A Role for the Hepatocyte Liver Assist System

A. Introduction

The purpose for conducting this study is to establish a role for the Hepatocyte Liver Assist System in the treatment of severe liver failure until the patient can be transplanted or recovers spontaneously. The management of severe acute liver failure remains a major clinical challenge with an extremely high mortality rate. This challenge has remained in place due to the fact that the pathophysiology of the disease is still not completely understood, especially why patients with acute liver failure tend to develop cerebral edema, while those with chronic liver disease usually do not. It is postulated that the etiology of the cerebral edema happens secondary to the neurotoxic substances that are not properly cleared by the failing liver, possible leading to herniation and brain death. This thinking has led to attempts to provide plasma exchange, specific and nonspecific binding of potentially toxic substances using various binding techniques, which have all been unsuccessful. There has been some success with liver transplant and xenogeneic whole liver perfusion, but major immunologic challenges present problems. The Hepatic assist device could allow for fewer transplants, especially since organs are limited. This device could also decrease the chances of immunologic problems as this is an extracorporeal device. -There have been only a few previous studies:

#1 The device used was referred to as an extracorporeal liver-assist device(ELAD), and was shown to be safe in a noncontrolled phase I clinical trial
11 patients (9y.o-67yo) with stage 3 or 4 hepatic encephalopathy, ELAD was used as a bridge to transplant
Results: 4 Liver tx/ 6 died/ and 1 recovered spontaneously (reseachers noted improvement of neurologic and biochemical signs in 10 of 11 patients) 5 of the 6 deaths attributed to cerebral edema.

#2 Three groups-Fulminant hepatic failure, primary non-function of the transplanted liver, and acute on chronic liver disease
Fulminant hepatic failure- 16 of 18 survived to liver tx (decr.cerebral edema) l recovered without tx and 1 died from severe pancreatitis
PNF- All 3 survived to liver tx (decrease. cerebral edema)
Each trial underscores the fact that there is still much more to learn about this system.

* I hope this clinical trial will determine whether patient survival with or without liver tx can be improved with the hepatic assist device. I would like to observe a 25% decrease in mortality.

B. Study Design

This will be a randomized, controlled trial of conventional medical therapy alone vs conventional medical therapy with hepatic assist system

I will enroll 150 patients from 10 medical centers that have developed Stage 3 or 4 hepatic encephalopathy while on standard medical therapy in the ICU setting.

C. Patient group

2 groups: Fulminant Hepatic Failure(n=75) and Primary non-function of transplanted liver (n=75)
Disease etiology (FHF) = 50 indeterminate/ 10 Viral / 8 Acetaminophen / 7 Ischemic
Disease etiology (PNF) = 65 autoimmune / 7 Viral / 3 indeterminate

a. Patient Demographics

- Age 21 - 50, both men and women, minorities (black, white, and hispanic)

- -Patients will be followed by members of the Liver Service @ their respective institutions, which includes nurses and physicians of multiple subspectialty services(transplant, ID, nephrology, neuro, etc.)
- -Patients will have invasive hemodynamic monitoring with peripheral arterial catheter and pulmonary artery catheter after there coagulopathy is corrected. Patients with signs of intracranial pressure will have a subdural monitor placed at the bedside. Medical support will be given if patient manifest signs (ie. mannitol,
- -Patients with stage 4 hepatic encephalopathy are intubated
- -Renal dialysis of hemofiltration are used when needed and electrolytes are corrected along with metabolic derangements. Patients will also receive ulcer prophylaxis and H2 antagonist
- -A double lumen catheter will be placed in the Right superficial femoral vein to accomodate the hepatic assist device. The hepatocytes were previously frozen and were obtained from fetal pigs. Plasma perfusion was chosen over whole blood, because of the decrease risk of hemolysis and thrombocytopenia. The plasma is first separated then citrate is added to prevent thrombosis with the system, and CaCI is infused to prevent chelation induced hypocalcemia. The system has a semi-permeable membrane that is in place to limit the transfer of xenozoonoses. The membrane porosity is important to prevent this, and the porosity in this study is 10 nm (viruses range from 30 - 200). The hepatic liver system will last approx. 6 hours/day until death, transplant, or clinical improvement. This will be done during regular business hours, allowing a large number of services to be readily available. This will also be cost effective as only 1 operator would be needed.

b. Inclusion Criteria

- men and women minorities
- age 20-50

c. Exclusion Criteria

- Stage lor 2 hepatic encephalopathy
- Hemodynamically unstable
- Overt signs of sepsis
- If not a transplant or re-transplant candidate
- Pregnancy

D. Medical Devices

According to the FDA, the extracorporeal use of hepatocytes to treat liver failure is considered a drug not a device, because there are exogenous substances released from the hepatocytes and the endogenous substances biotransformed by the hepatocytes.

E. Location of the study

The central location will be at CPMC, while 9 other medical centers will be involved in the study.

F. Risk and Benefits

Risk- the device may not be as effective, immune response Benefit- pt. may or may not benefit as a result of participation

G. Compensation

Nothing

H. Lay Abstract

The purpose of this study is to observe if the mortality of liver failure is decreased with the use of coventional medical therapy and a liver assist device versus that of conventional medical therapy alone. This liver assist device has been approved by the FDA.

Approximately 150 subjects will be enrolled from CPMC and 9 other medical centers. This study will involve only adults who will be recruited only after it has been ascertained that the patient is willing to participate in the study.

The patients chosen for alternative therapy will receive the liver assist device, which is attached to the patients blood stream so that it can function to filter the blood; the action that a normal healthy liver could do on its own.

There are no practical or ethical problems related to the performance of this study.