Cover Page: Study Protocol

Protocol Title: Comparison of furosemide alone versus the combination of furosemide and albumin for diuresis in cirrhotic patients with fluid retention

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I. Abstract:

a. A common complication of the progression of cirrhosis is fluid retention (ascites, edema, or pleural effusion). Loop diuretics are the treatment of choice for fluid retention in cirrhotic patients; however, many of these patients demonstrate diuretic resistance, requiring higher doses of the diuretics to achieve adequate diuresis. The cause of this diuretic resistance is hypothesized to be secondary to hypoalbuminemia which has led some providers to give human albumin in combination with loop diuretics to increase intravascular volume and facilitate diuresis. However, this practice remains controversial because minimal data exists to support its efficacy. The purpose of this study is to compare the efficacy of diuretics alone versus diuretics in combination with albumin in cirrhotic patients presenting with fluid retention.

II. Background and Significance:

a. Accumulation of fluid as ascites, edema, or pleural effusion is common in patients with advanced liver disease.[1] Typically, treatment of fluid retention is extrapolated from the practice guidelines by the American Association for the Study of Liver Diseases (AASLD) for the management of adult patients with ascites due to cirrhosis.[2] According to these guidelines, first line treatments for management of ascites are cessation of alcohol use (when applicable), restricting sodium and fluid intake, and using diuretics (such as loop diuretics). However, many patients with cirrhosis demonstrate diuretic resistance and require higher doses of these medications to obtain the desired clinical effect. Since hypoalbuminemia is postulated to be one of the causes of diuretic resistance in cirrhotic patients, some providers recommend giving albumin in combination with loop diuretics for the treatment of fluid retention. This recommendation developed from the current understanding of the pathophysiology of liver disease and its effect on intravascular space leading to fluid retention.[1] Despite this common trend in practice, there remains minimal data that compares the efficacy of diuresis using diuretics alone versus the combination of diuretics and albumin.

   Currently, there is only one randomized, controlled trial published in 1999 that compared the use of diuretics alone versus the combination of diuretics and albumin in cirrhotic patients.[3] This was a single center conducted in Italy where the investigators used potassium canrenoate and furosemide as diuretics in combination with albumin (25%) 12.5 grams daily. The doses of diuretics used were per center protocol and based on patient clinical response. The results from their study showed that the cumulative rate of response to diuretic treatment of ascites was higher (90.5% vs. 74.7%) ($p< 0.05$) and length of hospital stay was shorter ($p< 0.05$) in the group of patients that received diuretics and albumin versus diuretics alone. Although the results were favorable with the use of albumin, the external validity of this study is minimal since it was a single center conducted in Italy in 1999.

III. Study Aims

a. The purpose of this single center, prospective study is to compare the efficacy of two strategies for diuresis in patients with cirrhosis, the use of furosemide (Lasix®) alone versus the combination of furosemide (Lasix ®) and albumin (25%).

IV. Administrative Organization

a. All research regarding this project will be performed at Rush University Medical Center (RUMC). There will be no inclusion of outside study sites, laboratories, or data management centers.

V. Methods and Materials

a. Trial Design and sample size

i. We will perform a single-center, prospective study with data collected as result of standard of care at RUMC. Patients who are 18 years of age and older, have diagnosed cirrhosis, and present to RUMC with fluid retention will be identified by the Hepatology and/or Surgery attending and be screened for inclusion in the study. Each patient will be randomized into one of the two cohorts and will have 50% chance of being placed into either cohort.

Cohort 1 will receive furosemide (Lasix) 40 to 80 mg IVP BID for at least 48 hours and cohort 2 will receive combination of furosemide (Lasix) 40 to 80 mg IVP BID and albumin (25%) 12.5 grams BID for at least 48 hours.

ii. A sample size of 150 patients for this study was estimated based on the previously published study by Gentilini P and colleagues.[3] The estimation was based on a success rate of 70% in patients receiving diuretics alone and 90% in patients receiving diuretics plus albumin (alpha = 0.05; beta =0.25).

b. Process of Consent

i. This study is a prospective study so consent from the patient will be obtained prior to enrollment. To obtain consent, the physician will explain the purpose of the study, associated risk and benefits, and answer any additional questions or concerns the patient may ask. If patient decides to enroll in the study, the physician will provide them with the appropriate consent form and all signed forms will be in a securely locked filing cabinet.

c. Participants

i. Adult patients (age $\geq$18 years old) who have cirrhosis and present to RUMC with fluid retention (ascites, edema, or pulmonary effusions).

d. Inclusion/Exclusion Criteria

i. ***Inclusion criteria***: Adult patients (age $\geq$18 years old), diagnosis of cirrhosis and presents with fluid retention as defined as ascites, edema, or pulmonary effusions requiring diuresis.

ii. ***Exclusion criteria***: Patients who are younger than 18 years of age or currently pregnant or who presents with a serum creatinine greater than 2 mg/dL will be excluded.

e. Outcomes

i. ***Primary outcome***: Urine output greater than or equal to 0.5 ml/kg/hour over 24 hours or reduction in weight defined as weight loss of 1 kilogram or greater in a 24-hour period. *(While urine output is the best measure for diuretic efficacy, it can often be an unreliable measurement due to patient's not collecting urine properly. Therefore, changes in weight after initiation of diuretic therapy is often used as a surrogate marker for the efficacy of the diuretic therapy, regardless of patient weight at baseline. Several heart failure trials use a change in weight as the endpoint for assessing diuretic efficacy, and this endpoint is also commonly used in clinical practice. Therefore, that is why this endpoint was chosen for this study.)*

ii. ***Secondary outcome:*** Change in renal function as defined by a chance in serum creatinine from admission to discharge, hospital length of stay, 30-day readmission rates, and patient survival at 6 months and 1 year.

VI. Risk/Benefit Assessment

a. Potential Risks

This study is a prospective trial however minimal risk to the patient is associated with participation in this study as he/she will be receiving one of two standard of care treatments at our center. Minimal risks associated with the study include experiencing common side effects from the FDA-approved medications used for treatment. The most common side effects of furosemide administered intravenously are low blood pressure, dizziness, headache, or irritation of the skin at the site of injection. In addition, the most common side effects of albumin administered intravenously are high blood pressure, headache, nausea/vomiting or irritation of the skin at the site of injection. There is also a potential risk for invasion of privacy since medical records will be accessed but all data will be de-identified to limit the chance of exposure of PHI.

b. Protection against risks

Physicians will be assessing patients in the study daily and will take precautions against the potential common side effects associated with the FDA-approved medications in this study as stated previously. Precautions include daily monitoring of patients through labs and physical examination and making medical interventions as deemed appropriate.

Data will be collected from the electronic medical record which will be de-identified and maintained in Research Electronic Data Capture (RedCap).

c. Potential benefits to subjects

Patients may benefit from taking part in this study. Based on experience with the use of furosemide (Lasix) and albumin in patients with similar conditions, researchers believe it

may be of benefit to people with cirrhosis. However, because individuals respond differently to therapy, no one can know in advance if it will be helpful for these patients. If the current therapy is not deemed helpful by the physician, the physician will start an alternative standard of care treatment for the patient.

d. Alternatives to participation
Patients may choose to not participate in this study. If participants choose to not participate in this study, the physicians will determine an alternative treatment plan for their fluid retention.

VII. Confidentiality of data and information storage

a. Data collection will take place on a data collection tool, which will be separate from PHI and will not contain identifiers. RedCAP will be used for data collection and storage. Patient confidentiality will be maintained by recording only de-identified data onto the data collection form. Although the data collected and stored in REDCap will be exported for analysis, the exported data will contain no unique, patient-identifying information. Access will only be available to the research investigators.

Data collected from the electronic medical record at RUMC will include:

1. Patient demographics
2. Daily lab results including chemistry panel, INR, liver function tests, renal function tests
3. Physician's rating of patient's edema (if applicable)
4. Dose, frequency, and administration of furosemide (Lasix ®) and/or albumin

VIII. Analysis Plan

a. Statistical analysis will be performed with SPSS statistical package. Patient characteristics will be described using frequencies, means $\pm$ standard deviations or medians ± interquartile ranges. Student's t-test will be used to compare continuous variables. Comparisons between groups or categories will be made using chi-squared test. The threshold for statistical significance will be $p<0.05$.

IX. Literature Cited

1. Kashani A, Landaverde C, Medici V, and Rossaro L. Fluid retention in cirrhosis: pathophysiology and management. Q J Med 2008; 101:71-85.
2. American Association for the Study of Liver Diseases (AASLD): Practice guidelines for the management of adult patients with ascites due to cirrhosis 2012. Hepatology 57(4), 2013.
3. Gentilini P, Casini-Raggi V, Di Fiore G, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. J Hepatol. 1999 Apr;30(4):639-45.