Artificial Liver Support Systems

J George

Abstract

Though artificial support systems for kidney failure have been widely available for the past several decades, it is only recently that they have become a promising treatment modality for liver failure. The various liver support systems include conventional dialysis, charcoal hemoperfusion, high volume plasma exchange, liver dialysis using sorbent technology, molecular adsorption recirculating system using albumin as the dialysate, bioartificial livers, extracorporeal liver assist device and extracorporeal organ perfusion. They are mainly used as a bridge to liver transplantation and occasionally in acute liver failure till the liver regenerates. The various methods of extracorporeal liver support that are available at present are assessed and those that appear to be promising are described.

INTRODUCTION

Unlike renal failure, artificial support systems were not widely used in liver failure, mainly because hepatic toxins are albumin-bound unlike most uremic toxins and hence cannot be removed by conventional dialysis. It has been only recently that advances have been made concerning removal of hepatic toxins. It is thus now possible to support the patient with liver failure till the liver recovers or until liver transplantation is feasible. This article describes the various methods of artificial liver support systems and highlights the recent developments in this field.

TYPES OF ARTIFICIAL LIVER SUPPORT SYSTEMS

1. Peritoneal dialysis

Though this has been used occasionally in patients with combined liver and renal failure with ascites, it has a limited role due to inadequate removal of hepatic toxins especially in those having poor peritoneal blood flow.

2. Hemodialysis

Conventional hemodialysis (HD) removes only water soluble small molecules by diffusion, including some removal of ammonia and amino acids. However, since majority of hepatic toxins are albumin-bound or lipid soluble, they are not removed by HD and hence this has a limited role.

3. Hemofiltration (HF)

Highly permeable membranes like polysulphone or polyacrylonitrile have been used in hepatic failure with an aim of removing fluid, including some hepatic toxins and ammonia. Improvement of hepatic encephalopathy and survival of patients with fulminant hepatitis has been reported, though others have not found a favourable outcome.

4. Continuous renal replacement therapy

Use of permeable membranes with a slower blood pump speed for prolonged periods in hepatic encephalopathy is associated with greater cardiovascular and intracranial stability compared to intermittent HD or HF. When an arterial line is obtained, a blood pump is not required and is termed continuous arteriovenous hemodialysis (CAVHD). With venous lines, a pump is required and is called continuous venovenous hemodialysis (CVVHD). This method may improve hepatic encephalopathy by decreasing intracranial pressure, and may be useful when sepsis is a precipitating factor by removing inflammatory cytokines. Lactate based replacement fluids or dialysate are however to be avoided in liver failure due to defective conversion of lactate to bicarbonate. Hence bicarbonate based fluids have to be used.

5. Charcoal hemoperfusion.

Blood is passed through a cartridge containing charcoal particles which adsorbs lipid-soluble toxins and thus is theoretically superior to HD or HF though randomized controlled trials have not shown any additional benefit in prolonging survival.

6. Plasma exchange

By using high volume plasma exchange using highly permeable plasma filters, it is possible to remove lipid-soluble and albumin-bound hepatic toxins. An additional charcoal sorbent cartridge can have additive effect in removal of toxins and can support patients with fulminant hepatic failure for several days.
7. Biologic - DT sorbent system (Liver dialysis)

This uses a cellulose membrane dialyzer with the dialysate consisting of a charcoal suspension and a sodium loaded cation exchange resin. Small molecular weight toxins that pass through the cellulose membrane can be removed. Modifications include use of plasma filters with powdered sorbent surrounding it. A decrease in bilirubin and creatinine levels with improvement in encephalopathy can occur, but overall improvement in patient survival was not noted. The cost of each sitting of 6 hours duration is around Rs.2 lakhs. Generally, 1-5 sittings may be needed.

8. Molecular adsorbents recirculating system (MARS) dialysis

This is a modification of dialysis in which an albumin-based dialysate is employed with the aim of removing albumin-bound toxins which accumulate in liver failure. These include aromatic amines, bile acids, bilirubin, indoles, phenols, mercaptans, middle chain fatty acids, etc. This is hence also called albumin dialysis. This is based on the fact that albumin molecules have important transport and detoxification functions due to a large number of binding sites. This simulates the normal transfer of albumin bound toxins to the hepatocytes. The MARS system consists of three compartments: a blood circuit, an albumin circuit and either a HD or HF compartment (Fig. 1). The blood circuit generally employs a venovenous access with a blood pump at a speed of around 150 ml/min. Blood is passed through a special non-albumin permeable high flux dialyzer membrane usually made of polysulphone, which is capable of adsorbing albumin-bound toxins. The albumin circuit generally contains about 600 ml of 20% human albumin and is also driven by a pump at a speed of around 150 ml/min. This is passed through the dialysate compartment of the blood dialyzer where it removes the toxins bound to the dialyzer membrane. The dialysate is then regenerated by passing through an activated charcoal column and then through another column containing an anion exchange resin. In addition, water-soluble toxins are removed from the dialysate by passing it across a low flux HD membrane with a bicarbonate dialysate as in conventional HD. Heparin is used as anticoagulant at a dose of 250 - 1000 IU / hr. Each session is around eight hours and is performed either daily or on alternate day. The number of sessions is decided based on the patient’s response. Generally five sittings may be adequate in acute liver failure where a decrease in bilirubin, bile acids, liver enzymes, plasma ammonia levels as well as urea levels can occur. Beneficial effects have been shown with a decrease in mortality in type I hepatorenal syndrome patients and acute alcoholic hepatitis where a marked fall in serum bilirubin can occur. An improvement in cardiovascular hemodynamics and subsequent renal function can occur. Improvement in encephalopathy and a decrease in intracranial pressure and pruritus has been shown. Its efficacy has also been demonstrated in small children. Thrombocytopenia is a common though usually mild complication and occasionally arrhythmias can occur. Though more than 400 patients have been treated worldwide with MARS, there has been no systematic controlled prospective study of its benefits. Although improvements in encephalopathy can occur, whether eventual survival is prolonged is not clear unless the patient undergoes liver transplant. The approximate cost for the disposable items used in each session is around 2 lakhs. However, studies have shown that overall costs may be less when compared to conservative management as complications, which require costly interventions, can be avoided.

9. Bioartificial liver (BAL)

In this system, patient’s blood or plasma is pumped into bioreactors, which are hollow fibre devices, seeded on the dialysate side with freshly isolated or cryopreserved porcine hepatocytes or transformed human hepatoma cell line. Blood initially passes through a plasma filter and the plasma filtrate perfuses through the bioartificial liver and is returned to the patient after passing through a charcoal adsorption column. Thus, this has the advantage of performing hepatic synthetic functions in addition to detoxification functions performed by the other ALS systems. They have been employed in treatment of acute liver failure and in primary non-function of a liver transplant. An improvement in encephalopathy and an increase in cerebral perfusion
pressure were noted. The effective hepatocytes account for only 2% of a normal hepatic function and is hence not very successful in acute decompensation of chronic liver disease. Though there is theoretical risk of transmission of porcine endogenous virus, no such incident has been reported.\textsuperscript{26} There is however still the potential risk of exposure to xenogenic proteins and serum sickness like reactions. Hence further studies are required to establish their safety and efficacy.

10. Extracorporeal liver assist device (ELAD)

In this system, blood is made to pass through one or more hollow fibre devices containing up to 200 gm of human hepatocytes, usually derived from hepatoblastoma cell line, on the dialysate side.\textsuperscript{27} Patients generally tolerate the procedure well with improvement in encephalopathy and can be used in patients awaiting liver transplantation.

11. Xenogenic perfusion

Attempts to prolong life in fulminant hepatic failure using extracorporeal whole organ perfusion with baboon or pig liver have not shown significant advantage over conventional treatment.\textsuperscript{28}

12. Extracorporeal hepatic perfusion

Performing extracorporeal perfusion using human liver not suitable for transplantation may show a transient improvement.\textsuperscript{29} This may hence have a role just prior to liver transplantation.\textsuperscript{30}

**Indications for Considering Artificial Liver Support Systems**

The main indication for considering artificial liver support (ALS) systems in liver failure is to give additional time for liver regeneration or spontaneous recovery to occur. The usual situations include acute fulminant hepatitis due to hepatitis A and B, toxicity due to acetaminophen and occasionally in severe acute alcoholic hepatitis, conditions producing an acute exacerbation of a chronic liver disease like a gastrointestinal bleed, spontaneous bacterial peritonitis and sepsis may also benefit as a return to previous compensated state can occur. In hepatorenal syndrome type 1, sudden deterioration of liver function with acute renal failure following precipitating events may warrant use of ALS systems as well as dialytic support.\textsuperscript{31} In chronic liver disease and in hepatorenal syndrome type 2 where a slow deterioration of liver function occurs, ALS systems are seldom justified unless it is to buy time till a liver transplant is feasible. In patients awaiting liver transplantation, ALS may be indicated to tide over complications like hepatic encephalopathy where accumulation of toxins could produce permanent brain damage due to cerebral edema. It may also be employed in irreversible liver damage when there is a delay in procuring a suitable organ,\textsuperscript{32} though this is more applicable to countries where cadaver transplantation is well established. Following liver transplantation, ALS may be indicated in primary non-function or delayed function of the graft.\textsuperscript{33} Intractable pruritus may also be reversed by ALS.\textsuperscript{31}

**Summary and Conclusions**

A variety of extracorporeal therapies of liver failure have been developed in the last decade which now offer management options in liver failure which was till recently widely available only in the case of renal failure. Since nephrologists are familiar with extracorporeal therapy, they are often involved in this treatment modality.\textsuperscript{34} Their main aim is to provide support to the liver while it recovers or regenerates and often as a method of stabilizing patients prior to liver transplantation. In the absence of facilities for liver transplantation, indications for extracorporeal therapy should be limited to conditions where the liver would recover like in hepatitis A, acetaminophen toxicity, etc. Of the available extracorporeal therapies, MARS and its modifications appear to be the most promising while peritoneal dialysis, HD, HF and charcoal perfusion have been mostly given up due to their limited efficacy. With the rapid progress made in this field, it appears that ALS systems may play an important role in the future management of liver failure. However, since there is limited experience with the use of these modalities, further studies are needed with regard to their safety as well as whether they contribute to the long-term survival of patients with liver failure.

**References**


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**Announcement**

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