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Current updates on extracorporeal liver support systems

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Abstract:

Extracorporeal liver support (ELS) has been shown to have positive development in recent years. Despite the increase in liver transplants, the outcome of patients who are not eligible for transplant remains poor. ELS could potentially be a bridging therapy for these patients. However, adequate data is lacking and no definitive survival benefits by ELS devices exist ELS has been shown to provide clinical improvement in liver failure symptoms as well as improved hemodynamics. Therefore, it likely can add to liver recovery and provide a bridge to liver transplantation or recovery of natural liver function. This study reports several indications for ELS devices and an overview of recent trials using ELS principles, including albumin dialysis, High-volume plasma exchange, and native hepatocytes.

Key Words: extracorporeal liver support; liver dialysis; albumin dialysis; acute liver failure

Introduction:

Extracorporeal liver support (ELS) systems can be used to remove harmful metabolites that tend to that accumulate in liver failure. This could be due to a primary insult like shock liver, hepatitis, or alcoholic liver cirrhosis. Insufficient clearance of toxic metabolites tends to intensify the decline in a cirrhotic liver. The liver has a fantastic potential to regenerate and function to near-normal capacity. This provides the rationale to develop extracorporeal liver support systems that can provide support while keeping the patient alive and allowing adequate time for cellular regeneration. Furthermore,

ELS systems can be utilized in liver failure as a bridge when liver transplantation is needed. Patients with hepatic encephalopathy or hepatorenal syndrome can benefit while awaiting longer transplantation times. The concern with liver dialysis is adequate membrane structure and inadequacy of plasma filtration. The use of a regular pore size plasma filter vs. selective filter has been linked to increased mortality and poor survival rates [1]. More recent observations of the hydrophobic nature of toxic molecules and their dependence of transport by serum albumin have initiated a pathway for artificial ELS systems. ELS devices allow blood or plasma passage through a special filter to remove circulating toxins. In 2004, the use of hemodiabsorption was introduced by Ash et al. [2]. This process used a dialyzer that had a dialysate composed of sorbent particles. In 2006, the Prometheus system was introduced utilizing a similar approach as by Ash et al. However, the separation membrane was more permeable for albumin, and fixed columns achieved increased adsorption than mobile sorbent suspension [3]. One widely studied mechanism is the use of albumin in dialysis. Albumin-bound toxins can be dialyzed via dialysis membranes with albumin dialysate as a molecular acceptor [5]. The use of albumin allows maintenance of the dialysis process selectivity through small pore membranes and their removal of albumin-bound toxins [4].

Main text:

Principles of liver dialysis

ELS support consists of biological or artificial devices. Biological devices combine hepatocytes and mechanics to provide a system to detoxify a patient's blood. Conversely, artificial devices do not use any biological components.

Albumin based systems:

To date, the best-studied artificial devices are based on the albumin dialysis principle. Albumin has multiple roles, and it functions as a vital plasma binder. In liver failure, albumin production is affected with the binding capacity of circulatory toxins reduced leading to a toxin burden in the human body resulting in liver failure [5]. Albumin dialysis supports this function and removes the toxic burden while giving the native liver time to recover. The molecular adsorbent recirculating system (MARS) is one of the best studied ELS devices. In this device, blood circulates across an albumin-impermeable membrane against a human albumin solution dialysate [6]. MARS has been widely studied in patients with acute and acute on chronic liver failure. It has not been shown to have a statistically significant mortality benefit in acute liver failure. However, it does have definitive benefits in acute on chronic liver failure [7]. In patients with acute on chronic liver failure, beneficial effects include improved portal hypertension, hepatic encephalopathy, renal function, and pruritus [6, 8, 9]. MARS demonstrated a significant reduction in serum creatinine, bilirubin, and hepatic encephalopathy grade in the RELIEF study, which compared MARS therapy and standard therapy for acute on chronic liver failure. In a French multicenter randomized controlled trial called the FULMAR study MARS therapy showed no difference in 6-month survival compared to conventional therapy with a non-significant primary outcome of 28-day survival [10, 11]. However, a subsequent meta-analysis reported improved 10-day and 30-day survival with five or more sessions being required for a meaningful response [12].

Prometheus is another ELS device that uses the principles of albumin dialysis. It separates albumin from the blood by fluxing whole blood across a larger cutoff membrane into a secondary circuit with two filters. These filters help improve albumin adsorption capabilities [13]. Prometheus was compared to standard medical therapy in the HELIOS study which demonstrated a reduction in bilirubin levels but no improvement in 28 or 90-day survival. Improvement in serum creatinine and ammonia levels was also been reported [14].

Plasma exchange:

Two comprehensive clinical trials were conducted using High-volume plasma exchange (HVP) which allows for plasma separation and elimination from whole blood. A significantly improved 90-day survival and median survival was shown for the hepatitis B virus cohort [15]. Improvement in transplant-free survival to hospital discharge was also reported along with reduced systemic inflammatory response syndrome and sequential organ failure assessment scores [16].

Biological ELS systems:

The Extracorporeal Liver Assist Device (ELAD) utilizes a biological dialyzer. These dialysis cartridges are composed of hollow fibers and contain human hepatoblastoma cells which mimic in vivo albumin synthesis and cytochrome P450 activity. Currently, no trials have demonstrated any survival benefit using ELAD and these devices have poor ammonia detoxification capabilities limiting hepatic encephalopathy benefits [17].

Indications for ELS support:
Hypoperfusion of liver:

One of the main indications for ELS is to provide improved blood supply in acute or acute on chronic liver failure. Prior MARS treatments have demonstrated an increased systemic vascular resistance index and patients presenting with systemic hypotension have improved mean arterial pressures after treatment [18,19]. MARS treatments provide isolated organ perfusion that mainly affects the liver Another phenomenon is improved renal blood flow which can be beneficial l in hepatorenal syndrome [18]. Lastly, patients have been shown to have increased cerebral perfusion after MARS treatments [20].

Hepatic encephalopathy and cerebral edema:

Acute and chronic liver failure can result in hepatic encephalopathy which is correlated with worsening morbidity and mortality. Liver dialysis is beneficial for acute on chronic liver failure patients with grade III and IV hepatic encephalopathy [21]. Improvement in intracranial pressure was also reported however, evidence is currently lacking [20]. One study using animal models demonstrated a reduction in increased cranial pressure after initiating dialysis. Furthermore, patients undergoing liver dialysis have reduction in ammonia concentration in blood [22].

Hepatorenal syndrome:

Albumin based ELS devices have reported improved kidney function during treatments with a decrease in serum creatinine improving urine output and resolution of hepatorenal syndrome [18,23, 24]. These findings were studied in patients with type I hepatorenal syndrome (HRS) and the mechanism is poorly understood [6]. However, these results could be secondary to reduced plasma renin concentrations in patients with acute on chronic liver failure resulting in increased renal perfusion. Albumin-based ELS could be a viable option for HRS [25, 26]. Unfortunately, no meaningful data currently points towards synthetic improvement in liver function while receiving Albumin-related ELS [27,28There is a current need for trials is to make a definitive conclusion on the utility of Albumin-related ELS

Liver transplantation:

Patients with acute liver failure could be candidates for Albumin based ELS while awaiting liver transplantation. This treatment option is reportedly safe, and benefits include improved patient survival and sustained liver regeneration. A study by Koivusalo et al. showed a one-year survival of 84% after MARS treatment. Recovery of native liver function was reported in 30 out of 56 patients with a one-year survival of 79%. Patients who underwent liver transplantations had a one-year survival of 94% [29]. One multicenter randomized controlled trial investigated the role of Albumin based ELS as a tool to bridge patients with acute liver failure to transplantation however, it was unable to provide superior efficacy secondary to many patients receiving transplantation before appropriate intervention could occur [10].

Symptoms of chronic liver disease:

ELS has a positive response in refractory symptoms of chronic

liver disease such as pruritis. Multiple liver diseases and their association with pruritus have been studied including primary sclerosing cholangitis, chronic viral hepatitis, and primary biliary cirrhosis. Symptom relief lasted up to three months but not every patient was responsive to therapy [30, 31]. The mechanism behind improved pruritus symptoms is poorly understood but could be explained by the removal of hydrophobic bile acids resulting in a bile acid pattern shift [32]. Another use for albumin based ELS, particularly MARS, is intoxication due to medication overdose with substances such as acetaminophen [33,34] This therapy allows for the removal of albumin-based drugs and improved acute liver failure in the settings of toxins.

Current prospects:

Current liver dialysis major studies are summarized in table 1:

Trial Name	Year	Mechanism	Device used	Patient cohort	Number of patients	Survival data compared to SMT
FULMAR [10]	2013	Albumin based ELS	MARS	Acute liver failure	110	75.5 vs. 82.9%, P= 0.50 (6-Month survival)
RELIEF [11]	2013	Albumin based ELS	MARS	Acute on chronic liver failure	189	60.7 vs. 58.9%, P = 0.79 (28-Day survival)
HELIOS [14]	2012	Albumin based ELS	Prometheus	Acute on chronic liver failure	145	66 vs. 63%, P = 0.70 (28-Day survival)
Larsen et al. [16]	2016	High-volume plasma exchange (HVP)	N/A	Acute liver failure	183	58.7 vs. 47.8%, P = 0.0083 (Survival to hospital discharge higher with HVP)
Thompson et al. [37]	2018	Biological: HepG2/C3A cells in dialysis cartridges	ELAD	Alcoholic hepatitis	203	Not significant

Table 1: Prominent extracorporeal liver support devices trials.
ELS: Extracorporeal Liver support.

ELAD: Extracorporeal liver assist device.

MARS: molecular adsorbents recirculating system.

SMT: Standard medical therapy.

Patients with acute, chronic liver failure who did not respond to standard medical therapy should be considered for extracorporeal liver support as early introduction of ELS could be beneficial Patients who have sepsis or septic shock may need to delay their ALS treatment and instead initially receive antibiotic therapy. Patients with acute on chronic liver failure coagulopathy with platelet count less than 50,000, INR greater than 2 or 3, or concurrent kidney failure requiring dialysis may not benefit from extracorporeal liver dialysis [35]. Treatment regimens should vary depending upon patient comorbidities and during treatment, anticoagulation might be necessary [35]. In the last ten years MARS was the most studied artificial liver dialysis technology and it has the potential for wide clinical application [36].

Conclusion:

While extracorporeal liver dialysis devices have had limited benefit in previous clinical trials they have provided symptomatic relief of refractory symptoms of chronic liver disease Recent trials and new devices have helped provide better understanding of acute and acute on chronic liver cirrhosis management especially in regards to treatment duration and initiation of therapy. These devices could provide a bridge between the occurrence of liver failure and transplantation. Albumin dialysis may have better outcomes however, biological devices have not been widely tested. Further comparative data is currently needed to assess survival benefits. Complications such as hepatic encephalopathy, pruritus secondary to increased bilirubin, and hepatorenal syndrome may all be managed with ELS.

Abbreviations:

ELS: Extracorporeal liver support
MARS: Molecular adsorbent recirculating system
HVP: High-volume plasma exchange

ELAD: Extracorporeal Liver Assist Device

HRS: Hepatorenal syndrome

Declarations:

Author contributions:
The author contributed solely to the work

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The authors declare that they have no conflicts of interest.

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References:

1. Ho DW, Fan ST, To J, et al. Selective plasma filtration for treatment of fulminant hepatic failure induced by D-galactosamine in a pig model. Gut. 2002;50(6):869-876.
2. Ash SR, Carr DJ, Sullivan TA. Sorbent suspension reactor for extracorporeal detoxification in hepatic failure or drug overdose. ASAIO J. 2004;50(6): lviii-lxv.
3. Vienken J, Christmann H. How can liver toxins be removed? Filtration and adsorption with the Prometheus system. Ther Apher Dial. 2006;10(2):125-131.
4. Mitzner S, Klammt S, Stange J, Schmidt R. Albumin regeneration in liver support-comparison of different methods [published correction appears in Ther Apher Dial. 2006 Dec;10(6):518]. Ther Apher Dial. 2006;10(2):108-117.
5. Anraku M, Chuang VT, Maruyama T, Otagiri M. Redox properties of serum albumin. Biochim Biophys Acta. 2013;1830(12):5465-5472.
6. Mitzner SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl. 2000;6(3):277-286.
7. Kantola T, Koivusalo AM, Höckerstedt K, Isoniemi H. The effect of molecular adsorbent recirculating system treatment on survival, native liver recovery, and need for liver transplantation in acute liver failure patients. Transpl Int. 2008;21(9):857-866.
8. Sen S, Mookerjee RP, Cheshire LM, Davies NA, Williams R, Jalan R. Albumin dialysis reduces portal pressure acutely in patients with severe alcoholic hepatitis. J Hepatol. 2005;43(1):142-148.
9. Catalina MV, Barrio J, Anaya F, et al. Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. Liver Int. 2003;23 Suppl 3:39-43.
10. Saliba F, Camus C, Durand F, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med. 2013;159(8):522-531.
11. Bañares R, Nevens F, Larsen FS, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013;57(3):1153-1162.
12. Bañares R, Ibáñez-Samaniego L, Torner JM, et al. Meta-analysis of individual patient data of albumin dialysis in acute-on-chronic liver failure: focus on treatment intensity. Therap Adv Gastroenterol. 2019; 12:1756284819879565. Published 2019 Sep 27.
13. Rifai K, Ernst T, Kretschmer U, et al. Prometheus--a new extracorporeal system for the treatment of liver failure. J Hepatol. 2003;39(6):984-990.
14. Kribben A, Gerken G, Haag S, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology. 2012;142(4):782-789.e3.
15. Qin G, Shao JG, Wang B, et al. Artificial liver support system improves short- and long-term outcomes of patients with HBV-associated acute-on-chronic liver failure: a single-center experience. Medicine (Baltimore). 2014;93(28): e338.
16. Larsen FS, Schmidt LE, Bernsmeier C, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatol. 2016;64(1):69-78.
17. Nyberg SL, Remmel RP, Mann HJ, Peshwa MV, Hu WS, Cerra FB. Primary hepatocytes outperform Hep G2 cells as the source of biotransformation functions in a bioartificial liver. Ann Surg. 1994;220(1):59-67.
18. Mitzner SR, Stange J, Klammt S, Peszynski P, Schmidt R, Nöldge-Schomburg G. Extracorporeal detoxification using the molecular adsorbent recirculating system for critically ill patients with liver failure. J Am Soc Nephrol. 2001;12 Suppl 17: S75-S82.
19. Laleman W, Wilmer A, Evenepoel P, et al. Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. Crit Care. 2006;10(4): R108.
20. Mitzner SR, Stange J, Klammt S, Koball S, Hickstein H, Reisinger EC. Albumin dialysis MARS: knowledge from 10 years of clinical investigation. ASAIO J. 2009;55(5):498-502.
21. Hassanein TI, Tofteng F, Brown RS Jr, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007;46(6):1853-1862.
22. Sen S, Rose C, Ytrebø LM, et al. Effect of albumin dialysis on intracranial pressure increase in pigs with acute liver failure: a randomized study. Crit Care Med. 2006;34(1):158-164.
23. Hetz H, Faybik P, Berlakovich G, et al. Molecular adsorbent recirculating system in patients with early allograft dysfunction after liver transplantation: a pilot study. Liver Transpl. 2006;12(9):1357-1364.
24. Saich R, Collins P, Ala A, Standish R, Hodgson H. Benign recurrent intrahepatic cholestasis with secondary renal impairment treated with extracorporeal albumin dialysis. Eur J Gastroenterol Hepatol. 2005;17(5):585-588.
25. Cárdenas A, Ginès P. Therapy insight: Management of hepatorenal syndrome. Nat Clin Pract Gastroenterol Hepatol. 2006;3(6):338-348. doi:10.1038/ncpgasthep0517
26. Moreau R, Lebrec D. Diagnosis and treatment of acute renal failure in patients with cirrhosis. Best Pract Res Clin Gastroenterol. 2007;21(1):111-123.
27. Yuan JZ, Ye QF, Zhao LL, et al. Preoperative risk factor analysis in orthotopic liver transplantation with pretransplant artificial liver support therapy. World J Gastroenterol. 2006;12(31):5055-5059.
28. Hassanein T, Oliver D, Stange J, Steiner C. Albumin dialysis in cirrhosis with superimposed acute liver injury: possible impact of albumin dialysis on hospitalization costs. Liver Int. 2003;23 Suppl 3:61-65.
29. Koivusalo AM, Vakkuri A, Höckerstedt K, Isoniemi H. Experience of Mars therapy with and without transplantation in 101 patients with liver insufficiency. Transplant Proc. 2005;37(8):3315-3317.
30. Saliba F. The Molecular Adsorbent Recirculating System (MARS) in the intensive care unit: a rescue therapy for patients with hepatic failure. Crit Care. 2006;10(1):118.
31. Bellmann R, Graziadei IW, Feistritzer C, et al. Treatment of refractory cholestatic pruritus after liver transplantation with albumin dialysis. Liver Transpl. 2004;10(1):107-114.

32. Stadlbauer V, Krisper P, Beuers U, et al. Removal of bile acids by two different extracorporeal liver support systems in acute-on-chronic liver failure. ASAIO J. 2007;53(2):187-193.
33. Koivusalo AM, Vakkuri A, Höckerstedt K, Isoniemi H. Experience of Mars therapy with and without transplantation in 101 patients with liver insufficiency. Transplant Proc. 2005;37(8):3315-3317.
34. Lee KH, Lee MK, Sutedja DS, Lim SG. Outcome from molecular adsorbent recycling system (MARS) liver dialysis following drug-induced liver failure. Liver Int. 2005;25(5):973-977.
35. Faybik P, Bacher A, Kozek-Langenecker SA, et al. Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study. Crit Care. 2006;10(1): R24.
36. Mitzner SR. Albumin dialysis: an update. Curr Opin Nephrol Hypertens. 2007;16(6):589-595.
37. Thompson J, Jones N, Al-Khafaji A, et al. Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: A multinational, prospective, controlled, randomized trial. Liver Transpl. 2018;24(3):380-393.