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Albumin dialysis with molecular adsorbent recirculating system (MARS) for the treatment of hepatic encephalopathy in liver failure

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ABSTRACT

Acute, acute-on-chronic and chronic liver diseases are major health issues worldwide, and most cases end with the need for liver transplantation. Up to 90% of the patients die waiting for an organ to be transplanted. Hepatic encephalopathy is a common neuropsychiatric syndrome that usually accompanies liver failure and impacts greatly on the quality of life. The molecular adsorbent recirculating system (MARS) is a recently developed form of artificial liver support that functions on a base of albumin dialysis. It facilitates the dialysis of albumin-bound and water-soluble toxins, allowing the patient to survive and even improving some clinical features of liver failure. The following manuscript reviews the technical features of MARS operation and some of the clinical trials that analyze the efficacy of the system in the therapy of liver diseases.

Key words. Molecular adsorbent recirculating system. Hepatic encephalopathy. Acute liver failure. Acute-on-chronic liver failure.

INTRODUCTION

Acute liver failure (ALF) and acute-on-chronic liver failure (AoCLF) can cause death in up to 90% of patients and, within the survivors, a decrease in 5-year life expectancy of 50% after each event in a cirrhotic patient.[1] This is assumed to be secondary to the accumulation of toxins, the massive inflammatory process that arises from the necrotic liver[2] and the coagulation and hemodynamic alterations that will eventually lead to lethal complications including hepatorenal syndrome, hepatic encephalopathy (HE), brain edema, severe hypotension, bleeding and opportunistic infections.

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Until recent years, the treatment of ALF was based on treating the etiology, monitoring, supportive therapy and orthotopic liver transplantation. However, not all patients are candidates for transplantation, and even within the appropriate population, up to 70% of the patients die waiting for a donor.[3,4] Thus, several extracorporeal liver support methods have been studied to find an equivalent to hemodialysis, which can act as a bridge until transplantation or as a temporary support for the failing organ until it is able to recover by itself. This would lead to a decrease in morbidity, mortality and the costs related to ALF.[5]

Given the unique functions that the liver performs, the roles that artificial liver support devices must perform are: removal of toxins (such as ammonia and aromatic amino acids), synthesis of plasma proteins (including coagulation factors and albumin)[2] and the reversal of the massive inflammatory process that results from the cytokines and mediators produced by the necrotic liver.

At present, the known liver support systems can be classified into bioartificial (those involving living hepatocytes) and noncellular or artificial systems. The latter have included plasmapheresis, hemodialysis, hemofiltration and hemoperfusion. The most recently developed systems use hemodiabsorption (hemodialysis in combination with adsorption using charcoal or albumin) such as the molecular adsorbent recirculating system,[6,7] the subject of our review.

MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS)

MARS, also known as albumin extracorporeal dialysis, was used for the first time in 1993. Nowadays, it consists of elements for extracorporeal renal replacement techniques as well as adsorption. To do this, it contains a three-circuit system: one in direct contact with the blood of the patient, one embedded in albumin solution and the last encompassing hemodialysis and hemofiltration functions (replacing renal function).[8] It therefore requires a standard dialysis machine to control the dialysate circuit, and an extra device (monitor) to control and monitor the closed-loop albumin circuit.

The physiological basis on which MARS was developed is that as a result of liver damage, many of the liver-dependent processes (such as the urea cycle and the metabolism of protein) are impaired in ALF or AoCLF. Because many of the toxic products that accumulate in the body (most of them bound to albumin in the plasma) have been associated with the development of end-organ dysfunction,[9] selective removal of such substances from the blood should lead to redistribution of their metabolites. This in turn should prevent their toxic effects and, therefore, improve the clinical outcome of patients.[10]

MECHANISM OF ACTION

The mechanism of MARS was developed in order to support the detoxification function of the liver without influencing its metabolic or synthetic functions. Therefore, the operation of this system is divided into two steps.

- ***First step.*** Using heparin as an anticoagulant for the entire system, the blood obtained from a venous access is dialyzed through an albumin-impermeable membrane at a flow rate of 150-250 mL/min. The albumin circuit contains an albumin solution at 20-25% in a closed circuit where a steady volume of the solution is being recirculated.[11,12]

Albumin-ligated toxins are recruited by a concentration gradient. The membrane is impermeable to substances with a molecular weight over 50 kDa; therefore, albumin, α-1 glycoprotein, α-1 antitrypsin, α-2 macroglobulin, transferrin and hormone transporter proteins circulate back to the patient.[13]

- ***Second step.*** The ultrafiltrate obtained passes through the hemodialysis circuit, where all the water-soluble toxins are removed, then returns to the bloodstream of the patient. The dialysate passes through the third compartment containing a bicarbonate-buffered dialysate, after which the flow continues to two sequential columns: the first containing uncoated charcoal and the second containing an anion exchange resin.[10]

Thanks to the characteristics of the system, MARS therapy can extract at least two groups of compounds: albumin-bound and water-soluble substances. The efficiency of the system to depurate indirect bilirubin, fatty acids, aromatic compounds and drugs with high affinity for albumin (teophilin) or proteins (phenol) has been corroborated in several *in vitro*, animal and clinical studies.[13] Figure 1 shows a schematic of the functioning of the system, and table 1 summarizes the elements dialyzed with MARS.

Knowing the mechanism of function of this therapy is important for knowing when its use is appropriate. Saliba, *et al.* proposed some indications for the use of MARS therapy that are summarized in table 2.[14]

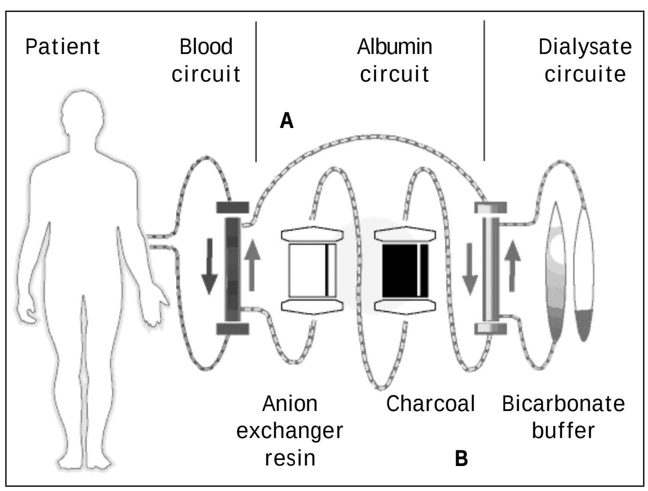

Figure 1. *Schematic of the functional mechanism of MARS.* ***A.*** *Dialysis of albumin-bond toxins.* ***B.*** *Dialysis of water-soluble toxins.*

Table 1. Elements dialyzed with the MARS therapy organized according to affinity.

Water-soluble	Albumin-bound
• Ammonia • Urea • Creatinine	• Bilirubin (indirect, principally) • Bile acids • Tryptophan • Fatty acids (middle- and short-chained) • TNF-a, IL-6 • Copper • Benzodiazepines (diazepam, principally)

Table 2. Suggested indications for MARS therapy.[10]

Indications

1. Acute Liver Failure.
2. Acute Decompensation on Chronic Liver Disease.
   a) Complicated by progressive jaundice.
   b) Complicated by hepatic encephalopathy.
   c) Complicated by renal dysfunction.
3. Intractable Pruritus in Cholestasis.
4. Acute Intoxication or Overdose with Albumin-bound Substances.
5. Other indications:
   a) Acute hepatic failure after major hepatectomy.
   b) After liver transplantation.
      - Primary non-function or primary dysfunction of the graft.
      - Acute decompensation of the graft.
      - Secondary liver failure or multi-organ failure.

Table 3. Grades of hepatic encephalopathy.

HE grade	Clinical assessment
I	Sleep disorders Tremor
II	Lethargy Loss of time Slurred speech Hyperactive reflexes Inappropriate behavior
III	Somnolence Confusion Disorientation Bizarre behavior (anger/rage) Clonus/Rigidity/Nystagmus/Babinsky
IV	No eyes open No motor response No verbal response

CLINICAL EVALUATION OF MARS

Sen, *et al.* [15,16,17] performed several studies analyzing the efficacy of MARS, finding interesting results related to a greater depuration of midazolam and fentanyl. They also concluded that the observed reduction in ammonia levels after MARS therapy was correlated with intracranial pressure and augmentation of the brain perfusion pressure, while reduction in plasma nitric oxide was correlated with an improvement in hemodynamic stability.

There have also been some studies that compared medical therapy with liver support (MARS). Laleman, *et al.*[18] performed one of these studies and found that in patients with AoCLF, MARS produced a better outcome than medical therapy for hemodynamic variables such as mean arterial pressure, heartbeat volume and peripheral vascular resistance. Donati, *et al.*,[19] also demonstrated that this mode of therapy was beneficial for cirrhotic patients without a transjugular intrahepatic portosystemic shunt, in whom a reduction in the resistance of splenic and renal blood flow and an increase in portal blood flow, peripheral vascular resistance and mean arterial pressure were seen. Improvement of other biochemical and clinical features such as hyperbilirubinemia, secondary pruritus[20] and HE,[21] and of circulatory and renal function in patients with ALF[22] has also been demonstrated.

Even in cases with ALF and positive criteria for transplant,[23] MARS therapy was satisfactorily tolerated, and it resulted in a significant improvement in encephalopathy levels, conjugated bilirubin and international normalized ratio, with the most common complications being post therapy hypotension (10%), which was reversible with volume expanders, and thrombocytopenia (6%). Both complications are considered among the most common associated with this form of therapy. The study also reported early coagulation of MARS and technical difficulties in 4% of cases.

Wagholikar, *et al.*,[24] also analyzed the efficacy of MARS therapy in patients with chronic liver disease waiting for transplant, and they concluded that it is quite successful as a bridge to the surgical event, diminishing levels of urea, creatinine, bilirubin and ammonia. They have also proposed that the hemodynamic improvement together with the decrease in cholestatic and serum toxin levels allowed graft regeneration to be accelerated, improving at the same time the prognosis of transplanted patients. The latter finding was supported by a prospective pilot study coordinated by Choi, *et al.*,[25] that included 10 patients with liver failure: 5 received only MARS therapy, and 2 received only transplant, while the other 3 received both MARS and transplant. The first 7 patients who received MARS only or transplant only unfortunately died within the first 2 weeks of the study, while the other 3 that received both therapies, survived that period. Nevertheless, it is also important to mention that studies performed in critically ill patients with an advanced malignancy have shown that although MARS therapy is well tolerated, it has no significant impact on the mortality of the patients.[26]

In regard to mortality analysis, Kjaergard, *et al.*[27] performed a systematic review of the artificial and bioartificial support systems, and found that mortality was significantly different between the use of any of these systems and medical therapy in cases of AoCLF, but they could not find a significant difference in ALF.

Lemoine, *et al.*[28] reported a case in which they treated a pregnant woman with intractable pruritus in whom deoxycholic acid was contraindicated because of its teratogenic properties. They found a satisfactory improvement in clinical features. Wu and Wang also reported a case of Amanita poisoning during pregnancy that was treated with this form of therapy with encouraging results. Both of these groups of investigators concluded that MARS is safe in the pregnant population.[29]

MARS therapy has shown questionable results with respect to its effects on inflammatory mediators. Some studies have found that a reduction in proinflammatory cytokines such as interleukin (IL)-8 and IL-6 after the therapy is beneficial for the clinical progress of patients. However, it is known that the half-life of cytokines is short and their production is rapid; therefore, this clinical improvement could be secondary to a lower rate of production of the cytokines rather than a direct response to MARS.[30] Nevertheless, the clinical improvement in the patients is unquestionable.

Regarding the cost efficacy of the treatment, a study was performed comparing the worsening of encephalopathy and liver function together with the intrahospital mortality of 12 patients with cirrhosis and liver injury treated with MARS, and 11 patients with similar conditions treated with medical therapy. Six patients of the control group but only 1 of the MARS group died while hospitalized. The study also found that liver-kidney syndrome, encephalopathy, severe hypotension and hydroelectrolytic disorders were more frequent in the control group than in the group treated with the liver support therapy. Although each session of MARS cost 2,500 dollars, the cost calculated per survivor was 4,000 dollars less than for the control group. Therefore, it was concluded that the therapy had a better cost efficacy.[31] Kantola, *et al.*,[32] also found that the cost effectiveness was greater with MARS, although the-

Table 4. Comparison of the standard medical therapy versus MARS therapy.

	SMT				MARS therapy			
Test	Baseline	EOS	p	% Change	Baseline	EOS	p	% Change
Creatinine (mg/dL)	1.7 (0.6-5)	1.4 (0.4-5.7)	0.09	-13 (-77~67)	1.7 (0.4-4.5)	1.4 (0.4-4.5)	0.001	-18 (-68~133)
BUN (mg/dL)	42.5 (2-136)	48 (3-147)	0.97	-1 (-68~229)	40 (6-171)	20 (4-84)	0.0001	-38 (-88~217)
Bilirubin (mg/dL)	12.2 (2.3-58.9)	12.8 (3-57.4)	0.13	10 (-79~91)	15.8 (1.8-54.5)	16.1 (3-38.5)	0.064	-7 (-60~352)
Bile acids (umol/L)	65.4 (12.2-247.1)	54.5 (2-230)	0.008	-30 (85~9)	65.2 (38.1-249)	61 (11-207)	0.003	-35 (-79~51)
BCAA/AAA	1.17 (0.6-2.5)	1.04 (0.35-5.5)	0.20	10 (52~378)	0.96 (0.49-2.98)	1.44 (0.57-3.37)	0.031	26 (-30~271)
Ammonia (umol/L)	90.5 (34-786)	63 (32-308)	0.30	-24 (-74~106)	104 (43-449)	60.5 (22-182)	0.001	-35 (-84~30)

Biochemical parameters of standard medical treatment compared with those after MARS therapy. **SMT:** Standard medical treatment. **MARS:** Molecular adsorbents recirculating system. **EOS:** End of study. **BCAA/AAA:** Ratio of branched chain/aromatic amino acids.[34]

re were technical issues to analyze before making definite conclusions. Nevertheless, because very few studies analyzing this system have been performed, it is important to note that most come to the same conclusion.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities that can be seen in patients with liver dysfunction after excluding other anatomic and metabolic disturbances that may present in acute, acute-on-chronic or chronic diseases. The condition is reversible and is typified by global depression of central nervous system function. Even though the pathogenesis of HE is not completely understood, it was previously believed that intracranial hypertension because of cerebral edema caused by ALF was the direct cause of HE. However, recent studies have given rise to the current hypothesis that ammonia is central to the physiopathology, although there may be other substances involved.[33]

The clinical features of HE range from neuropsychiatric and motor disturbances that encompass short-term memory impairment, slowing of reaction time, poor concentration, psychomotor retardation and sensory dysfunction through to more clinically apparent neurological signs that can extend to confusion, stupor and coma.[34] The West Haven Criteria allow the stratification of HE into different grades (1-4) according to the clinical features (Table 3). It should be mentioned that there is also another classification based on the etiology:

- Type A for ALF.
- Type B for HE related to a portal-systemic shunt (bypass).
- Type C for an etiology that is related to cirrhosis or as a chronic manifestation.[35]

Some studies have attempted to analyze the impact of MARS therapy in patients with HE. As mentioned above, Heeman, *et al.* found that it does improve the clinical features of the syndrome. Schmidt, *et al.,* also performed a study analyzing the use of the system in patients with chronic liver disease (8 patients, all of them Child-Pugh grade C). They found that in 3 of the patients, the encephalopathy was alleviated, although statistical significance was not reached. Nevertheless, the mean arterial pressure was increased and the levels of ammonia, bilirubin, creatinine and urea were decreased after the therapy, allowing a better cerebral blood flow as measured by transcranial Doppler; all of these differences did reached statistical significance.[36]

An improvement in the clinical features after MARS therapy has been reported even in patients with AoCLF of alcoholic etiology. A study performed by Mora, *et al.* found that the therapy decreased the albumin-bound toxins and improved kidney function. The authors also mentioned that the encephalopathy that was present in the reported case disappeared completely after three sessions of MARS.[37] This and other trials emphasize the beneficial impact of the therapy in HE. As an example, table 4 shows the results obtained by Hassanein, *et al.,* in a group of 70 cirrhotic patients with HE grade 3 or 4 who were treated with either standard medical treatment or MARS, in which a significant improvement was found in the second group compared with the first.[38]

CONCLUSIONS

Several studies have been performed showing that MARS therapy is well tolerated and reduces the blood concentrations of diverse toxins, although more studies are needed before the efficacy of the therapy is confirmed. A study performed by our group in 2004 reported three patients who were treated with MARS, finding that although the two most severe cases (one with severe chronic liver failure secondary to hepatitis B virus infection and the other with ALF due to an advanced bladder malignancy) did not survive, a notable recovery in the clinical and biochemical values was observed in all patients.[39]

Although a specific conclusion has not yet been reached with respect to MARS therapy, it seems to be a very good option for the purpose for which it was created: to provide some time to allow patients to reach transplantation or to allow the liver to regenerate and recover its functions in ALF and AoCLF, and to improve the clinical features of HE.

ABBREVIATIONS

- **MARS:** Molecular adsorbent recirculating system.
- **ALF:** Acute liver failure.
- **AoCLF:** Acute-on-chronic liver failure.
- **HE:** Hepatic encephalopathy.

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