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Artificial Liver Support Systems

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Abstract

Unlike renal replacement therapy wherein only detoxification function needs to be provided, liver replacement therapy requires replacement of a number of functions in order to maintain homeostasis. Provision of artificial support to a failing liver is thus a challenging job. The ideal form of liver replacement therapy is liver transplantation but its usefulness is limited on account of several factors. Existing artificial support devices are discussed.

Introduction

Liver is a large organ of our body which participates in synthesis of vital proteins, metabolism of glucose and fat and detoxification of drugs and toxins. Therefore, unlike renal replacement therapy, wherein, only detoxification function needs to be provided, liver replacement therapy requires replacement of a number of functions in order to maintain homeostasis. Provision of artificial support to a failing liver is thus a challenging job and till date remains largely unsatisfactory. For obvious reasons the ideal form of liver replacement therapy is liver transplantation but its usefulness is limited by the high cost, limited availability of donor organs and need for life long immunosuppression.

Artificial liver support devices

Artificial liver support is required in patients with acute liver failure till the time the liver regenerates on its own, in acute on chronic liver failure till the time the effect of acute injurious agent wears off and in cirrhotics with end stage complications such as hepatorenal syndrome as a bridge

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to transplantation. Any device which provides artificial liver support should ideally be able to provide functions of synthesis, detoxification and metabolism. However, the function of synthesis and metabolism are the most difficult to provide and cannot be provided unless the device contains either immortalized or animal derived hepatocytes. It has been demonstrated that the plasma from patients with liver failure is cytotoxic and pro-apoptotic. Accumulation of toxins in liver failure can result in the characteristic hemodynamic derangements and multiorgan dysfunction. So if a device is able to remove majority of toxins that accumulate in patients with liver failure, especially when it has to be applied for a short duration (till the time liver regenerates or as a bridge to transplant) it should serve the purpose even if it is not able to provide synthetic or metabolic support.

A number of liver replacement therapies have been tried till date such as hemodialysis, exchange transfusion, plasma exchange, activated charcoal hemoperfusion, cadeveric liver perfusion, extracorporeal zoonotic liver perfusion, human-human cross transfusion etc. Even though there was modest success with these techniques in improving hepatic coma, none was able to improve survival significantly and had a number of inherent limitations. The earlier prototypes of modern day artificial liver support systems were of two types; biological systems and non-biological systems. The biological systems circulated patient's blood through columns containing animal hepatocytes or hepatoma/ hepatoblastoma cell lines derived cells (e.g., bio-artificial liver (BAL) & extracorporeal liver assist device (ELAD)). These provided synthetic as well as detoxification functions, but there were the issues of allergic reactions to the foreign hepatocytes along with risk of transmission of zoonosis. Using porcine hepatocyte based bioartifical liver system (HepatAsist device) a large randomized controlled trial (enrolling 171 patients) was carried out in acute liver failure patients but similar to the previous experience, no improvement in survival could be demonstrated. The non-biological systems circulated patient's blood through polymer or polysulfone fibers and provided only detoxification function (eg, molecular adsorption and recirculating system (MARS) & fractional plasma separation and adsorption (FPSA)). In these non-biological systems also, the risk of bio-incompatibility remains. In recent years, large experience has been gained world wide on the use of MARS in various forms of liver failure.

The concept of albumin dialysis

The toxins which accumulate in patients with liver failure are bile acids, bilirubin, unconjugated bilirubin, nitric oxide, indol/phenol metabolites, toxic fatty acids, thiols, mercaptans, ammonia, short

and medium chain fatty acids, digoxin like substances and benzodiazepine like substance. These toxins can initiate a vicious cycle of necrosis and apoptosis in liver as well as other organs ultimately leading to multiorgan failure. But most of the toxins which accumulate in liver failure are water insoluble and are bound to albumin and therefore can not be removed through normal renal dialysis membranes. These albumin bound toxins need to be removed along with albumin with either replenishment of fresh albumin from outside or regeneration of toxin bound albumin online. This is the concept of albumin dialysis.

Molecular adsorption and recirculating system (MARS) (Gambro, Stockholm, Sweden)

This form of artificial liver support is the major focus of discussion as there is maximum experience from all over the world, using this particular form of liver assist device.

It was developed by Stange and Mitzner in 1993. MARS uses 4 types of filters or membranes. One is the MARS membrane (it is a high flux albumin impregnated membrane; pore size of 50kDa) which removes both water soluble and albumin bound toxins from the patient's blood. The albumin bound toxins are transiently retained in the membrane before being transferred across a concentration gradient to the dialysate side (dialysate in this circuit is 20% human albumin). The toxin laden albumin is then regenerated on board by circulation through 3 more filters; the standard hemodialysis membrane (removes water soluble toxins), activated charcoal filter (removes toxins such as aromatic amino acids, fatty acids, mercaptans, middle molecules and cytokines) and ion exchange resin (removes bilirubin, bile acids, middle molecules and cytokines). The regenerated albumin is then recirculated as a dialysate for the MARS membrane.

MARS in acute liver failure (ALF)

There have been a number of case series and cohort studies in ALF patients which have demonstrated improvement in encephalopathy, hemodynamics and biochemical parameters of these patients and improved transplant free survival in up to 60%, but there is no randomized controlled trial demonstrating improvement in survival in ALF patients. Raised intracranial pressure (ICP) is one of the most common causes of mortality in ALF patients and MARS therapy has been shown to reduce the ICP among these patients. In a study of a large collection (n=116) of different types of ALF (fulminant hepatitis, primary graft non function, delayed non-function), it was demonstrated that MARS treatment could effectively bridge these patients to transplant. The authors are presently carrying out an open labeled randomized trial of MARS among

patients with ALF at the Department of Gastroenterology of All India Institute of Medical Sciences, New Delhi. Up till now 23 patients have been randomized to either MARS therapy (n 12; the patients received 1-3 session of 4-8 hours therapy, in addition to standard medical therapy) or standard medical therapy (n=11). This was a select group of patients who had 3 or more poor prognostic indicators with expected mortality of > 90%. No effect on survival in the MARS group was demonstrable; one patient survived in both groups. However more patients are in the process of being recruited to reach the required sample size.

Thus, even though MARS can improve cerebral edema, biochemical profile and hemodynamics in ALF patients, till date there is not enough convincing evidence to suggest that MARS improves survival in ALF without transplant, so there is an urgent need for a large randomized controlled trial on this issue.

MARS in acute on chronic liver failure (AoCLF)

Initial studies on MARS were performed on AoCLF patients. Subsequently there were a few randomized controlled trials. Stange *et al* demonstrated significant improvement in survival with 17 of 26 (65%) patients surviving after 2-14 sessions of MARS treatment. But this as well as other initial studies were uncontrolled. Subsequently, small randomized controlled trials (RCT) have been conducted in AoCLF patients. The first one, which was carried out in AoCLF patients with hepatorenal syndrome did demonstrate significant improvement in 30 day mortality (75% in MARS group vs 100% in standard medical therapy group ; $p < 0.01$), but it was a very small study and there was only one long term survivor. Another RCT in 24 AoCLF patients demonstrated significantly better 30 day survival in patients receiving MARS again concluding that this prolongation of survival was good enough to bridge the patients to transplant. Jalan's group carried out an RCT in 18 patients with alcohol induced AoCLF and demonstrated that, even though there was improvement in encephalopathy, there was no reduction in levels of inflammatory cytokines or on survival. Similar results without significant improvement in survival have been described in recent uncontrolled studies. Even though not enough patients have been included in the trials of MARS in AoCLF, but two meta analyses have been carried out which have come out with conflicting results on the effect of MARS on mortality in AoCLF patients. So, till the time results of large perspective RCTs become available, MARS in AoCLF will, at best remain as a tool to bridge the patients to transplant and therefore a futile and expensive exercise in centers where transplant programs have not yet started.

Other indications for MARS are summarized in Table 1.

Table 1 : Indications of MARS therapy

Indications for MARS therapy
Acute liver failure
Acute on Chronic liver failure
Acute alcoholic hepatitis
Primary and delayed graft non-function
Intractable pruritus in chronic cholestatic disorders
Post hepatectomy liver failure

Fractional plasma separation and adsorption (FPSA)

A new device based on the concept of albumin dialysis has been introduced in recent years, called the Prometheus (Fresenius, Bad Homberg, Germany). It works on the same principle as MARS, but the only difference is that instead of albumin being used from outside, it utilizes the patient's own albumin, after separating it from the patient's blood. This process is called fractional plasma separation and adsorption (FPSA). It has got two circuits. In the primary circuit the patient's albumin is filtered across an albumin permeable polysulfone membrane. This albumin is then carried through the secondary circuit to detoxify it and is returned to the patient.

Rifai *et al* carried out the first pilot study of Prometheus system among 11 patients with AoCLF. They demonstrated that two sessions of therapy were able to significantly reduce the levels of bilirubin, bile acids, ammonia and urea but the improvement in encephalopathy and Child Pugh score was not significant. Further, the survival remained dismally low. However, the treatment was well tolerated.

In a direct comparative study of MARS and Prometheus, it was demonstrated in 8 patients that though both the systems were equally effective in filtration of most water soluble and albumin bound toxins, but the removal of toxins was significantly higher with the use of Prometheus system. The level of unconjugated bilirubin, a marker for strongly albumin bound toxins was only improved with Prometheus. Similar results were obtained in a retrospective comparison of these two systems.

Both the systems are associated with adverse effects related to prolonged extracorporeal circulation of blood through an artificial membrane. These include the risks of thrombocytopenia and coagulopathy, hypotension, loss of blood volume due to clogging of filters and sepsis.

Although significant improvement and refinement of systems for liver dialysis (especially the knowledge of the albumin bound toxins and their removal), has resulted in improved short term survival in patients with advanced liver failure, so far, it has not translated in to prolonged transplant free survival in most studies on ALF and AoCLF patients. In centers where effective transplant programs have not

taken up, use of such artificial liver support systems may not only prove to be futile but prohibitively expensive as well. In conclusion, till the time, large prospective RCTs are available which show significant improvement in transplant free survival, MARS and Prometheus may best be regarded as bridges to transplant, benefiting only a small proportion of patients in developed countries.

References :

1. Wagholikar GD, Lee KH, Pandey D, Leong SO, Singh R, Tan KC (2007). Pre-transplant optimization by molecular adsorbent recirculating system in patients with severely decompensated chronic liver disease. *Indian Journal of Gastroenterology* **26**: 110-12

2. Hughes RD, Cochrane AM, Thomson AD, Murray-Lyon IM, Williams R (1976). The cytotoxicity of plasma from patients with acute hepatic failure to isolated rabbit hepatocytes. *Br J Exp Pathol* **57**: 348-53.

3. Saich R, Selden C, Rees M, Hodgson H (2007). Characterization of pro-apoptotic effect of liver failure plasma on primary human hepatocytes and its modulation by molecular adsorbent recirculation system therapy. *Artif Organs* **31**: 732-42.

4. Trey MB, Burns DG, Saunders SJ (1966). Treatment of hepatic coma by exchange blood transfusion. *N Eng J Med* **274**: 473-81.

5. Sabin S, Merritt JA (1968). Treatment of hepatic coma in cirrhosis by plasmapheresis and plasma infusion (plasma exchange). *Ann Intern Med* **68**: 1-7.

6. Burnell JM, Dawborn JK, Epstein RB, Gutman RA, Leinbach GE, Thomas ED *et al.* (1967). Acute hepatic coma treated by cross-circulation or exchange transfusion. *N Eng J Med* **276**: 935-943.

7. Abouna GM, Boehmig HG, Serrou B, Amemiya H, Martineau G (1970). Long-term hepatic support by intermittent multi species liver perfusions. *Lancet* **2**: 391-396.

8. Demetriou AA, Brown RS Jr, Busuttil RW, Fair J, McGuire BM, Rosenthal P et al. (2004). Prospective, randomized, multicentre, controlled trial of a bioartifical liver in treating acute liver failure. *Ann Surg* **239**: 660-7.

9. Felldin M, Friman S, Backman L, Sievert-Delle A, Henriksson BA, Larsson B *et al.* (2003). Treatment with the molecular adsorbent recirculating system in patients with acute liver failure. *Transplant. Proc.* **35**: 822-3.

10. Novelli G, Rossi M, Pretagostini R, Novelli L, Poli L, Ferretti G *et al.* (2003). A 3-year experience with molecular adsorbent recirculating system (MARS): our results on 63 patients with hepatic failure and color doppler US evaluation of cerebral perfusion. *Liver Int* **23**: 10-5.

11. Stefoni S, Coli L, Bolondi L, Donati G, Ruggeri G, Feliciangeli G *et al.* (2006). Molecular adsorbent and recirculating system (MARS) application in liver failure: clinical and hemodepurative results in 22 patients. *Int J Artif organs* **29**: 207-18.

12. Chiu A, Chan LM, Fan ST (2006). Molecular adsorbent and recirculating system treatment for patients with liver failure. The Hong Kong experience. *Liver Int.* **26**: 695-702.

13. Pugliese F, Ruberto F, Perella SM, Cappanoli A, Bruno K, Martelli S *et al.* (2007). Modifications of intracranial pressure after molecular adsorbent and recirculation system treatment in patients with acute liver failure. *Transplant. Proc.* **39**: 2042-4.

14. Novelli G, Rossi M, Pretagostini R, Pugliese F, Ruberto F, Novelli L *et al.* (2005). One hundered and sixteen cases of acute liver failure treated with MARS. *Transplant. Proc.* **37**:2557-9.

15. Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KS, Tandon A *et al.* (1996). Fulminant hepatitis in a tropical population. Clinical course, cause and early predictors of outcome. *Hepatology* **23**: 1448-55.

16. Stange J, Mitzner SR, Klammt S, Freytag J, Peszynski P, Loock J *et al.* (2000). Liver support by extracorporeal blood purification. : a clinical observation. *Liver transplantation* **6**: 603.

17. Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD *et al.* (2000). Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled trial. *Liver Transplantation* **6**: 277-8.

18. Sen S, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R *et al.* (2004). Pathophysiological effects o falbumin dialysis in acute on chronic liver failure. A randomized controlled study. *Liver Transplantation* **10**: 1109-19.

19. Wolff B, Machill K, Schumacher D, Schilzki I (2007). MARS dialysis in decompensated ALD: a single centre experience. *Liver Transplantation* **13**: 1189-92.

20. Rifai K, Ernst T, Kretschmer U, Bahr MJ, Schneider A, Hafer C *et al.* (2003). Prometheus- a new extracorporeal system for the treatment of liver failure. *J Hepatol* **39**: 984-90.

21. Krisper P, Haditsch B, Stauber R, Jung A, Stadlbauer V, Trauner M *et al.* (2005). In Vivo quantification of liver dialysis: comparison of albumin dialysis and fractional plasma separation. *J Hepatol* **43**: 451-7.

22. Evenepoel P, Laleman W, Wilmer A, Claes K, Kuypers D, Bammens B *et al.* (2006). Prometheus versus molecular adsorbents recirculating system: comparison on efficiency in two different liver detoxification devices. *Artif Organs* **30**: 276-84.