Extracorporeal Non cellular Liver Assisted Devices

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Key Concepts

- Mortality in patients with liver failure remains high.
- Liver assisted devices may assist in bridging patients who are waiting for liver transplantation
- More randomized controlled trials are needed to establish the effective use of liver assisted devices.

66.1 Introduction

Liver is a very complex organ that performs some of the most vital functions such as blood detoxification and purification, synthesis and storage that is crucial in maintaining function of other organs [1]. Even though the liver has the capacity to regenerate there are occasions whereas the insult to the liver is extreme in a such a way that recovery and regeneration is suboptimal and the patient develops cerebral edema, infections and multi-organ failure among others.

Liver diseases are responsible for more than one million deaths worldwide and the number continues to rise as per the study published by Naghavi and colleagues [2]. Some of the deaths are related to acute liver failure while others are due to acute on chronic liver failure. In acute liver failure, the adult mortality is approximately 50% despite the increase in the number of patients receiving liver transplants. In acute on chronic liver failure, the mortality is increasing with repeated hospitalizations due to acute decompensation.

Liver transplantation is a life saving procedure, though mortality while on the least is substantial. In order to decrease the mortality rate there is a high demand for modalities that can bridge the gap until a graft is available. Extracorporeal liver support devices have therefore been developed in order to clinically stabilize the decompensated patient and either act as a bridge to liver transplantation or allow the liver to recover from injury [3].

The ultimate liver assist device would eliminate the need for liver transplantation and may offer a chronic replacement for patient with end stage liver disease, as, potentially in renal dialysis. Liver assist devices are far from ready to be routinely used as renal dialysis but with research in this field we are making remarkable strides towards achieving the goal.

66.2 Types of Extracorporeal Liver Assisted Devices

Effective liver assisted devices would be expected to perform three key functions in patients with liver failure 1) detoxification, 2) synthesis of clinically important proteins and 3) facilitated regeneration of native hepatocytes [4].

Liver assisted devices can be divided into two types:

- Extracorporeal Non Cellular Liver Assisted Devices
- Extracorporeal Cellular Liver Assisted Devices

In this chapter, we will be focusing on the Extracorporeal Non Cellular Liver Assisted Devices (Table 66.1) such as Molecular Adsorbent Recirculating System (MARS™), Fractionated Plasma Separation and Adsorption System—FSPA (Prometheus™), Single Pass Albumin Dialysis System (SPAD), and Selective plasma filtration therapy (SEPET).

Table 66.1 Artificial liver support devices (non-cell based liver support devices)

Molecular Adsorbents Recirculating System (MARS)
Fractionated plasma separation and adsorption (Prometheus)
Single pass albumin dialysis (SPAD)
Selective Plasma Filtration therapy (SPFT)

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These systems are based on the concept of albumin dialysis (removal of albumin bound toxins). These toxins have been associated with Hepatic Encephalopathy (HE), renal failure due to hepatorenal syndrome (HRS) and cardiovascular failure. These devices can also remove water-soluble substances such as creatinine or urea, ammonia, and smaller proteins such as some cytokines, by standard dialysis. Non cellular assisted devices are based on the principles of adsorption and filtration and are aimed at removing circulating toxins by using membranes with different pore sizes and adsorbent columns [5].

66.3 Molecular Adsorbent Recirculating Systems (MARS)

MARS was originally developed by Strange and colleagues [6] in 1993. The system provided a combination of conventional dialysis with hemodialysis against an Albumin dialysate solution over an Albumin impermeable membrane.

MARS consists of an albumin hemodialyzer, a standard hemodialyzer, an activated carbon adsorber and an anion exchanger (Fig. 66.1). This circuit is filled with 600 ml of 20% human albumin solution. The albumin acts as a dialysate and is pumped through a hollow-fibre membrane hemodialyzer (High Flux Dialysis Filter) countercurrent to the blood flow. Protein-bound toxins and water-soluble substances diffuse into the albumin solution. The albumin is then passed through another dialyzer countercurrent to a standard buffered dialysis solution where diffusive clearance of water-soluble substances occurs. The albumin solution is then cleaned of its albumin-bound toxins by passage through an activated carbon adsorber and an anion exchanger [7].

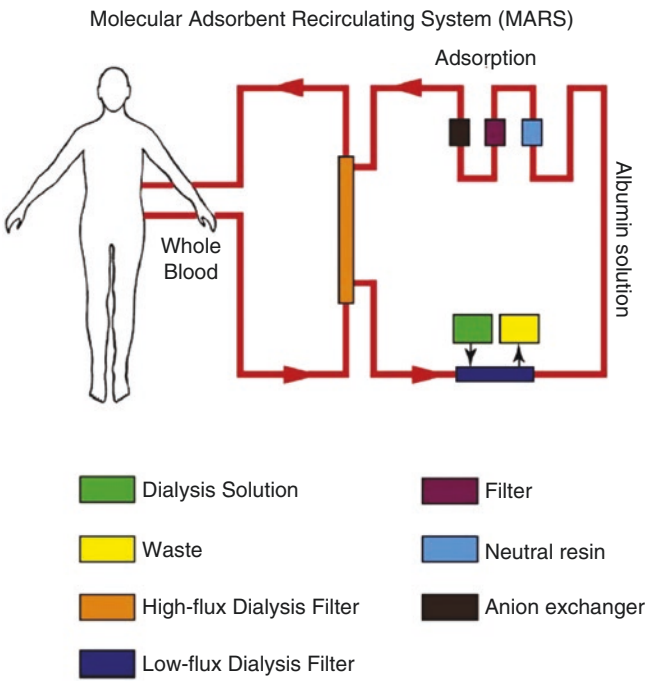

Fig. 66.1 Molecular adsorbent recirculating system

The MARS High Flux dialyzer has a surface area of 2.1 m^2, a membrane thickness of 100 nm and a molecular cut-off of about 50 kDa. The irregularities in the membrane surface provide deep crypts, which act as binding sites for albumin when the circuit is primed with albumin solution. The albumin molecules on the dialysis side of the membrane are in very close proximity to the surface of the membrane in contact with patient's blood. Albumin-bound toxins move by physicochemical interactions between the plasma, albumin molecules bound to the dialysis side of the membrane and the circulating albumin solution. A concentration gradient is maintained by circulation of the albumin solution and disposal of the albumin-bound toxins by passage through the activated charcoal and anion-exchange columns [8, 9].

In the first randomized controlled trial [10], 13 patients with cirrhosis were divided into two groups: A control group (n = 5) receiving standard medical treatment and hemodiafiltration, and a group (n = 8) additionally being treated with MARS. The MARS treatment was applied 1–10 times for 6–8 h. A significant decrease in creatinine and bilirubin levels as well as increase in serum sodium level and prothrombin activity was detected in the MARS group. Mortality of control group was 100% after 7 days, where it was 62.5% in the MARS group.

A prospective, controlled study was performed to test whether hyperbilirubinemia, 30-day survival, and encephalopathy would be improved by extracorporeal albumin dialysis (ECAD) [11]. Twenty-four patients were studied; 23 patients had cirrhosis; one had a prolonged cholestatic drug reaction and was excluded from per protocol (PP) analysis. Patients had a plasma bilirubin greater than 20 mg/dL and had not responded to prior standard medical therapy (SMT). Patients were randomized to receive SMT with ECAD or without (control). ECAD was performed with an extracorporeal device that dialyzes blood in a hollow fiber dialyzer against 15% albumin. Albumin-bound molecules transfer to dialysate albumin that is regenerated continuously by passage through a charcoal and anion exchange column and a conventional dialyzer. ECAD was associated with improved 30-day survival (PP, 11 of 12 ECAD, 6 of 11 controls). Plasma bile acids and bilirubin decreased on average by 43% and 29%, respectively, in the ECAD group after 1 week of treatment, but not in the control group. Renal dysfunction and hepatic encephalopathy improved in the ECAD group, but worsened significantly in the control group. ECAD was safe, with adverse events being rare and identical in both groups. In conclusion, ECAD appeared to be effective and safe for the short-term treatment of patients with cirrhosis and superimposed acute injury associated with progressive

hyperbilirubinemia and may be useful for increasing survival in such patients awaiting liver transplantation [11].

A prospective randomized controlled multi-center trial was performed in 19 tertiary hospitals in Europe known as Relief Trial. One hundred eighty-nine patients with acute on chronic liver failure were randomized either to MARS (n = 95) or to standard therapy (SMT) (n = 94). Ten patients (five per group) were excluded due to protocol violations. In addition, 23 patients (MARS: 19; SMT: 4) were excluded from per-protocol (PP) analysis (PP population n = 156). Up to ten 6–8-h MARS sessions were scheduled. The main endpoint was 28-day intention to treat (ITT) and PP survival. There were no significant differences at inclusion, although the proportion of patients with Model for End stage Liver Disease (MELD) score over 20 points and with spontaneous bacterial peritonitis (SBP) as a precipitating event was almost significantly greater in the MARS group. The 28-day survival was similar in the two groups in the ITT and PP populations (60.7% versus 58.9%; 60% versus 59.2% respectively). After adjusting for confounders, a significant beneficial effect of MARS on survival was not observed. MELD score and HE at admission and the increase in serum bilirubin at day 4 were independent predictors of death. At day 4, a greater decrease in serum creatinine (P = 0.02) and bilirubin (P = 0.001) and a more frequent improvement in HE (from grade II–IV to grade 0–I; 62.5% versus 38.2%; P = 0.07) was observed in the MARS group. Severe adverse events were similar. So in conclusion at scheduled doses, a beneficial effect on survival of MARS therapy in patients with acute on chronic liver failure could not be demonstrated. However, MARS has an acceptable safety profile, has significant dialysis effect, and non-significantly improves severe HE [12].

An additional randomized controlled trial of MARS that included 102 patients (n = 53 MARS vs. 49 SMT) in 16 French transplant centers to determine whether MARS improves survival in acute liver failure was contacted. The main end point was to evaluate the 6 month survival. one hundred two patients (mean age, 40.4 years [SD, 13]) were in the modified intention-to-treat (mITT) population. The per-protocol analysis (49 conventional, 39 MARS) included patients with at least 1 session of MARS of 5 h or more. This study showed no survival benefit of MARS at 6 months (84.9% vs. 74.4% SMT, p = 0.28). A significant criticism of this study was the short time from randomization to liver transplantation (median 16.2 h), which may have limited any demonstrable effect from albumin dialysis. This randomized trial of MARS in patients with acute liver failure was unable to provide definitive efficacy or safety conclusions because many patients had transplantation before administration of the intervention. Acute liver failure not caused by paracetamol was associated with greater 6-month patient survival [13].

66.4 Prometheus System

The Prometheus system is based on fractional plasma separation and adsorption (FPSA) and hemodialysis. It uses a membrane with a cut-off of 250 kDa, being permeable for albumin. The toxin-loaded patient albumin crosses the membrane and passes a neutral resin adsorber and an anion exchanger, where the toxins bind to the adsorbers and free albumin is brought back to the patient. The method is combined with additional hemodialysis, therefore being able to remove water-soluble toxins as well as albumin-bound toxins.

A small clinical study was performed including nine patients with acute on chronic liver failure and documented cirrhosis due to alcohol or chronic viral infection, to confirm the efficacy of the system, to outline the effect of the single components and to evaluate the saturation effect of the adsorber columns [14]. It was shown that water-soluble toxins were almost exclusively cleared by the dialyzer, whereas bilirubin was cleared by the adsorber column, as expected. However, the clearance of bilirubin and bile acids strongly decreased in time, suggesting a saturation of the adsorbers. In general, the Prometheus system was shown to be effective in the removal of various toxins and to trigger no adverse events [15–18].

The first Prometheus trial was published in 2003 and included 11 patients with acute on chronic liver failure and accompanying renal failure [19]. While on treatment there was a significant improvement in serum levels of conjugated bilirubin, bile acids, ammonia, cholinesterase, creatinine, urea, and blood pH. Major complication of the procedure included hypotension in two patients due to infection and one patient developed uncontrolled bleeding.

Over the last few years, only a limited number of studies have used clinical endpoints. The most important was the HELIOS study, which was published in 2012 by Kribben et al. [20]. This was a multi-centric randomized controlled trial comparing Prometheus with SMT in 145 patients with acute on chronic liver failure, and the primary endpoint was the probabilities of survival at 28 and 90 days (irrespective of liver transplantation). This RCT scored 3 on the Oxford quality scoring system. This trial failed to prove a survival benefit with Prometheus in the overall patient population, and the patient recruitment was interrupted after the interim analysis (90 patients) due to futility (204 patients were initially planned for inclusion in the study). It is important to note that in the overall population the probability of survival was slightly higher in the Prometheus group compared to the SMT group (90-day survival probability: 47% vs. 38%) but without statistical significance.

66.5 Single Pass Albumin Dialysis (SPAD)

Single Pass Albumin Dialysis (SPAD) applies similar principles. The patient's blood also passes a high flux dialysis membrane. Albumin solution streams along the other side of the membrane counter-directionally, accepting toxins from the plasma. However, in SPAD the albumin solution is discarded after a single passage of the membrane without being recycled. The concept enables CVVHDF using the same dialysis filter [21].

With respect to clinical data on SPAD, only a few case reports were published in the early years, and there are currently no published studies that focus on demonstrating the clinical benefits of SPAD versus standard medical therapy (SMT) in acute liver failure or acute on chronic liver failure. Two retrospective uncontrolled studies reviewing data from patients with liver failure treated with SPAD as rescue therapy were identified. One included pediatric patients with ALF of different etiologies [22], and the other included adults patients with severe liver dysfunction in a context of alcoholic liver disease who were treated with SPAD or Prometheus [23]. Neither of these studies allow us to draw conclusions about the clinical usefulness of SPAD, and they only show us its relative ease of use and the absence of unexpected complications from its use.

The only randomized study using SPAD was recently published by Sponholz et al. [24]. This is a randomized, controlled crossover study comparing the detoxification capacity and influence on clinical and para-clinical parameters of SPAD (4% albumin dialysate solution; 700 mL/h dialysis flow rate) and MARS (20% albumin flow rate equal to the blood flow rate, 2000 mL/h dialysis flow rate). The authors found similar reductions in the total plasma bilirubin levels, without significant differences between the two devices. The reductions in the total bile acids and γ-glutamyl transferase levels in the SPAD arm were non-significant. The creatinine and urea levels were not significantly reduced with SPAD compared to those of MARS. In contrast to other studies, neither MARS nor SPAD induced a reduction in the systemic cytokine levels. Moreover, the patients treated with SPAD presented some metabolic derangements such as increasing lactate levels or decreasing calcium levels, which are probably explained by the preferential use of citrate anti-coagulation with a low dialysis flow rate. The effects of MARS and SPAD on the clinical parameters (HE and hemodynamic status) were small and equivalent. Currently, SPAD may be an easy-to-use alternative to MARS, but the optimal albumin dialysate concentration, dialysate flow rate and treatment regimen are not yet fully established.

66.6 Selective Plasma Filtration Therapy (SEPET)

In Selective Plasma Filtration Therapy (SEPET) the patient's blood is lead through a single-use cartridge containing hollow fibers with a molecular weight cut-off at 100 kDa. A plasma fraction containing several of the accumulated toxins in the blood is discarded after passing the membrane. This fraction contains toxins of small molecular weight and free pro-inflammatory cytokines but not for example immunoglobulins. Molecules with a molecular weight close to 100 kDa pass the membrane in only limited amounts so that large portions of for example albumin, HGF, as well as several clotting factors, are retained. The fluid loss is replaced by electrolyte solution, human albumin solution, fresh frozen plasma or a combination thereof. The system is designed for use with any commercially available kidney dialysis unit and/or plasmapheresis system utilizing hollow-fiber cartridges.

66.7 Discussion

There continues to be great interest and potential for extracorporeal non cellular liver assist devices. At present it is difficult to make an evidence-based recommendation supporting artificial liver assisted devices. Of this group, MARS is the best-studied albumin dialysis technology in acute liver failure and acute on chronic liver failure. Although studies have consistently demonstrated biochemical improvement and improvement in HE with MARS [11], recent large randomized studies in acute on chronic liver failure (RELIEF) [12] and acute liver failure (FULMAR) [13] showed no survival benefit. The HELIOS study examining Prometheus in acute on chronic liver failure was also disappointing [20]. These studies shared some common methodological limitations in study design. Within studies in acute liver failure and acute on chronic liver failure, heterogeneous groups of patients with varying causes with different natural histories were often lumped together. Several studies did not stratify patients based on severity of illness (e.g., MELD, CLIF-SOFA); hence, it is difficult to assess patient matching and, furthermore, the impact of underlying disease on patient mortality with or without treatment. Furthermore due to co-interventions, such as liver transplantation, not all patients received pre-specified durations of extracorporeal non cellular liver assist device therapy. When examining RELIEF AND HELIOS, it may have been more parsimonious to examine only acute on chronic liver failure patients who were candidates for liver transplantation because acute on chronic liver failure patients with multi-organ failure portends poor outcomes. Successfully bridging patients to liver

transplantation may warrant further consideration because the primary endpoint over a 30-day to 90-day survival.

66.8 Conclusion

Severe liver failure is associated with high mortality, as patients succumb despite undergoing optimal medical treatment. Liver transplantation can be a life saving procedure though approximately a quarter of patients will succumb while waiting for a liver transplant. Consequently, there is a clear need for liver support systems to provide a "bridge" to a final treatment. Over the last two decades, several artificial liver support systems with promised advances were introduced. However, whether such devices that can lead into survival benefit are still in need.

Self Study

Questions

1. Which of the following is not an Extracorporeal Non Cellular Assisted Device?
   (a) Molecular Adsorbent Recirculating System (MARS™)
   (b) Extracorporeal Liver Assist Device (ELAD®)
   (c) Fractionated Plasma Separation and Adsorption System—FSPA (Prometheus™)
   (d) Single Pass Albumin Dialysis System (SPAD)
   (e) Selective plasma filtration therapy (SEPET)
2. Which of the following non cellular liver assisted devices have survival benefit?
   (a) Molecular Adsorbent Recirculating System (MARS™)
   (b) Fractionated Plasma Separation and Adsorption System—FSPA (Prometheus™)
   (c) Single Pass Albumin Dialysis System (SPAD)
   (d) Selective plasma filtration therapy (SEPET)
   (e) None of the above

Answers

1. Which of the following is not an Extracorporeal Non Cellular Assisted Device?
   (a) Molecular Adsorbent Recirculating System (MARS™). This is a non cellular liver assisted device.
   (b) CORRECT ANSWER. Extracorporeal Liver Assist Device (ELAD®). It is a bioartificial liver assist device.
   (c) Fractionated Plasma Separation and Adsorption System—FSPA (Prometheus™). This is a non cellular liver assisted device.
   (d) Single Pass Albumin Dialysis System (SPAD). This is a non cellular liver assisted device.
   (e) Selective plasma filtration therapy (SEPET). This is a non cellular liver assisted device.
2. Which of the following non cellular liver assisted devices have survival benefit?
   (a) Molecular Adsorbent Recirculating System (MARS™)
   (b) Fractionated Plasma Separation and Adsorption System—FSPA (Prometheus™)
   (c) Single Pass Albumin Dialysis System (SPAD)
   (d) Selective plasma filtration therapy (SEPET)
   (e) CORRECT ANSWER. None of the above

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