Investigation of Ambulatory Blood Pressure in Cirrhosis Patients
AmbBP-C Study

Hypothesis

We will test the hypothesis that a proportion of patients with cirrhosis experience hypotension in the ambulatory setting, and this occurrence is associated with significant morbidity (e.g., acute kidney injury) and mortality.

Aims:

What is the burden of masked hypotension (i.e., Proportion of patients with normal clinic visit mean arterial blood pressure but with >1 episode of ambulatory hypotension)?

What is the association between ambulatory blood pressure and clinic visit blood pressure and the development of acute kidney injury?

What is the association between ambulatory blood pressure and clinic visit blood pressure and death?

Design:

This is an observational study. We will approach patients with cirrhosis who are seen at the outpatient UCSF Liver Clinics. If willing, patients will be provided an ambulatory blood pressure monitor with an integrated cellular signal (i.e., not wifi or bluetooth) that is listed on the US Blood Pressure Validated Device database (VDL). After an instructional meeting at the time of enrollment, participants will be asked to take their ambulatory blood pressure twice daily (i.e., morning and night). Participants will partake in this study for 1-year. The ambulatory data will be provided to the researchers through an encrypted, HIPAA compliant server provided by the blood pressure monitor manufacturer (i.e. Withings). Simultaneously, we will periodically (i.e., monthly) review the participant's medical records and will extract clinic visit notes including clinic visit blood pressure measurements, demographics, hospitalization records, and all available laboratory values. After 1-year, the cellular signal on the device will be disabled. The participant will be able to keep the device for their own personal use. After 1-year, we will review their records every 6 months for an additional 2-years (3-years total). We will investigate the proportion of patients who experience masked hypotension. We will determine the association between ambulatory blood pressure and clinic visit blood pressure and the development of AKI and mortality.

Background and Significance:

Cirrhosis affects 1 in every 50 US adults and is the 4th leading cause of death in those ages 45-64 years. Acute kidney injury (AKI) in patients with cirrhosis is: i) common, occurring in one of every two patients; ii) lethal with nearly 75% of patients having AKI at death; iii) expensive, hospitalizations in cirrhosis patients with AKI cost ~$2 billion in 2016. A common risk factor of AKI in cirrhosis patients is hypotension. Patients with cirrhosis intrinsically have low blood pressure - a consequence of the altered venous return from portal hypertension and the impaired degradation by the liver of endogenous vasodilatory molecules. Despite this association, blood pressure in cirrhosis patients is currently only measured sparsely - every 3 to 6 months at

clinic visits. As a result, the burden of ambulatory hypotension and the impact of ambulatory hypotension on AKI and mortality in this population are unknown.

Preliminary Studies:
To date, no study in cirrhosis patients has investigated ambulatory blood pressures in cirrhosis patients. One study by Tsien et al has investigated the association between clinic visit blood pressure and the development of AKI. No study has investigated the association between ambulatory or clinic visit blood pressure on mortality in cirrhosis patients.

Procedures/Methods:
Patients will undergo the following procedures to this study:

1. We will pre-screen patients coming to the UCSF outpatient liver clinic 48 hours prior to their visit.
2. To set the device and allow for distribution at the time of their visit, we will call all possible participants 48 hours prior to their clinic visit and determine if they are interested in partaking in this study.
3. After their clinic visit, potential participants will be approached and provided the consent for this study. If willing, participants will be enrolled, provided a 5-minute device tutorial, and participants will be given the device on their visit day.
4. After which, participants will complete a morning blood pressure (e.g., prior to breakfast) and nighttime blood pressure (e.g., prior to sleep) for 1-year.
5. Patients at the time of enrollment will elect if they would like free text message reminders if they do not complete their measurements for a 24-hour period. If participants, do not complete their measurements for a 72-hour period, then a member of the research team will call them to remind all patients.
6. Should patients be hospitalized or traveling, we will instruct patients to not perform any measurements.
7. All measurements will be provided to the researchers through an encrypted, HIPAA compliant portal provided by the manufacturer (Withings).
8. We will review their medical records monthly for a 1-year period and every 6 months for an additional 2-year period. This review will include all clinic notes, demographics, and laboratory values.

There will be no extra clinic visits, lab tests, biopsies, tissue collection, or additional scans outside the routine care and monitoring provided by the UCSF Liver Clinic. We will not monitor the portal for episodes of hypotension in real-time - meaning that if a patient has hypotension, they will not be called to review for symptoms. Instead, at the time of consent and the monitor tutorial, we will review with patients the signs and symptoms of hypotension. We will instruct patients to review any new developments with their provider, who can be reached 24 hours 7-days a week through the clinic number, or to seek urgent/emergent care.

Statistical Methods
We will divide our cohort into 4 groups: Ambulatory Hypotension/Clinic Hypotension, Ambulatory Normotension/Clinic Normotension, Ambulatory Hypotension/Clinic Normotension, Ambulatory Normotension/Clinic Hypotension.

Our primary outcome will be acute kidney injury, defined as a doubling in serum creatinine from outpatient baseline requiring hospitalization. Baseline will be defined as the most recent outpatient serum creatinine prior to enrollment in this study. Death will be defined as death.

Survival analyses will determine the unadjusted and adjusted association of our 4 groups and AKI and death. We will censor those lost to follow-up. We will adjust for the variables obtained during our record review.

References

Cullaro, Giuseppe, Meyeon Park, and Jennifer C. Lai. 2018. "'Normal' Creatinine Levels Predict Persistent Kidney Injury and Waitlist Mortality in Outpatients With Cirrhosis." *Hepatology* 68 (5): 1953–60.

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Cullaro, Giuseppe, Elizabeth C. Verna, Brian P. Lee, and Jennifer C. Lai. 2020. "Chronic Kidney Disease in Liver Transplant Candidates: A Rising Burden Impacting Post–Liver Transplant Outcomes." *Liver Transplantation: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 26 (4): 498–506.

Tsien, Cynthia D., Rania Rabie, and Florence Wong. 2013. "Acute Kidney Injury in Decompensated Cirrhosis." *Gut* 62 (1): 131.

Moon, Andrew M., Amit G. Singal, and Elliot B. Tapper. 2019. "Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis." *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association* 18 (12): 2650–66.

Baki, Jad A., and Elliot B. Tapper. 2019. "Contemporary Epidemiology of Cirrhosis." *Current Treatment Options in Gastroenterology* 17 (2): 244–53.

Sample Size Justification

Based on prior literature, we suspect the following distribution in our 4 groups: 50% ambulatory normotensive/clinic normotensive; 25% ambulatory hypotensive/clinic hypoptensive; 12.5% ambulatory hypotensive/clinic normotensive; 12.5% ambulatory normotensive/clinic hypotensive. As best we can estimate 20% of the ambulatory normotensive/clinic normotensive group; 45% of the ambulatory hypotensive/clinic hypoptensive group; 40% of the ambulatory hypotensive/clinic normotensive; and 40% of the ambulatory normotensive/clinic hypotensive group will develop AKI during 1-year of follow-up. Based on these effect sizes, we found that we would need to recruit 274 patients to have 80% power to detect at a significance level of 0.05.

Age Range:

18-64

65+

Study Populations:

Outpatients

Special Subject Groups:

Subjects unable to read, speak or understand English

Roughly <10% of our population at the UCSF Liver Clinic are non-English speaking. The majority of these patients are either Cantonese, Mandarin, or English speaking. Through our clinic infrastructure, we have access to either in-person or video interpreters (Language Lines Solutions). Not including these potential participants would create a bias in our study based on English-speaking status. Given that we have available interpreter services and the minimal risk associated with this study, we feel that we can accurately and safely include these participants in our study.

We will evaluate the capacity of the individual to consent for this study by confirming with their outpatient provider that they have capacity.

We will provide the consent information in the participant's native language. We will ask them to perform teach-back to confirm comprehension.

We have designed the payment for this study to reflect the amount of time needed to participate.

Inclusion criteria:

We will approach all patients with cirrhosis who are seen at the outpatient UCSF Liver Clinic.

Recruitment and Consent

We will pre-screen the UCSF Liver Clinic schedule and identify patients with a diagnosis of cirrhosis. This will include a review of patients' conditions, history, test results, etc.

Searching of Medical Records

Investigators' own patients or patients seen within the same practice
Self-search in APeX or other medical records source
We have an ongoing relationship with the Department of Medicine bioinformatics group. We in the future will develop a cohort selection tool that automates the selection of patients who are eligible for this study.

Determination of Eligibility:

Eligibility will be determined by the study team after the chart review as outlined above. This will include a patient seen in the UCSF liver clinic with a chart diagnosis of cirrhosis, medications for a cirrhosis indication, a cirrhosis-related complication, or laboratory values (thrombocytopenia, elevated total bilirubin, elevated INR, low albumin level) suggestive of cirrhosis.

Initiation of Contact

Investigators/study team

How is contact initiated:

In person, phone

Recruitment Plan

A member of our research team will review all UCSF outpatient liver clinics in the following 48 hours to screen which patients are presenting with a cirrhosis diagnosis.

Each potential participant will be called 48 hours before their visit to see if they would be willing to meet with the research team after their clinic visit.

Those who are willing will be met after their clinic visit by our research team either in-person or virtually via zoom that will be set up by our clinic staff. We will then discuss the consent process as outlined below.

Consent Methods:

Sign a paper consent form at the end of the consent discussion (signed consent)
Sign an electronic consent form using DocuSign (signed consent)

Consent Procedures:

The outpatients are scheduled to be seen by a provider in the UCSF liver clinic. After their visit, they will meet either in-person or virtually via zoom with a member of our research team. If this meeting is virtual, our clinic staff will facilitate the meeting via an available clinic room in the same office building. Consent will be obtained by a member of the investigation team. This will be a ~ 15-minute meeting where the consent will be reviewed.

After this meeting, the potential participant will be asked about consent. If they are willing, we will proceed. if they would like further information, we will approach patients at their subsequent clinic visit. If consent is obtained, we will provide an additional 5-10 minute tutorial on how to use the blood pressure monitor. We will review signs and symptoms of hypotension and ensure that all participants express understanding regarding the study, the indications to seek urgent/emergent care, and the clinic's 24-hour number.

The study team has undergone training to consent patients for clinical studies. The principal investigator will review this consent with each member of the study team.

The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation

Given that <10% of our patients with cirrhosis in the UCSF Liver Clinic are non-English speaking, we do not foresee that we will need to consent non-English speaking patients often. Additionally, given the minimal risks associated with this study, we believe that it is reasonable to utilize the Short-Form.

This study involves 2, 1-minute blood pressure measurements daily for 1 year. That is roughly 12-hours of time for year. Patients will be compensated for this time in 2 ways: 1). All patients will be able to keep their ambulatory blood pressure monitor after the study ($85 value); 2). Participants who complete >75% of their daily blood pressure measurements will receive a $25 Target gift card every 3 months for 1 year.

Risks and benefits:

Risk of pain or physical discomfort caused by the research intervention

There is the risk of discomfort with the measuring of ambulatory blood pressure.

There is the risk of loss of protected health information.

There is the risk of undiagnosed hypotension.

We have minimized the risk of pain by: 1) We will during our tutorial perform a monitored blood pressure measurement in the clinic. We will ensure that it is tolerated by the patient and if there are any concerns, the participant can withdraw from the study; 2) We have limited our measurements to just twice daily. This should limit the inconvenience to the participant.

We will take several steps to protect PHI. All records and patient identifiers will only be kept in an encrypted REDCAP database. When exporting data or completing analyses, we will only use identifiers uniquely generated for this study. We have partnered with Withings who provides a HIPAA compliant, encrypted server to provide the ambulatory blood pressure measurements to the research team.

There is the risk that patients will experience hypotension in the outpatient setting. That being said, typically this information is not available to providers. Therefore, this is not an added risk to what is tolerated normally. To mitigate this risk, during our tutorial we will review the signs of hypotension and indications to seek

urgent/emergent care. Additionally, we will provide the clinic number with 24-hour, 7-days a week coverage should there be uncertainty or clinical questions. This service is available to all members of our practice.

Resources
Our staff is all clinically trained in clinical research including in the consent of patients and safe and responsible conduct in clinical research.

We have obtained cellular-enabled devices that do not require WIFI or Bluetooth connection. As a result, this obviates many financial inequities that may present with the utilization of most ambulatory blood pressure monitors in clinical research.

our clinic has the staffing and resources to provide the time and space to consent patients and inform patients about this study.

We have access to our clinic answering service and we will provide the clinic number with 24-hour, 7-days a week coverage should there be uncertainty or clinical questions regarding possible hypotension symptoms.

Benefits
Closer follow-up than standard care may lead to improved outcomes or patient engagement

Health and lifestyle changes may occur as a result of participation

Knowledge may be gained about their health and health conditions

Feeling of contribution to knowledge in the health or social sciences field

Risk to benefit Ratio:
The measurement of ambulatory blood pressure is a minimally invasive procedure. We have taken several steps to limit the risks to the participant. There is a marked opportunity to improve the care for the participant. If they are having hypotension, they can review these values with their provider. they may recognize behaviors that lead to hypotension and change those. There is significant potential to understand better how blood pressure mediates outcomes in cirrhosis patients. This may allow for future studies and clinical trials where blood pressure is modulated with vasoconstricting medications.

Confidentiality
Conduct conversations about the research in a private room
Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject’s permission

No stigmatized or illegal behavior will be obtained

No breach of confidentiality could lead to significant consequences to the participant
We will only leave PHI in the REDCAP database. We will utilize a study-specific, uniquely generated patient identifier for any analysis or export of the data outside of the REDCAP database.

HIPAA Applicability: Study Data will be Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)

Clinical Data:
Study investigators or their designees will be responsible for data collection from the patient's medical chart using standardized methodologies described below. We propose to perform a manual chart review on a subsample of outpatients from the UCSF liver clinic. No sensitive information.