A Double Blinded Prospective Study to Investigate the Efficacy of Octreotide, Midodrine and Albumin vs. Terlipressin and Albumin for the Treatment of Hepatorenal Syndrome.

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A. Study Rationale

Hepatorenal Syndrome (HRS) is defined as acute renal failure, a common complication seen in patients with advanced liver cirrhosis. The renal failure is due to severe vasoconstriction of the renal vasculature as a result of complex alterations in systemic hemodynamics. The diagnosis of HRS relies on excluding any other identifiable causes for the renal failure. It is estimated that ~20% of patients with hepatic failure, ascites, and some renal dysfunction will develop HRS in the first year of diagnosis. The estimated mortality once patients develop HRS is as high as 85-90%. Once patients develop HRS the most effective treatment is liver transplantation. Due to the stringent transplant requirements not everyone is eligible and without a liver transplant their median survival as estimated by Capling et al, to be less than 2 weeks. Hemodialysis is often times used as a bridge to liver transplant with a mean survival of 236 days as per Capling et al.

Currently, as previously stated, the best treatment is liver transplantation and since this option is not always available, other therapies are being used. Albumin infusion have been used with vasopressin analogues and have shown promising results however, most studies have been retrospective, have been very small, or are based out of Europe. Midodrine and Octreotide have also been used and have shown mixed results but most studies have been very small. Angeli et al. showed an impressive improvement in Glomerular filtration rate and overall renal function in eight patients using the combination of Midodrine, octreotide, and albumin. Other studies using either midodrine or octreotide alone have not shown any significant improvement. Given the high mortality and current treatment options there is a definite need for further larger prospective studies.

This prospective double-blinded randomized trial will be used to see the efficacy of using Midodrine, Octreotide, and albumin vs. Terlipressin and albumin for the treatment of HRS.

As previously mentioned HRS is a consequence of vasoconstriction of arterioles, which leads to decreased renal flow and decreased glomerular filtration rate (GFR). They also have marked splanchnic vasodilation, which causes further reduction in systemic vascular resistance thereby decreasing effective arterial blood volume. This induces an over activation of vasoconstrictors in the sympathetic and rennin-angiotensin system. All of this further contributes to renal vasoconstriction and therefore causes hypoperfusion of the renal system leading to renal failure. Midodrine is a selective alpha-1 adrenergic agonist-a systemic vasoconstrictor. Octreotide a somatostatin analog acts as an inhibitor of endogenous vasodilator release. Together they would improve renal flow by counteracting the action of vasoconstrictors on renal perfusion. Terlipressin has been used mainly in Europe as it is undergoing Phase III trials in the United States under EPS Pharma and will therefore require an Investigational Drug application. Terlipressin is an analog to antidiuretic hormone with a longer half-life than it's counterpart drug used here vasopressin. It acts to reduce splanchinic vasodilation along with volume expansion can help reduce the release of renal vasoconstrictors which would in turn improve renal perfusion and glomerular filtration.

B. Study Design and Statistical Analysis

This prospective double-blinded randomized trial will be used to see the efficacy of using Midodrine, Octreotide, and albumin vs. Terlipressin and albumin for the treatment of HRS. Residents, fellows, and attendings will be made aware of the study via flyers and a conference. There will be an investigator available via beeper to recruit patients. Most patients will be recruited from the medical intensive care unit will be eligible after meeting the proposed criteria. Subjects will be recruited only if their primary care physicians are in agreement with the study and if the subject or the subject's proxy is in agreement then they will be consented.

Using a Chi-square test a total of 105 patients will be needed in each arm in order to achieve 80% power, testing at P=.05.

The primary outcomes will be based on improvement in creatnine clearance by 30%

within 72 hours of initiating treatment. This will take into account Cr improvement and Urine output. Secondary outcome will include decrease in serum creatnine and mortality. Because the mortality is so high in these patients >2 weeks without a transplant, mortality will not be used as a primary endpoint. Drug safety will be evaluated on a twice-daily basis via monitoring their vascular exam to detect peripheral vascular compromise as well as vital signs.

C. Study Procedure

After informed consent is obtained, subjects will be selected based on the inclusion exclusion criteria for HRS by the investigator on call. Subjects will then be randomized into one of the two arms 1-midodrine,octreotide, albumin, and placebo 2-trelipressin, albumin, and placebo pill + placebo subcutaneous injection. The house staff taking care of these patients will be blinded to treatment unless severe adverse affects are seen. At that time these patients will be released from the study and there treatment method will be unveiled.

Inclusion criteria :

- chronic or acute liver disease with advanced liver failure and portal HTN
- creatnine>1.5
- urine output <500ml/day
- Urine protein excretion <500mg/day
- No improvement in renal function despite 1.5L of normal saline and 50% albumin 50cc infusion every four hours x 24 hours

Exclusion criteria:

- Transplant eligible patients
- Patient's in shock defined as: tachycardia, tachypnea, metabolic acidosis, cool/clammy skin, SBP<90mmHg, oliguria with a change in mental status
- Current bacterial infection including spontaneous bacterial peritonitis
- Treatment with nephrotoxic medicines during their hospital admission
- Renal obstruction evident by renal ultrasound
- Parenchymal renal disease
- Gastrointestinal blood loss
- Cardiac disease-including history of myocardial infarction, angina, coronary artery disease, or congestive heart failure
- Treatment with diuretics, vasopressors, or inotropes in the preceding 24hours

Subjects will be randomized into one of two groups Octreotide, Midodrine and albumin vs. Albumin and Terlipressin. Midodrine will be administered as an oral agent and will be given at 10mg oral three times a day along with Octreotide which will be administered initially at 100mcg subcutaneous three times a day. These doses will be titrated to max 12.5mg three times a day and 200mcg three times a

day respectively to obtain an increase in mean arterial pressure of at least 15 mmHg. In the terlipressin arm they will receive an initial dose of 1mg every 4 hours intravenous on day one. If there are no observed vascular events and SBP<160 patients will then receive 2mg every 4 hours on the second day. All patients will receive the same amount of albumin-50cc of 25% intravenous every 6 hours.

Subjects will remain on their respective treatment for 72 hours. They will be classified as responders if creatnine clearance improves by 30%. Initial responders will remain on their drug therapy until a steady state is reached. The steady state will be defined as no change in creatnine level for 48-72 hours. If they do not reach their steady state but improve by 30% in 72 hours, they will then be classified as initial responders but not sustained responders. Subjects who do not improve creatnine clearance by 30% by 72 hours will be classified as nonresponders and will be released from the study. Subjects who acutely need dyalisis due to acidosis, electrolyte abnormalities, or volume overload refractory to medical management will also be released from the study. After patients respond or become steady via creatnine they will be released from the study and at that point the primary team will continue their management.

The protocol will be stopped if the patient develops any of the following:1.signs of ischemia 2.cardiovascular compromise including chest pain, tachycardia heart rate>120, hypertension SBP>180 mmhg 3.allergic reaction 4.any acute indication for dyalisis.

In both groups routine labs including chem10, complete blood count, liver function test will be collected at 8am and at 8pm. They will also have close monitoring of urine output via a foley every hour. Creatnine clearance will be calculate by a 3-hour urine collection during the night blood draw. Lastly a twice-daily complete physical exam to assess any ischemic changes.

Information regarding patient gender, age, medical history, child and melds scores will be obtained and kept in a separate file and will not be a part of the medical record.

Endpoint: at the end of the study daily urine output and creatnine clearance will be calculated and compared for both arms.

D. Study Drugs

Midodrine is a selective alpha-1 adrenergic agonist-a systemic and splanchnic vasoconstrictor in combination. It is FDA approved for treatment hypotension.

Octreotide is a somatostatin analog a natural occurring hormone produced by the hypothalamus. It works by inhibiting endogenous vasodilator release that in turn would improve renal flow by counteracting the action of vasoconstrictors on renal perfusion. It is FDA approved mainly for carcinoid tumor or vasoactive intestinal peptide secreting tumor. Terlipressin has been used mainly in Europe as it is undergoing Phase III trials in the United States under EPS Pharma and will therefore require an Investigational Drug application. Terlipressin is an analog to antidiuretic hormone with a longer half-life and lower side effect profile than its counterpart drug, which is, used here vasopressin. Due to its longer half-life it may be administered as a bolus infusion. It acts to reduce splanchinic vasodilation along with volume expansion can help reduce the release of renal vasoconstrictors which would in turn improve renal perfusion and glomerular filtration. Albumin is produced in the liver and has been used in patients who are intravascularly depleted. It is a useful plasma expander to help maintain cardiac output.

E. Medical Devices

No medical devices will be used in this study.

F. Study Questionnaires

No questionnaires will be used in this study.

G. Study Subjects

Patients who are 18 years or older who have chronic or acute liver disease-decompensated with portal hypertension. They will need to meet the following inclusion and exclusion criteria:

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H. H. Recruitment of Subjects

There is a Liver service team at Columbia Presbyterian, which receives a majority of cirrhotic patients. This service will be surveyed on a daily basis to enroll eligible patients. We will also inform medical house staff including residents, fellows, attendings about this study via flyers and via a conference. Both the flyers and the conference will inform them on the study's inclusion and exclusion criteria as well as provide education about the study. A contact person will be available via beeper 24 hours a day. The investigator on call will consent the patients, review the study with their primary physician, and will evaluate their eligibility.

I. Confidentiality of Study Data

All information gathered from this study including labs, and urine outputs will be recorded on a separate data sheet and will not be part of the medical record. Any information regarding the patient's or physician's personal information will not be used.

J. Potential Conflict of Interest

None of the investigators would benefit monetarily from the drugs under investigation.

K. Locality of the Study

This study will be conducted on the medical intensive care unit.

L. Potential Risks

The biggest risk is the use of the drug Terlipressin. There have been few events associated with peripheral vasoconstriction leading to ischemic limbs, however the doses in which this has been seen has been much higher than what we propose. Terlipressin unlike its analogs does not reportedly cause coronary artery constriction, despite this we are excluding patients who may be at risk. Midodrine has a fairly safe profile. Some adverse affects that we will monitor for include hypertension and bradycardia. Octreotide also has a relatively safe profile, most serious affects include bradycardia, which we will closely monitor.

Since both groups are blinded there will be an unblinding protocol in an event of any suspected serious side effect.

M. Potential Benefit

Given the high mortality associated with the development of HRS the possibility of finding a better treatment will benefit patients.

N. Alternative Therapies

There are no proven effective therapies that have clearly shown beneficial. Dyalisis has been used to sustain life but is not considered a definitive treatment.

O. Compensation to Subjects

Subjects will not receive compensation for participating in this study.

P. Costs

Since the treatment of HRS will not differ from the normal costs they would incur, subjects or the subject's insurance will be responsible for hospital cost, labs, and medications except for terlipressin. Terlipressin will be obtained from its manufacturer.

Q. Minors

No minors are involved in this study.

R.

Radiation or Radioactive substances

No radioactive subjects or radiation are involved.