Journal of Community Hospital Internal Medicine Perspectives

Volume 12 | Issue 4 Article 8

2022

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Recommended Citation

Nguyen, Anthony; Mirza, Samir; Javed, Nismat; Hanif, Hamza; Ryu, Moon; Mirza, Rida Tariq; and Sheikh, Abu Baker (2022) "Extracorporeal Liver Support: An Updated Review of Mechanisms and Current Literature," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 12: Iss. 4, Article 8.
DOI: 10.55729/2000-9666.1064
Available at: https://scholarlycommons.gbmc.org/jchimp/vol12/iss4/8

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Abstract

Introduction: **Acute liver failure is a cause of major mortality in the United States. Although the liver possesses regenerative capabilities, liver transplantation is the mainstay of treating acute liver failure. This modality is associated with many financial and logistic challenges. In this regard, Extracorporeal Liver Support (ECLS) might help in reducing mortality as well as bridge a patient to liver transplant. In some cases, the sequelae of liver failure such as hepatic encephalopathy and multi-organ failure can be postponed long enough for the native liver to self-recover function. With this rationale, we sought to describe the mechanism of various ECLS modalities, provide an overview of the current evidence regarding its use and to highlight future advancements that could overcome hindrances in its use.**

Methods: **A scoping review was performed using PubMed and other databases from 1990 to 2020 with the keywords: 'extracorporeal liver support', 'acute liver failure', 'acute on chronic liver failure', 'albumin dialysis', 'artificial' and 'bioartificial'.**

Results and conclusions: **ECLS has shown significant improvements in bilirubin and urea levels. Various forms of ECLS might also reduce mortality due to liver failure. However, many complications, such as hypotension, anemia, bleeding issues, sepsis, can be anticipated. There are a few barriers to mainstream use of ECLS, such as specific design requirements and high cost that reduce the overall utility of this modality in a small group of liver transplant candidates. Furthermore, a multidisciplinary team approach is required to supervise ECLS, a luxury only available at major academic hospitals. Some advancements for overcoming these barriers include investigation of new scaffolding systems. In order to expand the usage of ECLS, clinical trials focusing on a comparison of different modalities of ECLS with renal replacement therapy in patients with liver failure should be promoted.**

Keywords: Extracorporeal liver support, Acute liver failure, Acute on chronic liver failure, Albumin dialysis, Artificial and bioartificial

1. Introduction

Acute liver failure (ALF) describes a state of severe liver dysfunction that causes either altered mentation or impaired synthetic function while acute-on-chronic liver failure (ACLF) describes an exacerbation of baseline chronic liver disease. The estimated incidence of ALF in the United States is 5.5 cases per million people with acetaminophen toxicity being the leading etiology, while the estimated incidence of ACLF is 24% with alcoholic cirrhosis and chronic hepatitis C infection being the leading etiologies.[1] The liver is one of the most resilient organs in the human body and can regenerate from a partial hepatectomy or a significant toxic insult such as acetaminophen poisoning while still maintaining sufficient liver function to maintain homeostasis.[2] However, in cases of both ALF and ACLF, liver transplantation is often required for long term survival as current

Received 15 September 2021; revised 20 February 2022; accepted 1 March 2022.
Available online 4 July 2022

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https://doi.org/10.55729/2000-9666.1064

therapeutic options are temporizing measures that are not able to fully replace hepatic function in the same way that long term dialysis can replace the function of the kidneys. Liver transplantation can be both taxing to the healthcare system and logistically challenging as it requires both a viable donor as well as a suitable transplant recipient.

Extracorporeal Liver Support (ECLS) is a system that performs the essential functions of the liver via filtration and detoxification of blood within an external device with the end goal of reducing mortality or to bridge a patient to liver transplant. In some cases, ECLS can temporarily mitigate sequelae of liver failure such as hepatic encephalopathy and multi-organ failure long enough for the native liver to recover function on its own.

The aim of this review is to describe the basic mechanism of different ECLS modalities, provide an overview of the current evidence for and against its use and to highlight future advancements that could help remove barriers to its use.

2. Methods

For the purposes of this study, PubMed/MEDLINE, Web of Science, CINAHL, Google scholar, and independent websites for free-text words and medical subject heading using keywords were searched. The keywords used in the review were 'extracorporeal liver support', 'acute liver failure', 'acute on chronic liver failure', 'albumin dialysis', 'artificial' and 'bioartificial'. We reviewed literature from 1990 to 2020. Case reports, case series, original studies, reviews, systematic reviews, and meta-analyses written in English were searched and selected, focusing on the following topics: mechanism of extracorporeal liver support, complications, mortality, clinical outcomes and the current clinical evidence on ECLS modalities were included.

3. Review

3.1. Mechanism of ECLS

The overall concept of ECLS is similar to ECMO and renal dialysis, where the goal is to prolong patient survival (via mitigating acute sequelae such as multi-organ failure) in order to allow the native organ to recover.[3,4] ECLS involves removal of blood from the patient via a catheter which then passes through an external device where detoxification can occur before it is returned to the body.

The two main modalities of ECLS are divided into artificial (MARS, Prometheus, SPAD and HepaWash) and bio-artificial categories (HepatAssist and ELAD).[5–10]

3.1.1. Artificial systems

Artificial ECLS systems utilize a cell-free technique that aims to replace the detoxifying function of the liver with the idea that removal of toxins from the bloodstream will reverse the sequelae of liver failure.[11] There are multiple artificial systems with the most prominent being MARS, Prometheus and SPAD. All of these systems share a common mechanism which is to pass the patient's blood through a dialysis filter that passes by a current of exogenous albumin, thereby passing the toxins bound to patient plasma to the exogenous albumin current. This exogenous albumin is then recycled and detoxified via exposure to activated charcoal or an ion-exchange column which removes toxins bound to albumin within the system. SPAD is a system that utilizes albumin but does not recycle albumin. MARS is associated with improved outcomes in patients with grade 3 and 4 hepatic encephalopathy, improved short term transplant-free survival in patients with grade 2 and 3 liver failure[12] and improvements in bilirubin (total and direct), bile acids, ammonia, lactate, urea, creatinine levels and GCS scores. Prometheus system is associated with significant survival benefit at both 28 and 90 days among more severely ill patients (MELD score of >30).[13] HepaWash demonstrated a significant decrease in serum levels of both protein-bound and water-soluble toxins, serum bilirubin levels, serum creatinine and BUN after a single treatment, respectively.[14]

3.1.2. Bio-artificial systems

Bio-artificial liver (BAL) systems use living cells to detoxify blood via separating and running plasma through a hollow-fiber network lined with hepatocytes that are either porcine in origin (HepatAssist) or derived from human hepatoblastoma cell lines (C3A). Bio-artificial systems have less robust detoxifying capabilities when compared to artificial systems but the theoretical advantage they have over artificial systems is that they can simulate the synthetic functions of the liver. However, there are currently very few clinical trials to support their clinical utility. There are also many logistical challenges surrounding the design of bio-artificial systems. Current hollow-fiber bioreactors have shortcomings related to the delivery of blood and nutrients to the hepatocytes (convection transfer) as well as maintaining sufficient levels of viable hepatocytes to support homeostasis.[15] New studies involving cryogel-based scaffolding systems have

been shown to improve hepatocyte viability and perfusion of hepatocytes which can be a promising alternative that can improve the overall functionality of BAL devices.[16] Patients treated with ELAD had reported deteriorations in survival and MELD score.[10,17]

HepatAssist demonstrated high survival rate among patients as well as successful bridging to liver transplantation.[18]

3.2. Indications

The major indications for ECLS use include hemodynamic compromise, hepatic encephalopathy, cerebral edema, and renal dysfunction or development of hepatorenal syndrome that are refractory to medical therapy and in cases in which organ transplantation is not an immediately available option. ECLS may also be indicated in certain uncommon causes of liver failure, including cardiogenic shock, acute on chronic liver failure, post partial hepatectomy failure and post-transplant graft failure.[19–21]

3.3. Benefits

Since its inception, ECLS has shown significant improvements in objective biochemical parameters. Recent meta-analyses have shown that ECLS can consistently lead to improvements in serum bilirubin, bile acids and urea levels.[22] Although biochemical improvement can be a surrogate marker for improvement in prognosis, initial clinical trials did not show that these biochemical improvements translated to increased survival. However, more recent meta-analyses have showed that although there may be improvement in overall survival or at the very least, a survival benefit that can be demonstrated in select subtypes of liver failure.

Alshamsi et al. published a meta-analysis that included 25 randomized control trials that showed that various forms of ECLS produced significant improvements in mortality in both ALF and ACLF subgroups.[23] While a recent network meta-analysis by Kanjo et al. show that only plasma exchange therapy demonstrated a statistically significant improvement in 3-month mortality and all other forms of ECLS did not show statistically significant outcomes.[24]

3.4. Complications of ECLS

ECLS has been shown to be associated with multiple complications including hypotension, hemodynamic instability, anemia, thrombocytopenia, coagulopathy/bleeding, hypoxia, renal failure and sepsis.[9,25,26]

Thompson et al.[25] demonstrated that patients treated with ELAD had a higher rate of anemia, thrombocytopenia, coagulopathy and hypotension than in the control group (treated with medical therapy only).

4. Discussion

ECLS systems have been in development for decades due to the increasing demand for liver transplantation and the inability of the healthcare system to meet these demands. In 2013, over 1700 patients died while on the waiting list for a liver transplant, with an additional 1200 eventually being removed after being deemed ineligible for various reasons.[27] According to the OPTN/SRTR 2018 Annual Data Report, in 2018 the waiting list mortality was 13.2 per 100 waitlist-years, with rates higher for candidates listed with ALF.[28] Given the high rates of patient mortality while on transplant waiting lists, alternative treatment options for liver failure are highly sought after.

Thus far, ECLS has shown improvements in biochemical surrogate markers however definitive evidence to suggest that these changes translate into improved long-term survival does not exist yet, although recent meta-analyses show promise that there can be survival benefit in select subgroups of patients with liver failure. Alshamsi et al.[23] and Kanjo et al.[24] both performed a meta-analysis and network meta-analysis, respectively. Alshamsi et al. found that overall mortality was reduced when compared to standard medical therapy while Kanjo et al. found that only plasma exchange therapy demonstrated a reduction in 3-month mortality while all other modalities did not reach statistically significant changes.[23,24] Although both analyses covered a number of prior RCTs (Alshamsi et al. covered 25 while Kanjo et al. covered 16), there are still several RCTs that were not included in either study which could possibly have led to different results.[23,24] The Alshamsi and Kanjo meta-analyses excluded several RCTs that may possibly change the outcome or provide more perspective in regard to ECLS benefits and clinical efficacy. Specifically, length of stay, quality of life and analysis of biochemical markers such as platelet counts, INR, bilirubin, cytokines, or albumin binding capacity which are discussed in the excluded RCTs (Supplementary Table 1) may have been relevant outcomes that were excluded.

We emphasize that more research is still needed especially for specific populations; however, the inclusion of these studies and outcomes in future meta-analyses may provide more clear effect of the clinical outcomes of ECLS alongside mortality. The studies that were not covered in either analysis are described in Supplementary Table 1.[29−37]

The main barriers to expanded use of ECLS are the current lack of definitive evidence along with high cost, issues with design relating to current hollow-fiber bioreactor models and the small pool of liver transplant candidates that would be eligible for its use. ECLS is also a high resource utilizing therapy that requires multiple disciplines including gastroenterology and hepatology, intensive care and transfusion medicine specialists that are often only available at a large academic medical center.

Despite these barriers, some advancement in the field could help to move ECLS towards more widespread use. Research has been conducted on Cryogel scaffolding systems that can improve upon the perfusion and viability issues that current hollow-fiber systems have.[16] Although this new system would then need to be studied in the clinical setting before being considered for clinical use. In regards to the use of ECLS to bridge patients to liver transplant, it is possible that the use of ECLS can be available to more patients if the pool of liver transplant candidates expands. One such scenario could occur based on a recent study that found that liver transplantation in patients with more than 6 months of abstinence from alcohol (currently a major criteria for liver transplantation) had similar overall survival, allograft survival and relapse-free survival compared to patients that were abstinent for less than 6 months.

Future steps that would help to expand the usage of ECLS would include clinical trials that directly compare modalities of ECLS against renal replacement therapy which is currently used more frequently in patients with liver failure.

5. Conclusion

ECLS is a very promising solution in reducing mortality and maintaining function in patients with liver failure who are potential transplant candidates at the risk of few side effects, particularly hemodynamic instability and hematological problems. However, the modalities under ECLS require large sums of investment to accommodate for the specific system requirements that reduces cost-effectiveness given the small population being targeted. Further large scale studies should target these requirements so that these barriers to mainstream implementation can be overcome.

Funding sources

None.

Author contributions

Conception and design: A.S., A.N., **Literature Review**: A.S., A.N., M.R., S.M., R.M., **Writing-first draft:** A.N., S.M., H.H., **Supervision, resources and final editing:** A.S., **Tabulation and figures**: N.J., R.M., H.H. All authors have contributed in manuscript writing and have provided final approval for the manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgements

None.

Appendix A.

Supplementary Table 1:. Findings of studies reviewed from other meta-analyses

Authors	Year	Patient population	Type of Intervention	Outcomes
Kramer et al.[29]	2000	20 patients with cirrhosis who developed HE (ACLF); median age: 56 years, range: 33–71 years, 13 men	BioLogic-DT (n = 10)	• Decreased platelet count (from 75 to 26 g/L; p = 0.01) and fibrinogen (from 185 to 106 mg/dL; p < 0.001) level • Increased INR (from 2.0 to 2.2; p < 0.001) • Decreased creatinine (from 1.0 to 0.9; p = 0.007) and BUN (from 28 to 25; p = 0.01) • No change in albumin, bilirubin, AST, ALT or ammonia
Kramer et al.[30]	2002	8 cirrhotic patients with hepatorenal syndrome; etiologies: -alcoholic (6) -Hepatitis C (1) -Cryptogenic (1)	Prometheus (n = 8)	• Significant decreases in bilirubin (p = 0.002), BUN (p = 0.02) and creatinine (p < 0.001) from baseline • No incidences of bleeding or hemodynamic instability observed
Stadlbauer et al.[31]	2006	8 patients with ACLF: -alcoholic cirrhosis (4) -Chronic HCV (1) - Metastatic colon cancer (1) - Liver graft dysfunction (1)	MARS and Prometheus, cross-over (n = 8)	• No significant changes in serum levels of any cytokine were found after treatments with MARS or Prometheus • In MARS treatments, IL-10 was cleared from plasma more efficiently than IL-6 • Clearance of IL-10 was higher in Prometheus than in MARS treatments.
Stadlbauer et al.[32]	2007	8 patients with ACLF: -alcoholic cirrhosis (4) -Chronic HCV (1) - Metastatic colon cancer (1) - Liver graft dysfunction (1)	MARS and Prometheus, cross-over (n = 8)	• Total and individual bile acids were removed efficiently by both systems • With both devices, absolute reduction of chenodeoxycholic acid (CDCA) was higher than that of cholic acid (CA) • Reduction ratios were significantly higher for CA than for CDCA in Prometheus, no difference with MARS
Klammt et al.[33]	2008	24 patients with ACLF	MARS (n = 12)	• Improvement of albumin binding capacity was more frequent in the albumin dialysis group than in the control group
Dethloff et al.[34]	2008	24 patients under evaluation for liver transplant: -Alcoholic cirrhosis (15) -Hepatitis C (2) -Autoimmune (2) -PBC, porthyria, cholesterol storage disorder, hemochromartosis, unknown (1 each)	Prometheus (n = 8) MARS (n = 8) Hemodialysis (control, n = 8)	• Increase in arterial pressure in the MARS group ($P = 0.008$) • Significant decrease in creatinine levels in the MARS ($P = 0.03$) and hemodialysis ($P = 0.04$)groups • Decreased platelet count in the Prometheus group ($P = 0.04$)
Iarustovski et al.[35]	2014	26 patients with ALF and MODS as postoperative complications after cardiac surgery	MARS (n = 9) Prometheus (n = 17)	• Decreased in serum total bilirubin (8.6% in MARS-group (p = 0.028) and 33% in Prometheus-group (p < 0.001)) • Decreased unconjugated bilirubin levels (29% in Prometheus-group (p = 0.003))
Klammt et al.[36]	2014	24 patients with a decompensation of a pre-existing cirrhosis (ACLF) with severe hyperbilirubinemia (total serum bilirubin >20 mg/dL)	MARS (n = 12)	• 11 out of 12 patients (91.7%) in the MARS group survived the study period; 6/12 patients (50%) in the control group died • No relationship was found between the decline of platelet count and the number of consecutive treatments
Sponholz et al.[37]	2016	32 patients with ALF, ACLF and graft failure	MARS and SPAD	• Plasma bilirubin levels were significantly reduced by both systems (MARS: median −68 μmol/L, $p = 0.001$; SPAD: −59 μmol/L, $p = 0.001$) • Only MARS significantly reduced bile salts (−39 μmol/L, $p < 0.001$), creatinine (−24 μmol/L, $p < 0.001$) and urea (−0.9 mmol/L, p = 0.024) • Albumin-binding capacity was increased by MARS (+10%, $p < 0.001$)

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