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Indian	ARIPET NON DEV	I-BIOLOGICAL ARTIFICIAL LIVER SUPPORT ICES- PAST, PRESENT AND FUTURE	KEY WORDS: .Artificial liver support device, Liver failure, Hepatic encephalopathy
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TRACT	Liver transplantation is the therapeutic modality of choice in patients suffering from liver failure. Due to the wide discrepancy between demand and supply of donor organs evolution of bridging devices is required to support potential recipients till transplantation. Over the years, important advances in liver support systems have been made and devices like MARS have proved		

beneficial in improving short term outcome. Still the current crop of bridging devices are far from ideal, with none of the devices

definitely proving to be of survival benefit. Further improvement in non-biological liver support devices is warranted.

Introduction

ABSTI

Liver failure results in a severe clinical syndrome in which various metabolic functions of the body are severely impaired leading to life-threatening complications. There is an increase in numerous endogenous substances (bilirubin, ammonia, glutamine, lactate, aromatic amino acids, free fatty acids, phenol, mercaptans, benzodiazepines and proinflammatory cytokines) which lead to a high mortality rate in these patients. This is reflected clinically as encephalopathy or hepatic coma (disturbed sleep patterns, behavioural changes, altered sensorium) jaundice, coagulopathy, and impairment of renal and pulmonary functions. Patients are also predisposed to the development of sepsis which ultimately leads to multiorgan failure and death.^{1,}

Hepatic failure results in significant mortality with rates as high as 80% with orthotopic liver transplantation as the only definitive treatment.³ Despite all the efforts to increase the donor liver pool by using extended criteria donors, split livers and living related donor livers, the availability of donor livers is far less than the demand. Given the scarcity of organ availability and the amount of time taken for assessment of donor in LDLT, a high percentage (33% to 50%) of patients with acute hepatic failure have been reported to die awaiting a liver transplant. Moreover, not all patients are candidates for transplants. A system or a device replicating liver functions can help the patient tide over the acute crisis and can thus serve as a bridge to liver transplantation. Further such a device can also be helpful for patients with primary allograft non-function and post hepatectomy liver failure.^{3,4} Thus, artificial liver systems are of keen interest and the subject of much research. Technology for artificial organ support systems has progressed remarkably over the last few years. Specifically, for patients of acute or chronic renal failure, various renal replacement therapies have led to significant survival benefit. The temporary replacement of heart and lung functions with the help of cardiopulmonary bypass proved to be a milestone for major improvements in the field of cardiothoracic surgery. The ability to replicate a similar feat is still elusive for the specialists practising in the field of hepatology as the clinical treatment of fatal hepatic failure with liver support systems has been far from satisfactory. For the last 60 years experts have been working to find a substitute for liver functions.^{5,6,12} Liver

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is the chief metabolic and synthetic organ and it carries out more than 500 different functions. The sheer complexity of functions carried out by the liver is one of the primary reasons, if not the only one; for the lack of success in the realm of liver support devices.⁷

Ideally, a liver assist device should be able to support all the main liver functions which are broadly detoxification, regulation of body functions, metabolism and synthesis. But the synthetic and regulatory functions of the liver are the most difficult to replicate by an artificial system.

Traditionally liver assist devices have been divided into two broad categories, biological and non - biological liver support devices. Bio - artificial liver support devices can have hepatic cells which can be either human or animal in origin (Table 1). Non-biological devices work on the principle of filtration or adsorption using charcoal columns or albumin dialysis. Biological devices utilize live cells in form of cultured hepatocytes. These are suspended within a bioreactor through which the blood or the plasma of the patient is perfused. The advantage of biological devices is that these not only remove circulating toxins but also replace the metabolic and synthetic functions of the liver to a certain extent.⁷

Initial attempts at treating the patients of liver failure included haemodialysis and charcoal haemofiltration which stemmed out of the belief that small (<5 kD) dialyzable water soluble molecules (NH_{3,} urea and mercaptans) are responsible for liver failure. Subsequently, many other mediators like inflammatory cytokines and chemokines, growth inhibiting factors, endotoxin were found to have an important role in the pathogenesis of ALF and ACLF.¹³ Large number of these toxins are bound to albumin which cannot be removed by simple haemodialysis and adsorption with charcoal. Further albumin also has been shown to have a positive modulatory effect on neutrophil functioning. Thus the foundation for discovery of detoxification methods using albumin was laid.^{9,10} Since then, Non-biological devices have come a long way from haemodialysis and plasma exchange to incorporating haemodiabsorption, hemofiltration and albumin dialysis. Table 1 summarizes both bio-artificial and the non-biological liver support devices or methods that have been used in patients of liver failure.

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This review of literature aims at exploring various non-biological artificial liver support devices used and the results that have been achieved so far.

Non albumin based artificial non-biological liver support devices

Historically, most liver assist techniques used were based on the assumption that small dialyzable molecules are responsible for the clinical picture of hepatic failure. As a result most of the earlier techniques basically relied on blood detoxification by either simple haemodialysis or with sorbents (charcoal and resins).

Haemodialysis

In 1958 Kiley et al. described symptomatic and clinical improvement in form of improved neurological status in four of the five patients of ammonia intoxication treated by haemodialysis. However no benefit was noted in long term survival of these patients. ¹² Similar findings were observed by Opolon et al. in 1976 when they tried haemodialysis to treat acute fulminant hepatitis. They used polyacrylonitrile membrane (PAN) which removed many molecules of higher molecular weight (up to a molecular weight of 15 kDa) associated with encephalopathy. No improvement in survival was noticed. However statistically significant improvement was noticed in grade of encephalopathy. ¹³ Over time, haemodialysis has had a limited role in the treatment of liver failure. However it must be emphasised that the modality can have an important role to play in acute liver failure associated with renal failure.

Charcoal haemoperfusion

Initially used in the treatment of barbiturate poisoning, charcoal haemoperfusion has been shown to remove many water-soluble molecules associated with encephalopathy in hepatic failure patients.14 It has been evaluated extensively and has a proven ability to improve physiologic parameters such as bilirubin levels.⁷ Yatzidis developed an activated charcoal column in 1965 for removing serum bilirubin, which is still used today for patients suffering from hyperbilirubinemia. In one of the earliest attempts at treating fulminant hepatic failure with this technique, Gazzard et al. used it in patients of grade IV encephalopathy. Twenty-two patients with fulminant hepatic failure who deteriorated to grade-IV coma despite full supportive therapy were treated by repeated periods of haemoperfusion through columns containing activated charcoal. Significant reduction in plasma level of amino acids involved in the pathogenesis of the encephalopathy such as phenylalanine, tyrosine, and methionine was noted. Fifty percent patients regained consciousness and 10 out of 21 left hospital. These survival figures were better than previous survival figure of 10% in a series of patients of fulminant hepatic failure and grade III or IV encephalopathy treated by full supportive measures.¹ However, when used in randomized controlled studies charcoal haemoperfusion was not found to have clinically meaningful efficacy. O'Grady et al studied 62 patients with established grade IV encephalopathy on admission randomized to a no-perfusion group or to have 10 h of haemoperfusion daily, and observed statistically similar survival rates (39.3% and 34.5% respectively). The authors concluded that orthotopic liver transplantation merits early consideration especially in the group with better "intrinsic" survival (acetaminophen, hepatitis A and B) with intensive management of complications.¹

Charcoal haemoperfusion also led to improved outcomes in patients with liver failure caused by intoxications. Charcoal is well known for its adsorptive functions for exogenous toxins and this may be the reason why it performed well in these subgroup of patients. Despite showing encouraging results and demonstrating the removal of various toxins in some of these earlier studies, the use of charcoal haemoperfusion has declined sharply over the years for treatment of hepatic failure due to its failure to show an improvement in long term survival in subsequent controlled, clinical studies.

Haemodiabsorption

Sorbent-based haemodialysis, or haemodiabsorption (Biologic-

DT) is a procedure that has the capability of removing toxins of less than 5000 Da. These include aromatic amino acids, glutamine, mercaptans, benzodiazepine-like substances, false neural transmitters, ammonia, and manganese.¹⁷Additionally the system also has the capability to remove protein bound toxins and large molecular weight toxins, including cytokines and bilirubin which is achieved by adding a plasma-permeable hollow-fibre filter downstream from the dialyzer.18 The ability to remove inflammatory mediators is an additional benefit of this device. In a clinical trial, 15 patients with acute deterioration of liver function with hepatic encephalopathy and raised serum ammonia levels were subjected to treatment with BioLogic DT for 8-12 hours daily. Statistically significant improvement was observed in neurological status during individual treatment, and a positive trend over 1-12 (average four) daily treatments. Four patients showed recovery of liver function and another four improved enough to undergo a liver transplant.¹⁹ Still the data related to the use of Biologic-DT is scarce; and larger, multicentre trials are needed to know whether this method of hepatic support can achieve significant survival benefit over standard medical therapy (SMT) or other artificial liver support devices, in patients of ALF and ACLF.

Plasma exchange

The rationale of using plasma exchange for treatment of hepatic failure is based on the fact that most of the complications of ALF are due to accumulation of toxins in plasma. Removal of patient's plasma and replacement with donor plasma can help to remove toxins and to supply defective components such as albumin and clotting factors.²⁰ In plasma exchange, plasma element is separated from cellular blood components of blood by using a hollow fibre filter made of cellulose diacetate and polyethylene membrane or other synthetic materials. Biocompatibility can be an issue, with synthetic material faring better in that regard with reduced production of proinflammatory cytokines and less complement activation.²¹ Sabin et al reported improvement of refractory hepatic coma in three patients with plasma exchange in 1969.²² Though therapeutic plasma exchange (TPE) has been shown to improve coagulation parameters (by supplementing clotting factors) and decreased level of various cytokines and endotoxin, no randomized trial or case series has reported significant improvement in neurological outcome and haemodynamics or mortality benefit.²³ Another variant of plasma exchange, High Volume Plasma exchange (HVP) was used by Kondrup et al in patients of fulminant hepatic failure in 1992. HVP is a more extreme method involving exchange of very high volumes of plasma (exceeding 10 litres). The technique results in improvement in splanchnic oxygen delivery and an increase in hepatic and cerebral blood flow with decrease in toxins levels.² Larsen et al. randomized 182 patients with ALF in to two groups; SMT alone (90 patients) and SMT plus HVP for three days (92 patients). The primary endpoint was liver transplantation free survival. Survival was 58.7% in the SMT plus HVP group vs. 47.8% in the control group although HVP prior to transplantation did not improve survival compared with patients who received SMT alone. Also, the authors reported better biochemical outcomes, vis a vis, ammonia, INR, bilirubin and ALT levels; and lower SIRS and SOFA score in the treatment group. As part of a sub study, the authors reported that HVP dampened innate immune response through removal of circulating DAMPS (Damage Associated Molecular Patterns), such as histone associated DNA. $^{\rm 26}$

The need for large supplies of fresh frozen plasma result in exceedingly high cost of treatment. Further controlled trials are needed to establish the beneficial effects of HVP on patient survival in cases of ACLF and ALF in comparison to other of liver support therapies.

Haemodiafiltration

Haemodiafiltration, as the name suggests; is a combination of haemodialysis and haemofiltration. Haemodialysis is useful for removing molecules which are less than 5000 Da and haemofiltration can remove molecules in the 5000 to 10000 Da range. A high-performance membrane such as a large-poresized polymethylmethacrylate (PMMA) membrane is used.²⁶ In 1986,

Yoshiba et al reported treating 27 patients of fulminant hepatic failure with plasma exchange in combination with haemodiafiltration using a PMMA membrane. They reported a 55% survival which was attributed to the early initiation of therapy²⁷ Similarly, Nitta et al. developed a combination of slow plasma exchange in combination with high-flow continuous haemodiafiltration and reported a retrospective clinical study of five patients with liver failure treated with this technique. The authors reported that the adverse effects associated with use of plasma exchange alone such as hypernatremia, metabolic alkalosis, and a sharp decrease in colloid osmotic pressure could be alleviated with the combination.²⁸

Albumin based dialysis

Hepatic failure leads to accumulation of a variety of small molecular weight toxins, inflammatory mediators, vasoactive substances, endotoxins and growth factors, which are the likely cause of the neurological abnormalities in these patients.²⁹

Limited and non-specific adsorptive capacity of chemical adsorbents makes removal of these compounds from the blood difficult and incomplete. This explains the failure of conventional haemodialysis/haemofiltration, charcoal haemoperfusion, haemodiabsorbtion in improving patient survival.

Considering the essential role of albumin in the treatment of liver failure, in the early 1990s, introduction of albumin dialysis appeared to revolutionize liver replacement therapy with great capacity of removal of water soluble toxins, drugs and albumin bound toxins (bilirubin, bile acids, aromatic amino acids and fatty acids). As a result most of the current commercially available artificial liver support systems are based on the principal of blood purification by albumin dialysis or by plasma separation and filtration (removal of protein-bound and water-soluble substances). The three main artificial liver support devices based on this principle and being used currently are: The MARS® (Molecular Adsorbent Recirculating System), the Prometheus® and the SPAD® (Single Pass Albumin Dialysis).

Molecular adsorbent recirculating system (MARS)

MARS (Gambro, Sweden) was developed at Rostock University by Stange and Mitzner and introduced in 1993.³⁰ It removes proteinbound substances by the use of a high-flux dialyzer and an albumin containing dialysate. It basically consists of two circuits. First is the albumin circuit in which patient's blood is drawn from a dialysis catheter to a high-flux albumin coated polysulfone haemodialyser with a cut-off of 50 kDa. Albumin-bound water-insoluble and water-soluble toxins are transferred to the 20% human albuminenriched dialysate running countercurrently. Next, is the renal circuit where the exogenous 20% human albumin dialysate is regenerated in a closed loop by dialysis (against a conventional bicarbonate or calcium free dialysate) and by adsorption through uncoated charcoal and anion-exchange resin columns. The albumin thus regenerated is then recirculated to the first albumin circuit for use.³⁰ Studies have shown that MARS effectively removes albumin bound toxins like unconjugated bilirubin, bile acids, tryptophan and free fatty acids. It improves the ratio of branched chain amino acids (BCAA) to aromatic amino acids (AAA) by preferential clearance of AAA.^{31,32} Clinically, improvement of HE has been shown with reduction in serum ammonia levels, decrease in intracranial pressure (ICP) and increase in cerebral perfusion pressure. Haemodynamic improvements in the form of increased mean blood pressure, systemic vascular resistance have been reported.

MARS is one of the most widely studied artificial liver support system. Initial evaluation of MARS involved non randomized studies with small number of patients, with the largest of these studies involving 26 patients of ACLF. Among these, 10 patients belonging to UNOS II b status showed 100 percent survival while from the rest 16 patients belonging to UNOS IIa status only 7 survived.³³

While several thousand patients have been treated with MARS till

date, number of RCTs comparing MARS to other forms of treatment with respect to patient survival rates are limited to single digits. Three such studies have been conducted in patients with ACLF and one in a patient with ALF. The first RCT reported short term survival benefit in patients treated with MARS therapy. Mortality rate in patients receiving varying number of cycles of MARS was 62.5 percent as compared to 100 percent mortality in patients treated with standard medical therapy (SMT) at 7 days. Twenty-five percent patients treated with MARS survived at 30 days.³⁴ The second RCT included 24 patients with ACLF not responding to conventional therapy. Thirty-day mortality was significantly better in MARS group compared to control group (8.3% vs 50 % p<0.05). However, long term survival at 6 months was similar in both groups (mortality rates of 50%).³⁵ In the recently completed RELIEF trial no difference was noted in patients treated with MARS and the control group. The study included 189 consecutive patients (95 MARS vs. 94 SMT group) with 33 patients excluded from final analysis. The primary end point, 28-day survival was 59.2% in the MARS group and 60.0% in the control group, showing no significant beneficial effect of MARS on short term survival rate. However a greater decrease in serum creatinine and bilirubin and a more frequent improvement in HE (from grade II-IV to grade 0-1; 62.5% versus 38.2%; P=0.07) was observed at day four in the MARS group.³

The first RCT using MARS in patients suffering from fulminant and subfulminant liver failure with survival rate as the primary endpoint is the FULMAR study, a multicentre trial in 16 French centers. It enrolled 102 patients and though better 6-month survival was reported in the MARS group, 84.9 vs 75.5%; it was not statistically significant. Patients were randomized for SMT or additional MARS treatment after being listed for high-urgency OLT. Two-thirds of 102 included patients underwent OLT within an extremely short listing to transplant time of only 16.2 h and three-fourths were transplanted within 24 hours.³⁷

In another RCT with difference in improvement proportion of hepatic encephalopathy as the primary endpoint, seventy patients with hepatic encephalopathy grade III-IV were randomly treated with MARS or SMT. Involving 70 patients, the 39 patients who were treated with MARS showed better improvement in grade of hepatic encephalopathy as compared to the SMT group (P=0.04). Also the rate of improvement of HE grade was faster and more frequent in the MARS group (P=0.04). During the 180 days of follow-up, 64% patients in the MARS and 71% patients in the SMT group died. Patients who responded to therapy with improvement of hepatic encephalopathy had a 4-week transplant-free survival of 47% vs. 20% in patients who did not.³⁸

It can be emphasised on the basis of the currently available data from RCTs that though improvement in grades of HE, laboratory parameters and systemic haemodynamics is seen with MARS treatment; this does not improve long-term survival. In various studies over time side effects profile of MARS was mild and the procedure was well tolerated. Thrombocytopenia and bleeding were the most commonly reported side effects especially in susceptible patients (INR> 2.3, platelet count < 5000/mm³, septicaemia).³⁹ Further trials and better patient selection are necessary to reveal the actual potential of MARS in future, more importantly in patients of fulminant hepatic failure awaiting liver transplant.

Fractional Plasma Separation/Absorbtion and Dialysis (Prometheus)

Prometheus System (Fresenius Medical Care, Bad Homburg, Germany), introduced in 1999, share the principle of albumin based dialysis with MARS, but relies on a different technique.⁴⁰ Patient's native albumin is selectively filtered from the plasma (fractioned plasma separation), purified by adsorption on a resin adsorber and anion exchanger (adsorption) followed by dialysis using a conventional high flux polysulfone dialyser against conventional dialysate and finally returned to patient's plasma. The filter used is albumin permeable polysulfone filter (Albu-Flow) with cut-off of 250 kDa. No external albumin is added during the

procedure.³⁴ The direct contact of separated plasma with the neutral resin and the anion exchanger may be responsible for the higher detoxification efficiency compared to MARS. However, the smaller loss of albumin than seen in MARS, can explain the lack in attenuating the hyperdynamic circulation in ACLF by FPSA as compared to the positive effects of MARS on systemic haemodynamics.

In comparison to MARS, clinical experience with Prometheus is limited; with most data being uncontrolled or retrospective. Kramer et al reported a case of cocaine induced fulminant hepatic failure successfully treated with Prometheus despite the presence of cardiac infarction, cerebral oedema and multiorgan failure.⁴¹ In another trial on 11 patients with ACLF treated with Prometheus, significant improvement in level of various water soluble and protein bound substances was noted along with improvement in parameters of renal function (urea, creatinine and blood pH). However the trial failed to show statistically significant improvement in HE grade or Child Pugh score.⁴

The first prospective RCT evaluating Prometheus in patients with ACLF (the HELIOS Trial) was published in 2012. Out of the total 145 patients, 72 patients received 585 FPSA treatment sessions in total. The primary endpoints were survival at days 28 and 90. The probabilities of survival on day 28 and 90 were statistically similar. However subgroup analysis revealed better survival in patients treated with Prometheus (28-day survival probability 57% in FPSA vs. 42% in SMT group and 90-day survival probability 48% in FPSA vs. 9% SMT group; p=0.02) in patients with Model of End-stage Liver Disease (MELD) >30, thus showing that FPSA may not improve survival in all patients with ACLF, but might be beneficial in patients with very severe liver failure defined by high MELD (>30) score.43

Although both, Prometheus and MARS function on the same principle of albumin detoxification; theoretically Prometheus seems to be a better modality since the albumin is regenerated and is available for toxin clearance. Studies have shown substances that are tightly bound to albumin, such as unconjugated bilirubin as well as ammonia and urea are better cleared by Prometheus. However no difference in clearance rate of bile acids has been found.^{44,45} A large trial may answer whether this apparently more efficacious clearance of toxin by Prometheus translates into superior clinical benefit.

Single pass albumin dialysis

MARS and Prometheus use charcoal and resins as adsorbents, which are not very effective in removing proteins such as mediators of inflammation and inhibitors of hepatic regeneration (e.g. TGF 1) from the blood. Therefore, these devices may not have great therapeutic efficacy in patients with severe hypercytokinemia, like in ACLF patients with chronic hepatitis B infection. Single-pass albumin dialysis (SPAD) can be helpful in situations like these and has shown promise in in vitro studies when compared against sorbent based methods of albumin dialysis.⁴⁶ Further this is performed using a standard dialysis setup with elimination of adsorbents thus can lower the cost of setup. Hollow fibres made of a high-flux albumin-impermeable membrane and human albumin (a more diluted albumin solution of 4.4%, as opposed to 20% in case of MARS) which is added to the dialysis solution (to enable solute transfer from the patient's blood to the dialysis solution) is used.47,48

When compared side by side, while one of the studies showed better clearance of ammonia, bile acids, and bilirubin by SPAD, another study suggested a greater clearance of bile acids by MARS.^{46,49} In patients with ALF or ACLF, SPAD treatment significantly improved the levels of total bilirubin, conjugated bilirubin, urea, and creatinine. However no significant change was observed in serum ammonia concentrations before and after the treatment. $^{\scriptscriptstyle 50}$ In another retrospective evaluation in 13 acetaminophen-induced acute liver failure (AALF) patients no significant changes were noted in clinical, physiological or biochemical parameters in patients treated with SPAD. Six patients

received a total of 21 sessions (total: 147 h, mean 3.5 runs or 24.5 h/patient). Compared with the controls, there were no significant differences in ICU or 1-year survival, liver recovery or referral for a liver transplant.⁵¹

Initial clinical experience with SPAD indicates that the procedure is safe, simple and cost effective (though need for albumin supply does increase the cost) to set up. Prospective trials and further studies are necessary to establish optimal concentration of human albumin in dialysate and flow rates of blood and dialysate during the procedure in different clinical scenarios.

Summarv

Liver transplantation has become the therapeutic modality of choice in patients suffering from liver failure. However, the wide discrepancy between demand and supply of donor organs requires evolution of bridging devices to support potential recipients till transplantation. Over the years important advances in liver support systems have occurred and devices like MARS have proved beneficial in improving short term goals. Still the current crop of bridging devices are far from ideal, with none of the devices definitely proving to be of survival benefit if used alone. Till date Bio artificial devices, though theoretically superior to artificial assist devices (in terms of providing synthetic and metabolic capabilities), have not shown better survival benefits. Further improvement in non-biological liver support devices is warranted with clear definitions of target population and duration/intensity of therapy. Well-designed, large, multi centric randomized trials are required to assess the capability and shortcomings of currently available systems.

Table -1

Artificial Non Biological Liver support devices Non Albumin based methods/ devices

- Haemodialysis
- Charcoal Haemoperfusion
- Haemodiafiltration
- Plasma Exchange
- High volume plasma exchange

Albumin based methods/ devices

- MARS
- Prometheus
- SPAD

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