CHALLENGES IN THE USE OF EXTRACORPORAL LIVERS TECHNOLOGIES

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Abstract

The human liver is a necessary organ in metabolism but when its working is harmed, can cause liver failure in varying degrees and raise the mortality rate. The only existing treatment for the disease so far is liver transplantation. Therefore, the objective of this research was to a evaluate the challenges of the artificial technologies of liver support (ATL) developed in the last nine years existing in the world. The technologies evaluated were those that consider the patient's need have a survival while waiting of the transplant or confirm that will not need the donated liver. This research is of type descriptive and bibliographical and was based on scientific articles published in the following databases: National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO), Academic Google, Latin American and Caribean Literature in Health Sciences (LACLHS), Virtual Health Library (VHL) and Capes Journal (Brazil). In the studies found, was verified that extracorporeal liver support technologies of the bioartificial type and artificial liver do not guarantee sufficient patient survival. Although this technologies have some clinical benefit with their use, is possible that the recipient patients suffer from metabolic intoxication. So that technologies can produce survival expected in patients, should be considered three pillars: the disease, the technology used and the dose of therapy. This research is important because it will help in the development of new methodologies better suited to recipientes.

Keywords: human liver, liver transplantation, extracorporeal liver support, survival.

1. Introduction

The liver is the largest gland in the human body and the main organ for metabolism of proteins, carbohydrates and lipids, albumin synthesis and blood clotting factors, detoxification, excretion of bile and metabolization of various drugs (HEYDARI *et al.*, 2019; YAO *et al.*, 2021).

In your anatomical division it has four lobes being them: right, left, tail and square. On a histolgical level, the lobe represents the functional unit of the liver and the biliary tract, the network of localized ducts inside and outside the liver. Microscopically, lobes are composed of two types of cells, epithelial cells, hepatocytes and bile cells or cholangiocytes that under conditions homeostatics, both the liver and how bile tissues are maintained by proliferation of existing hepatocytes and cholangiocytes (PASQUA *et al.*, 2021).

When arise some diseases, such as hepatic cirrhosis and hepatocellular carcinoma, the functioning of the liver gets harmed, may cause liver failure in degrees varied, being responsible for a number high number of adult deaths in the world (KHAJAVI, et al., 2021; ROSSI et al., 2021). Is estimated that the liveres diseases in terminal stage, cause approximately 2 million deaths around the world every year (HEMMANN *et al.*, 2007).

According to the World Health Organization, liver disease represents the 12th cause of death in the world, with progressive elevation in your prevalence and incidence, being that when developing acute liver failure, there is high mortality, with a survival rate of less than 70%. The only existing treatment for the disease, so far, in your final stage, is the liver transplant (HEYDARI *et al.*, 2019; WENG *et al*., 2021). However, the waiting list of patients that await a new liver is very big, being that many times these patients can't resist waiting, culminating in death. This fact demonstrates the need of developing new ways and new treatment methods to face these diseases (ROSSI *et al*., 2021).

How demand for human organs has grown around the world, there are a serious shortage of donors, making resource development necessary substitutes for these organs (DA-HYUN et al., 2021). This stimulated the development of a technique revolutionary in Bioengineering as solution to tissues and organs damage (GEETHA *et al.*, 2019). Tissue Engineering, Bioengineering and Hepatic Regenerative Medicine are integrated to be able to develop models with the phenotype and functionality of the human liver, apply extracorporeal liver support therapies seeking to reduce the difficulties in treatment of the patients (KIM *et al*., 2021; WIESMANN *et a*l., 2019).

Recellularization of the human liver with a cells line of human hepatocytes represents an advance fundamental in the development of Regenerative Medicine to benefit the transplant and also the application of extracorporeal device (AL-AKKAD *et al.* 2016).

Therapies for extracorporeal liver support (ELS) are options to promote recovery, reduce the effects of liver failure or allow transplant in patients with acute liver dysfunction as for example: acute liver failure (ALF), chronic liver failure acute (AoCLF) or chronic liver disease unbalanced (decomp. CLD) (WIESMANN *et al*., 2019).

Considering the content presented above, the purpose of this research was to assess the challenges of the use of extracorporeal liver technologies developed so that patients survive until transplantation occurs of liver or confirm that you do not need the transplant.

2. Methodology

This research is of type descriptive and bibliographical, because he tried to develop studies on existing extracorporeal liver technologies existing in which they were specified when to use each of them. The research was carried out through of the collect of data from scientific articles recently published in open access databases.

Then, was used up the search mecanism through the descriptors with the boolean operator “e” or “and” and was searched the terms “bioengineering engineering” , "transplante" and extracorporeal liver.

For inclusion purposes, scientific articles were considered written in Portuguese and in other languages, published between the years 2012 to 2021. The databases for consultation were as follows: National Library of Medicine (PubMed), ScientificElectronic Library Online (SciELO), Academic Google, Literatura Latino-Americana and from the Caribbean in Health Sciences (LILACS), Virtual Health Library (VHL) and Capes Periodical

As standard procedure for selection of related content were read the abstracts of the articles and, if they weren't within the goal from the research, they were excluded.

3. Literature review

Liver failure, be it acute or acute chronic, is a metabolic event life-threatening that impairs the performance of of most other organs, rapidly leading to dysfunction multiple organs and consequently to death becoming a clinically relevant question (STRUECKER *et al*., 2013). Mortality is very high because the available therapy at present it is liver transplantation being that in approximately one third of patients, a liver will not be available or others contraindications prevent the performance of the transplant (WIESMANN *et al*., 2019). Bioengineering emerged as a promising alternative for treatment of some diseases and, in the case of specifically from the liver, came to overcome the existing challenges, especially in the regarding the shortage of organs for transplantation and minimizing rejection often suffered (WENG *et al*.,2021).

Some extracorporeal therapies applied in case of organ failure, for example, dialysis for kidney failure, oxygenation by extracorporeal membrane (ECMO) for the severe pulmonary and/or heart failure are already well established. The causes of rapid clinical deterioration is due to the accumulation of endogenous toxins, mainly in chronic liver failure sharp, and the ELS device is an option invasive in an attempt to mitigate the effects of liver failure, through mechanisms of detoxification, synthesis, excretion, metabolic aspects and other regulatory functions of the liver (WIESMANN *et al*., 2019).

There are currently two types of extracorporeal/artificial liver support therapies (WIESMANN *et al*., 2019):

Bioartificial liver type (bioreactor): uses live cells, with the principle of detoxification and metabolic stabilization, but that so far only they are available in clinical trials (WIESMANN *et al*., 2019);

- Type artificial/extracorporeal liver support: for the purpose of purification/ detoxification of the blood, using a system of molecular adsorbent recirculation (MARS®, Gambro, Lund, Sweden); separation system of fractionated plasma, adsorption and dialysis technology of the Prometheus® system - FSPA (Fresenius Medical Care, BadHomburg, Germany; single-pass albumin dialysis - SPAD, HepaWash® procedure (HepaWashGmbH, Munich, Germany); and the therapy selective plasma exchange (SEPET ™, ArbiosSystems, Allendale, NJ, EUA) (STRUECKER *et al*., 2013; WIESMANN *et al*., 2019).

However, it is noteworthy that the support of artificial liver does not guarantee the necessary survival of patients, as is possible that they suffer from metabolic poisoning, demonstrating the need for extracorporeal to be accompanied by other resources, such as the bioartificial liver (WENG *et al*., 2021).

In addition to these mentioned devices, also there is the possibility of using stem cells for treatment, as these can offer a better understanding of biological mechanisms in development and of underlying diseases, favoring rapid screening for possible drugs, using hepatocytes and cholangiocytes for its treatment (PASQUA *et al*., 2021).

3.1 Extracorporeal artificial liver support (ELS) device

3.1.1 Prometheus System

The Prometheus system (Fresenius Medical Care, BadHomburg, Germany) based on the separation method and fractionated plasma adsorption (FPSA), allows the removal of a range of toxins linked to albumin and water solubles that have greater efficacy than any other device of detoxification in the context of liver failure. This system is also applied in the treatment of itching refractory cholestatic, Wilson's disease and liver poisoning (KRIBBEN *et al.*, 2012; STRUECKER *et al*., 2013).

3.1.2 Molecular Adsorbent Recirculation System

The Molecular Adsorbent Recirculation System (MARS®; Gambro, Stockholm, Sweden) uses a hollow fiber high flow with hemodiafilter and albumin as a molecule receptor of toxins, being that this solution of recirculating albumin is partially regenerated by passing by an anion exchanger and an adsorbent charcoal, allowing a purification process of these toxins (KATAREY and JAVAN, 2020; STRUECKER *et al*., 2013).

3.1.3 Single-pass albumin dialysis

Single-pass albumin dialysis is a simple variation of albumin dialysis using therapy machines of standard renal replacement. Similar to MARS® however, the albumin solution is discarded after passing through the filter (STRUECKER *et al*., 2013).

3.1.4 HepaWash® Procedure

The HepaWash® procedure (HepaWashGmbH, Munich, Germany) is another variation of albumin dialysis that, instead of regenerating albumin with adsorbents, uses of changes in pH and temperature for albumin to be regenerated (STRUECKER *et al*., 2013).

3.1.5 Selective plasma exchange therapy

Selective plasma exchange therapy (SEPET™, Arbios Systems, Allendale, NJ, USA) combines aspects of fractionated plasma separation, adsorption and dialysis of single-pass albumin, where the plasma

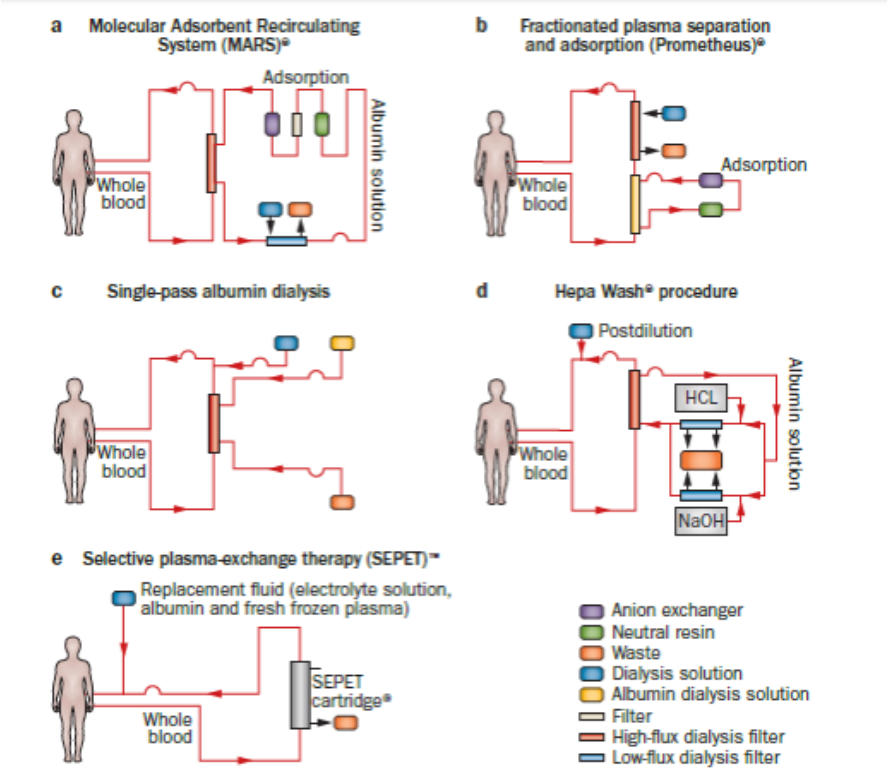
fraction passes through a selective membrane of permeable size to albumin, removing heavy substances molecular weight less than 100 kDa, such as toxins, no change in immunoglobulins, proteins and blood coagulation factors (STRUECKER et al., 2013).

The BioLogic-DT (Later LiverDilysis System™ [HemoCleanse, Lafayette, IN, USA]), based in a cellulosic dialyzer plate with suspension of powdered charcoal and cation exchangers as dialyzers, are no longer marketed (STRUECKER *et al*., 2013).

In Figure 1, the available extracorporeal artificial liver support devices are systematized.

Figure 1

Artificial life support system.



Fonte: STRUECKER *et al.*, 2013.

4. Results and Discussion

Table 1 shows the most studied artificial ELS devices which are based on the principles of albumin dialysis, plasma exchange, and the extracorporeal liver assist device (ELAD) (KATAREY and JAVAN, 2020). It was found that ELS devices had only benefits marginal in large clinical trials. these devices provided the necessary springboards to understand better the three fundamental pillars of successful ELS: type of disease, device and dose of therapy whose objective is to improve patient survival until transplantation. In mechanisms based on albumin dialysis and from selective plasma exchange therapy, there was no difference significantly in survival rates when compared to conventional methods of treatment.

Table 1

Currently available extracorporeal liver support devices and the most prominent multicenter randomized controlled trials in which they have been evaluated.

Membrane	Mecanism	Name	Multicenter RCT	Tipeo of patient	Numbers of patients	Rate of survival
Artificial	Albumin-based	MARS®	Fulmar (2013)	ALF	Total = 110 MARS = 57 SMT =53	6-Month survival 75.5% vs. 82.9%, P= 0.50
			Relief (2013)	ACFL	Total = 189 MARS = 95 SMT= 94	28-Day survival 60.7 vs. 58.9%, P =0.79
		Prometheus	Helios (2012)	ACFL	Total = 145 Prometheus = 77 MT=68	28-Day survival 66 vs. 63%, P = 0.70
	HVP	-	Larsenet al. (2016)	ALF	Total = 183 HVP =92 SMT = 91	Survivalto hospital dischargehigherwith HVP (58.7 vs. 47.8%, HR 0.56, 95% CI 0.36–0.86, P= 0.0083)

Fonte: Katarey; Jalan (2020).

In a study carried out on a 26-year-old man, with drug-induced liver damage was submitted to MARS® for four days and at therapy follow-up,
he managed to reduce the total bilirubin from 36 mg/dl to 3.3 mg/dl. Concluding the effectiveness of MARS in this type of severe liver disease (EAPE *et a*l. 2018).

A study of the use of ELS, in Germany, mortality rates were high being caused by acute liver dysfunction, in combination with cardiac surgery (68.39%) being
that ELS was rarely used in the transplant context of liver. In 2015 in Germany, more than 50% of all ELS cases were performed in the context of cardiac surgery. Use of ELS and liver related to cases of transplant rates were low (12.47%) while the use of ELS in cases of dysfunction primary liver had a mortality rate of 40.63%.

Kwon *et al*. (2020) observed a case of ELS, with recirculation of adsorbent molecular, which treated hyperammonemia after performing lung transplantation. It was the report of a 63 years old woman, no previous liver disease reported and without the use of alcoholic beverages. The patient was diagnosed with hyperammonemia and his treatment had no effect. However, after ELS, their ammonia levels have dramatically decreased and 24 days after the transplant, she was discharged from the hospital.

Therefore, can be verified that the treatments related to the use of ELS systems are increasingly being used and with better results, when well indicated, starting with the selection of eligible patients,

choice of methods and application of the intensity suitable for each situation. The results obtained have been positive in the case of liver diseases terminals, in reducing levels of toxic metabolites like ammonia and bilirubin in addition to symptomatic improvement, as for example, in hepatic encephalopathy. However, still without significant outcomes in the survival of these patients, thus demonstrate the need for an association with other support methods. Such reported failures are due to the lack of hepatocytes capable of addressing more sophisticated metabolic pathways, as is being studied in the bioartificial support of the liver, still with scant results due to the lack of safe sources of metabolically active human cells.

5. Conclusion

Although liver transplantation is the gold standard in therapy for end-stage liver disease, is known that there is a shortage of organs, and that, added to the contraindications, cause mortality provocada pela insuficiência hepática um problema de saúde pública mundial. This situation favored the emergence of studies on artificial extracorporeal liver support devices.

It was found that extracorporeal liver support devices do not guarantee the survival benefit because, despite generating some clinical benefit, patients may suffer from metabolic intoxication. However, evidence published recently suggested ways in which the three pillars main aspects of ELS: the disease (patient selection), device (ELS system) and the dose (intensity) can achieve a positive result in the treatment of this population in question.

Therefore, extracorporeal liver support devices showed no significant benefit in reducing mortality of patients when compared to standard therapies already existing, demonstrating the need for support extracorporeal be accompanied by other resources, like the bioartificial liver that still has limited applicability in clinical practice.

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