.
7. Herbetko J, Grigg AP, Buckley AR, Phillips GL. Venoocclusive liver disease after bone marrow transplantation: findings at duplex sonography. *AJR Am J Roentgenol.* 1992;158(5):1001-1005.
8. Bamber J, Cosgrove D, Dietrich CF, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med.* 2013;34(2):169-184.
9. Cosgrove D, Piscaglia F, Bamber J, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. *Ultraschall Med.* 2013;34(3):238-253.
10. Shiina T, Nightingale KR, Palmeri ML, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. *Ultrasound Med Biol.* 2015;41(5):1126-1147.
11. Stenzel M, Mentzel HJ. Ultrasound elastography and contrast-enhanced ultrasound in infants, children and adolescents. *Eur J Radiol.* 2014;83(9):1560-1569.
12. Ferraioli G, Filice C, Castera L, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. *Ultrasound Med Biol.* 2015;41(5):1161-1179.
13. Sugitani M, Fujita Y, Yumoto Y, et al. A new method for measurement of placental elasticity: acoustic radiation force impulse imaging. *Placenta.* 2013;34(11):1009-1013.
14. Kutty SS, Peng Q, Danford DA, et al. Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. *Hepatology.* 2014;59(1):251-260.
15. Leschied JR, Dillman JR, Bilhartz J, Heider A, Smith EA, Lopez MJ. Shear wave elastography helps differentiate biliary atresia from other neonatal/infantile liver diseases. *Pediatr Radiol.* 2015;45(3):366-375.
16. Ozmen E, Adaletli I, Kayadibi Y, et al. The impact of share wave elastography in differentiation of hepatic hemangioma from malignant liver tumors in pediatric population. *Eur J Radiol.* 2014;83(9):1691-1697.
17. Lin P, Chen M, Liu B, Wang S, Li X. Diagnostic performance of shear wave elastography in the identification of malignant thyroid nodules: a meta-analysis. *European radiology.* 2014;24(11):2729-2738.
18. Liu B, Liang J, Zheng Y, et al. Two-dimensional shear wave elastography as promising diagnostic tool for predicting malignant thyroid nodules: a prospective single-centre experience. *European radiology.* 2015;25(3):624-634.
19. Lacourpaille L, Hug F, Guevel A, et al. Non-invasive assessment of muscle stiffness in patients with Duchenne muscular dystrophy. *Muscle Nerve.* 2015;51(2):284-286.
20. Fontanilla T, Hernando CG, Claros JC, et al. Acoustic radiation force impulse elastography and contrast-enhanced sonography of sinusoidal obstructive

syndrome (Veno-occlusive Disease): preliminary results. *J Ultrasound Med.* 2011;30(11):1593-1598.

21. Son CY, Kim SU, Han WK, et al. Normal liver elasticity values using acoustic radiation force impulse imaging: a prospective study in healthy living liver and kidney donors. *J Gastroenterol Hepatol.* 2012;27(1):130-136.