INTRODUCTION

The liver performs a myriad of functions including immune, metabolic, synthetic and excretory functions, which play a crucial role in maintaining function of other organs and body homeostasis. Although the liver has a remarkable capacity for regeneration, after a severe acute insult in acute liver failure (ALF) or an acute hepatic insult in a patient with underlying pre-existing chronic liver disease (acute-on-chronic liver failure), the critical mass of hepatocytes required for maintaining homeostasis becomes impaired.

Liver failure is characterized by hepatic encephalopathy, jaundice, cerebral edema and coagulopathy. The mortality associated with liver failure – whether acute liver failure (ALF) or acute-on-chronic liver failure (AoCLF) – continues to remain high. While some patients with acute liver failure will have hepatic regeneration and recover, a significant number will die due to cerebral edema, infections and multi-organ failure.

While liver transplantation has revolutionized the management of such patients, many of them still die while waiting for transplantation. Extracorporeal liver support devices have therefore been developed in order to stabilize the patient and either act as a bridge to liver transplantation or allow the liver to recover from injury.

An ideal liver support device would eliminate the need for transplantation and may offer chronic replacement for end stage liver disease, as in renal dialysis. While the ideal liver support device is still far from realization, there have been many advances in the field over the last few decades.

TYPES OF LIVER SUPPORT DEVICES

Effective artificial liver support devices would be expected to perform three key functions in patients with liver failure detoxification, synthesis of clinically important proteins and facilitation of regeneration of native hepatocytes. The Liver support devices can be divided into two basic groups: Artificial liver support devices and Bio-artificial Liver support devices. The artificial liver support devices are purely mechanical devices or non-cell based liver support devices. The Bio-artificial liver support devices are cell-based liver support devices and have a cellular component such as primary hepatocytes or hepatic cell line. The artificial liver support devices can only provide the detoxification function while the addition of cellular component in bio-artificial liver support devices is aimed at replacing the important liver functions (oxidative detoxification, biotransformation, excretion and synthesis). The comparison between artificial and bio-artificial liver support devices is depicted in table 1. The types of artificial and bio-artificial liver support devices are enumerated in table 2.

In human blood toxic substances can be divided into two major groups: depending on they are either water-solved (e.g. ammonia, aromatic amino acids, creatinine, interleukin, Interleukin-6, GABA, urea, tryptophan) or mainly albumin bound (e.g. bilirubin, benzodiazepines, bile acids, Cytokines, protoporphyrin, middle-chain and short-chain fatty acids, para-cresol, protoporphyrin, nitric oxide, furancarboxylic acid, etc.).
Table 1: Comparison between the Artificial and Bio-artificial liver support devices

<table>
<thead>
<tr>
<th>Type of liver support device</th>
<th>Artificial liver support device</th>
<th>Bio-artificial liver support device</th>
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</thead>
<tbody>
<tr>
<td>Cellular component</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatic functions achieved</td>
<td>Detoxification only</td>
<td>All hepatic functions</td>
</tr>
<tr>
<td>Cost</td>
<td>Comparatively less</td>
<td>High cost for designing, operating and managing</td>
</tr>
<tr>
<td>Ease of use</td>
<td>Relatively easier</td>
<td>Complexity of maintain living components</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Limited</td>
<td>Expected results more promising</td>
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</table>

Conventional dialysis techniques (Hemodialysis, Hemofiltration, etc.) are only capable of removing water-solved toxins. However, as most liver toxins are albumin bound, additional techniques are required to remove these toxins. One approach is to add albumin to the dialysate for removal of albumin-bound toxins [as in Molecular Adsorbent Recirculating System (MARS) and Single Pass Albumin Dialysis (SPAD)]. An alternative approach is using large pore-filters, which would retain cellular components and separate plasma proteins including albumin [as in Prometheus and Selective Plasma Filtration System (SEPET)]. The filtrate may undergo readsoption to clean the toxin-attached albumin, which may be recycled [as in MARS and Prometheus] or the filtrate may be discarded [as in SPAD and SEPET].

ARTIFICIAL LIVER SUPPORT DEVICES (NON-CELL BASED LIVER SUPPORT DEVICES)

Early studies on non-biological liver support centers were initially done with charcoal haemoperfusion. While an initial uncontrolled study at King’s college Hospital, showed survival benefit, the same was not shown in randomized controlled trials. The Non-biological systems, which have been evaluated for liver failure, include the molecular adsorbent recirculating system (MARS), Prometheus, Single Pass Albumin Dialysis (SPAD) and the selective plasma filtration system therapy (SEPET).

Molecular Adsorbents Recirculating Systems

Molecular adsorbent recirculating system (MARS, Gambro GmbH, Hechingen, Germany) was introduced in 1990s and provided a combination of conventional dialysis with hemodialysis against an Albumin dialysate solution over an Albumin impermeable membrane.

MARS consists of two circuits: blood circuit and a secondary circuit. The blood circuit passes the patients blood through a high flux dialyzer over an albumin impermeable membrane. The opposing side of this membrane is 600 ml of 20% Human Albumin dialysate in the secondary circuit. The albumin in the secondary circuit is ‘refreshed’ by passage through anion-exchange resin and activated charcoal columns.

MARS has evoked interest and has prompted a lot of studies of its role in liver failure. The inconclusive role of MARS in liver failure has been summarized by an aptly named editorial titled “is there life in MARS?” A meta-analysis of four randomized controlled trials of MARS in liver failure failed to show any survival benefit. Short mortality rates of patients with MARS without transplantation have ranged from 78-100%. Hence MARS may be appropriately used as a bridge to stabilize patients prior to transplant and may not improve survival without transplantation.

While MARS treatment improves parameters like bilirubin levels and encephalopathy, it may also worsen coagulopathy, cause hypoglycemia and alter the pharmacokinetics of drugs. It may also be prudent to withhold albumin infusion prior to MARS to improve its efficiency.

Prometheus system

Fractional plasma separation and adsorption system (FPSA, Prometheus Bad Homburg, Germany) creates a filtrate through 250 kDa pore size filter. Unlike MARS where the membrane is albumin-impermeable, in Prometheus, the albumin-bound toxins diffuse across the albumin-permeable membrane of Prometheus. The filtrate is then passed over two columns of neutral resin and anion-exchange and then returned to the patient. Thus the patient’s albumin is cleansed of the bound toxins and no exogenous albumin is used.

Overall Prometheus provides higher clearance for most liver toxins especially if they are tightly albumin bound. However, for bile acids and cytokines no such differences have been found. In one study in patients with alcoholic cirrhosis with alcoholic hepatitis, which compared MARS vs. Prometheus, mean arterial pressure and systemic vascular resistance improved with MARS but not Prometheus.

Single Pass albumin Dialysis (SPAD)

This uses low albumin concentration (5%) unlike MARS and
Liver Support Devices

the albumin solution is discarded against a single counter-current pass against the patient’s blood in a hemofilter. SPAD is possible comparable to MARS in efficacy with respect to influence on clinical and standard laboratory parameters.

Selective Plasma Filtration therapy (SEPET)
SEPET utilizes hollow-fiber with a membrane pore size, which allows passage of molecules with molecular weight less than 100 kDa, thereby preserving immunoglobulins, complement proteins, clotting factors and hepatocyte growth factor. Part of the patient’s albumin is lost due to the pore size of the filter and has to be replaced. The removed fluid is replaced by Albumin, fresh frozen plasma and electrolytes. This system is currently under clinical evaluation.

The schematic depictions of artificial Liver support devices are shown in Figures 1-4.

BIO-ARTIFICIAL LIVER (BAL) SUPPORT SYSTEMS
The lack of survival benefit of artificial liver support systems highlights the importance of developing BALs. The aim of BALs is to provide both detoxification as well as synthetic functions.

While human hepatocytes appear to be the most cells for use in BAL, their widespread use is prevented by their lack of availability and the fact that they do not readily regenerate in vitro. Besides, the human hepatocytes have decreased efficacy when cultured. This problem has been addressed by attaching the hepatocytes to cell mattresses to simulate cell-to-cell interactions and polarity.

The alternatives to primary human hepatocytes, which have been used, include immortal cell lines like C3A human hepatoblastoma cell lines and porcine hepatocytes. There are however concerns of using potentially oncogenic cells with the former and xenozoonosis with the latter. The 3A cells have the theoretical benefit of unlimited expansion in vitro. However, hepatoblastoma cells such as C3A do not express normal metabolic profiles such as ureagenesis and have inferior metabolic activity when compared with primary hepatocytes.

The systems of BAL, which are currently under clinical evaluation, include Hepatassist, Extracorporeal Liver Assist Device (ELAD), Modular Extracorporeal Liver support (MELS), BLSS and AMC-BAL.

HepatAssist
HepatAssist by Arbios was the first FDA-approached biologically based liver assist device. This employs a hollow
fiber extracorporeal bioreactor loaded with cryopreserved porcine hepatocytes. While safety of the system has been demonstrated, improved survival has not been shown with HepatAssist. A survival benefit was found only in the subgroup of patients with fulminant/subfulminant hepatic failure, which showed a small reduction in mortality favoring the BAL group. 24

**Extracorporeal Liver Assist Device (ELAD)**

Extracorporeal Liver Assist Device (ELAD) by Vital Therapies (San Diego, California, USA) utilizes hollow fiber cartridges loaded with C3A human hepatoblastoma cell lines. While improvement in ammonia, bilirubin and hepatic encephalopathy has been shown, a clear survival benefit has not been shown and large multicenter trials are required. 25

**Modular Extracorporeal Liver support (MELS)**

The Modular Extracorporeal Liver support (MELS) system (Charite Berlin, Germany) is based on hollow fibers containing fresh porcine hepatocytes. Small initial study in eight patients with acute liver failure has shown safety with bridging to transplant. 26 However, it is relatively complex and has high cost, which may prevent widespread application of the device. 27

**Bioartificial Liver Support System (BLSS)**

Bioartificial Liver Support System (BLSS) by ExcorpMedical (Minneapolis, Minnesota, USA) utilizes porcine hepatocytes in a single hollow fiber cartridge and phase II/III studies are underway. 28

**Amsterdam Medical Center Bioartificial Liver (AMC-BAL)**

Amsterdam Medical Center Bioartificial Liver (AMC-BAL) utilizes porcine hepatocytes bound to a spiral-shaped polyester fabric with integrated hollow fiber. While preliminary studies are encouraging, larger trials are required. 29

**CONCLUSIONS**

Artificial and bioartificial liver devices represent a potentially useful options in management of patients with liver failure. While artificial liver devices have shown improvement in biochemical parameters, the benefit in terms of survival benefit has not been clearly demonstrated. The artificial liver devices provide detoxification alone. BAL on the other hand aims at replacing other liver functions as well and may be a more potential in the future. However, a lot of work needs to be done in developing BAL devices and carrying out clinical trials to demonstrate not only efficacy but also safety.

**REFERENCES**


