after 24 hours of MARS therapy. In both cases, liver function improved after some days of MARS therapy, and patients recovered with no need for liver transplantation. It should be highlighted that in reported series of patients with acute acetaminophen toxicity, individuals with acidosis, coagulopathy (INR > 7), and liver encephalopathy have a mortality rate of 80-90% in the absence of liver transplantation, and above 50% even in the presence of said transplantation (54).

Anecdotal cases of MARS therapy have also been reported in patients with acute-onset Budd-Chiari syndrome (34), amyloidosis (familial Mediterranean fever, with a positive outcome after 2 therapy sessions) (24), and mushroom poisoning (with a positive outcome after 2 therapy sessions) (24), and patients with grade-II or higher liver encephalopathy (13,20,24,33,44,45), increased intra-dysfunction (13,20,34,44), renal dysfunction with or without hepatorenal syndrome (13,19,20,32,41,46), and patients with grade-II or higher liver encephalopathy have a mortality rate of 80-90% in the absence of liver transplantation, and above 50% even in the presence of said transplantation (54).

Liver transplant complications

Experience with MARS in patients with liver transplant and graft malfunction is still scarce. Treatment goal is graft recovery to prevent retransplantation, or else clinical and hemodynamic improvement to increase transplant efficacy. Cases have been reported on patients with graft dysfunction (13,20,34,44), patients with grade-II or higher liver encephalopathy (13,20,24,33,44,45), increased intracranial pressure (20,24,33,45), renal dysfunction with or without hepatorenal syndrome (13,19,20,23,32,41,46), and transplants with progressive intrahepatic cholestasis (13,17,20,33,44).

Patients with primary graft dysfunction after liver partition have also been treated with MARS. Using this technique, two grafts are obtained for transplantation unto two receptors, usually an adult and a child, from a single donor liver (57). Three patients recovered and one was retransplanted in a center where MARS was used in 4 subjects with primary graft dysfunction and cholestasis (38). In another center, a child with graft dysfunction after split-liver transplantation (59) was treated with MARS, which allowed stabilization until retransplantation took place 2 weeks later. Of six patients with primary graft dysfunction and bilirubin above 15 mg/dl, five recovered without need for transplantation with MARS, and an improvement of neurological status and INR was demonstrated, as well as a decrease in ammonium and bilirubin levels (44). Four of five patients reported in 2 centers were maintained until retransplantation with MARS (60,61).

Liver failure after liver surgery

Data available on this indication are very scarce. Two patients with liver failure following liver resection were reported by Lamesch (34), which were treated with 3 sessions per patient on average; one survived and one died from intercurrent pneumonia.

Intractable pruritus in chronic cholestatic syndromes

Pruritus that is uncontrollable by standard drug therapies may develop in patients with primary biliary cirrhosis, primary sclerosing cholangitis, recurrent benign intrahepatic cholestasis, or biliary atresia, and an indication of liver transplant for this reason may even ensue. MARS can eliminate a number of yet unidentified substances that accumulate because of defective bile excretion, thus improving pruritus in these patients. Experience with MARS as a means to treat pruritus is still scant, but some series showing good results have already been reported (62,63).

Other

MARS has also been used in the treatment of patients with cholestasis following heart failure or cardiac surgery (64), and patients in the heart transplantation waiting list who develop right ventricular failure, because of its ability to increase mean blood pressure and systemic vascular resistance (65).

CONCLUSIONS

Albumin dialysis (MARS) in patients with both acute and chronic liver failure exerts obvious clinical, biological, and hemodynamic effects. However, a translation of these data into clinically relevant variables has not been demonstrated so far, although the possibility exists that a procedure allowing transient or definite recovery of some detoxification functions in the injured liver may be available. Further controlled, methodologically sound studies are needed to clearly establish this procedure’s indications, as well as its effects on survival. On the other hand, a detailed analysis of such studies may allow that the pathophysiological bases of some of these conditions be studied.

REFERENCES

the control group. No side effects were reported in the MARS group. The fact that this study included a deeply heterogeneous group of patients with a small sample size must be underscored, as results should be supported by new, larger studies. In addition, most patients had cirrhosis of alcoholic etiology with acute alcoholic hepatitis on top, and therefore new studies are needed to extrapolate these data to cirrhosis of a different origin.

Hepatorenal syndrome (HRS) is another potential indication for MARS. Even though conventional dialysis does not appear to exert any beneficial effects (39,40), albumin dialysis just might (23,32,41). In a prospective, randomized clinical trial comparing MARS to conventional dialysis (23) in patients with type I HRS, subjects who received MARS had a significant reduction of both bilirubin and creatinine serum levels, and increased serum sodium and prothrombin activity. All 13 patients had oligoanuria or anuria, with urine sodium below 20 mmol/L despite an adequate intravascular volume (mean central venous pressure was 10 mmHg). Mortality rates at 7 days were 100% in the conventional hemodialysis group, and 62.5% in the MARS group (75% after 30 days) (p < 0.01). It should be pointed out that the definition of hepatorenal syndrome used in the exclusion criteria of this study included oliguria and low urine sodium levels, but did not follow the definition proposed by the International Ascites Club (42), and therefore a number of patients meeting type I HRS criteria were likely excluded. Thus, these patients make up a group with particularly severe disease, and are therefore more difficult to manage. This may explain the fact that mortality in the control group is far above that reported by Ginés et al. (43), with a cumulative survival rate higher than 60% at 7 days.

Subsequent though uncontrolled studies in patients with HRS (19-21) also demonstrated that MARS therapy is followed by an increase in baseline mean blood pressure, and an improvement in baseline ascites, liver encephalopathy, Child-Pugh grade, and oliguria.

Acute liver failure

The goal of MARS treatment in patients with acute liver failure is to achieve complete liver recovery through liver regeneration, or to act as a bridge to liver transplantation by improving its clinical status. Spontaneous liver recovery may occur in up to 30-40% of such cases, depending on the underlying etiology.

Within this indication, MARS has been mainly used for patients with grade-II or higher liver encephalopathy (13,20,24,33,44,45), and increased intracranial pressure (20,24,33,45), ischemic liver injury with serum bilirubin above 8 mg/dl100 mmol/L, renal dysfunction or hepatorenal syndrome (13,19,20,23,32,40,46), progressive intrahepatic cholestasis (13,17,20,33,44), fulminant Wilson's disease (34,47-49), and acute liver failure secondary to acetaminophen (34,46,50) and phenytoin (51) overdosing. Continued therapies are recommended for acute liver failure, followed by intermittent therapies once the clinical and hemodynamic status becomes stable.

In an uncontrolled, phase I pilot study (33), MARS was evaluated in 9 patients with acute liver failure who were eligible for emergency liver transplantation (five were in the UNOS I stage, and four in the UNOS IIA stage). Mean duration of MARS sessions was 73.2 ± 12.2 hours. The procedure was well tolerated by all patients, and significant decreases of ammonium and creatinine levels, improvements in liver encephalopathy grade, and increases in Fisher's index (ratio of branched-chain amino acids to aromatic amino acids) were demonstrated. In addition, a significant increase in coagulation factor VII resulted, as a marker of liver synthesis. One UNOS I patient recovered baseline liver function, and 3 were transplanted.

Four patients received transplantation in another center where MARS was used for individuals with fulminant liver failure (44). In addition, a significant decrease of serum ammonium and bilirubin was also reported, as well as neurological improvement.

Several cases of fulminant-onset Wilson’s disease have also been reported (34,47-49), which were initially treated with MARS and then successfully transplanted. Although blood copper basically circulates bound to ceruloplasmin, around 20% (52) is transported by albumin and designated “free copper compartment”; this fraction increases in patients with Wilson’s disease. MARS-treated patients received continual therapy until an organ for liver transplantation was obtained (treatment intervals, 4 to 28 days). A significant decrease in serum copper, bilirubin, and ammonium levels was demonstrated, as well as an improvement in renal function and neurological status. Most significant decreases in serum copper occurred within 4 hours of treatment. The mechanisms through which MARS eliminates serum copper remain unclear; on the one hand, it appears to be largely adsorbed by free binding sites at the MARS™Flux membrane; on the other hand, another fraction goes directly into the albumin circuit but is not adsorbed by any of the intermediate columns (activated carbon or anion exchange resin columns).

A number of patients with fulminant liver failure from acute acetaminophen intoxication were also successfully treated (34,46,50). MARS-treated patients had hepatic coma, increased intracranial pressure, and severe coagulopathy. Initial medical management was performed with an early intravenous infusion of N-acetyl-cysteine, a precursor of glutathione that is recommended to treat this type of toxicity (53). MARS was initiated to stabilize patients until an organ for transplantation was available. Improved neurological and hemodynamic status, and decreased intracranial pressure were seen.
A wide experience in MARS therapy is currently available for patients with AoCLF, but the number of controlled clinical studies so far is not enough to evaluate which patient groups will obtain the greatest benefits from this therapy. The first study reported on MARS therapy that included a wide series of patients with chronic liver disease and acute impairment dates back to year 2000 (22). It included 26 patients with advanced, particularly alcohol-related liver disease who had not responded to conventional treatment. They had serum bilirubin levels above 20 mg/dl, and had failed to respond to standard therapy. MARS therapy was associated with improved 30-days survival (mortality was 8.3% with MARS versus 50% among controls; \( p = 0.02 \)). On average, bile acid and bilirubin serum levels decreased 43 and 29%, respectively, after one week of treatment in the MARS group, but not in the control group. Renal failure and liver encephalopathy also improved, and mean blood pressure increased with the use of MARS, whereas these same parameters worsened in per patient. After 6 hours of MARS therapy a significant reduction in bile acid and bilirubin serum levels was demonstrated, besides a significant improvement in liver encephalopathy and Child-Pugh grade.

Similar results have been subsequently reported by other groups managing patients with end-stage liver disease and liver encephalopathy (13,14,16,17,19-30,33-36), and significantly decreased biochemical parameters, including bilirubin, bile acid, and creatinine levels, have been demonstrated, as well as reduced intracranial pressure, decreased jugular bulb saturation, increased mean blood pressure, raised systemic resistance, diminished plasma renin, and clinical, particularly neurological improvement.

A prospective, controlled clinical study has been recently reported (31,37,38), including 24 patients with cirrhosis of diverse etiology who developed acute decompensation (gastrointestinal bleeding, acute alcoholic hepatitis, infection). Patients were randomized to receive either standard therapy only (controls) or conventional therapy in association with MARS. The potential improvement of hyperbilirubinemia, 30-days survival, and liver encephalopathy with MARS use was assessed. All patients had serum bilirubin levels above 20 mg/dl, and had failed to respond to standard therapy. MARS therapy was associated with improved 30-days survival (mortality was 8.3% with MARS versus 50% among controls; \( p = 0.02 \)). On average, bile acid and bilirubin serum levels decreased 43 and 29%, respectively, after one week of treatment in the MARS group, but not in the control group. Renal failure and liver encephalopathy also improved, and mean blood pressure increased with the use of MARS, whereas these same parameters worsened in
MARS membrane characteristics

This membrane is capable of mimicking the biologic characteristics of hepatocyte membranes, and transfers protein-bound toxins and hydrophilic toxic metabolites from the patient’s blood compartment to the albumin compartment. This is a perforated polysulphone dialysis membrane with an adsorption surface of 2.2 m² (11,12) and pores that will not allow substances with a molecular weight greater than 50 kD to go through. This particular pore configuration renders this membrane impervious to albumin, with a molecular weight of 66kD. However, it does clear albumin-bound toxins from the patient’s blood compartment, since complex physical and chemical interactions occur between toxins and their receptors through pores. Toxins are adsorbed by the membrane’s surface, whereas proteins remain in the blood compartment. Thus a toxin gradient is established from the patient’s blood compartment to the albumin compartment (Fig. 2), where the free receptors of albumin have greater affinity for toxic ligands when compared to the toxin-overloaded albumin of the patient. All water soluble substances with a molecular weight below 50 kD such as lactate, creatinine, and ammonium may go across the membrane, but other proteins such as hormones, coagulation factors, and antithrombin III in the patient’s blood cannot do so because of their higher molecular weight; such selectivity helps maintain the patient’s protein balance, which is not the case with other extracorporeal clearance techniques.

CLINICAL USE OF MARS THERAPY.
INDICATIONS

Even though MARS was first used in the clinical setting in 1993, results have not been available until the last 3-4 years; most work, nevertheless, is based on experience with a restricted number of patients, and must therefore be interpreted with caution. Most common indications of albumin-based dialysis are listed in Table II, but they are provisional and still undergoing evaluation. Table III summarizes the clinical effects of MARS.

Acute decompensation of a preexisting chronic liver disease (“acute on chronic liver failure”)

In these patients, the goal of treatment with MARS is to favour the recovery of liver function to pre-decompensation levels, to act as a short-to-medium term bridge towards liver transplantation, or to improve pre-transplantation clinical status in an attempt to reduce transplant complications.

It has been basically used for patients with serum bilirubin levels higher than 15 mg/dL (255 µmol/L) who did not respond to standard treatment (13-31), patients with renal failure or hepatorenal syndrome (13,15,18-21,23,31,32) with or without grade-II –or higher– liver encephalopathy (13-17,19-22,24-31,33-36).
Indications and therapeutic possibilities of albumin dialysis (MARS)

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INTRODUCTION

Despite remarkable medical advances during the last few years, liver failure –both acute and chronic– still results in high mortality (1). Since liver transplant programs were developed to improve survival in numerous hepatic end-stage disorders (2), fewer than 15% of patients with liver failure do actually receive a transplantation, because of the presence of procedural contraindications (toxic habits, age, concurrent disease,...), or of clinical conditions that may render surgery more difficult or worsen transplant prognosis.

All these circumstances encouraged the development of alternative procedures to increase liver graft availability, as is the case of liver partition techniques and living-donor transplantation (3). On the other hand, organ scarcity for transplantation during the 1960s encouraged the parallel development of liver support systems in an attempt to reduce mortality and to improve patient survival while waiting for a transplant. Such systems attempt to replace a number of synthesis and detoxification functions for the damaged liver parenchyma (4). During the past few years both bioartificial systems –also referred to as “bioartificial livers”– based on bioreactors containing functionally active living hepatocytes (5-8), and extracorporeal liver detoxification systems have been developed. The latter type includes the so-called MARS (molecular adsorbent recirculating system) system, which combines albumin-bound molecule clearance and novel dialysis membrane biocompatibility.

MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS)

This one is based on a detoxification system running on a standard hemodialysis or hemofiltration device provided with an adapted intermediate circuit with human albumin at a concentration of 10-20% in combination with a high-selectivity membrane, which allows selective detoxification of both albumin-bound toxic products and water-soluble substances (9-13) (Table I).

MARS described

MARS includes 3 different compartments or circuits: blood circuit, albumin circuit, and low-flow dialysis circuit (Fig. 1). The blood circuit is connected to the patient via a venovenous route (double-lumen catheter) so that blood goes through a high-flow dialysis membrane (MARS® Flux, Teraklin AG, Rostock, Germany) –which has special physical and chemical characteristics as we shall discuss below– and then reaches the albumin in a closed circuit, thus giving rise to toxin interchange. Albumin in the closed circuit goes through conventional low-flow dialysis membrane (diaFLUX®) where it is dialyzed by a bicarbonate buffer (making up the so-called dialysis circuit) and subsequently by an activated carbon column and then an anion interchange resin column, where it regenerates. The progression of albumin through these columns allows receptor-bound toxins to be eliminated, thus resulting in effective recirculation.