Review
Equipment review: The molecular adsorbents recirculating system (MARS®)

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Abstract

The molecular adsorbents recirculating system (MARS®) is a form of artificial liver support that has the potential to remove substantial quantities of albumin-bound toxins that have been postulated to contribute to the pathogenesis of liver cell damage, haemodynamic instability and multi-organ failure in patients with acute liver failure (ALF) and acute-on-chronic liver failure (AoCLF). These toxins include fatty acids, bile acids, tryptophan, bilirubin, aromatic amino acids and nitric oxide. Data from controlled clinical trials are limited so far. One of two studies performed on small numbers of patients with AoCLF suggest a survival benefit, but no controlled data are available in the ALF setting. Our preliminary experience with MARS therapy, instituted late in the clinical course of five patients with severely impaired liver function, including three with AoCLF precipitated by sepsis and two with liver dysfunction due to sepsis in the absence of pre-existing chronic liver disease, indicates some clinical efficacy. However, the overall survival rate (1 of 5; 20%) remained poor. More data obtained from larger cohorts of patients enrolled in randomised controlled studies will be required in both the AoCLF and ALF settings to identify categories of liver failure patients who might benefit most from MARS treatment, to ascertain the most appropriate timing of intervention and to determine the overall impact on outcome, including cost-effectiveness.

Keywords artificial liver, liver failure, toxins

Introduction

The editors of the Health Technology Assessment Section of *Critical Care* have facilitated the preparation article. This article maintains our previous format for such reviews in which the manufacturer provides answers to a standard questionnaire of our own design and an independent early adopter describes and reviews their own experiences using the device.

Carrying out and completing prospective studies of the usefulness of new therapies is always a challenging task and that is especially true for this device. It is also true that a single intensive care unit is unlikely to be able to acquire a large amount of experience using this liver support therapy over a short period of time.

These articles are not able to resolve this dilemma, but they do illustrate the real world difficulty in deciding when and where to deploy a promising new technology at the bedside when that technology is hard to test scientifically and its use is both resource and labour intensive.

ALF = acute liver failure; AoCLF = acute-on-chronic liver failure; CRRT = continuous renal replacement therapy; CVVHD = continuous veno-venous haemodialysis; MARS = molecular adsorbents recirculating system.

Technology questionnaire

Christian Steiner

What is the science underlying the technology?

Molecular adsorbents recirculating system (MARS®) therapy is a blood detoxification system based on albumin dialysis that is able to remove albumin-bound and water-soluble substances selectively. 'Cleaning' the body's albumin pool restores its ability to balance several systems in the body in pathological situations.

What are the primary indications for its use?

- Primary and secondary liver failure/dysfunction
  i. Primary:
     a. Decompensated chronic liver disease (re-compensation/bridge to transplant)
     b. Acute liver failure (recovery/bridge)
     c. Liver failure after liver transplantation
  ii. Secondary liver failure and multi-organ failure/dysfunction

What are the common secondary indications for its use?

- Intractable pruritus in cholestasis
- Liver failure after liver surgery

What are the efficacy data to support its use?

- Effective and selective removal of water-soluble and albumin-bound substances [1] including nitric oxide
- Impact on neurological [2], hemodynamic [3,4], renal [5,6] and other end-organ functions in liver failure [7,8]
- Decrease of oxidative stress [8]

Are there any appropriate outcome data available?

- Acute decompensated chronic liver disease [5]
- Hepato-renal syndrome [6]

- Overview of MARS-treated patients [9]

What are the costs of using the technology?

- The average number of treatments per therapy course is three to five depending on the aetiology. The costs are on average between 9000€ and 15,000€ for the therapy.

Should there be any special user requirements for the safe and effective use of this technology?

- Hospital or non-hospital environment suitable for the performance of extracorporeal blood therapy (comparable to renal replacement therapy).
- Intensive care set-up if indicated by the patient's condition

What is the current status of this technology and, if it is not in widespread use, why not?

- More than 4,500 patients have been treated in over 17,000 single treatments all over the world (status June 2004, Teraklin AG). Germany and Austria are the first countries to have included MARS therapy into the reimbursement catalogue (in-hospital therapy) 5 years after introduction to the market in Europe. Reimbursement is awaited as well in other European countries.
- FDA clearance has been applied for, and is pending.

What additional research is necessary or pending?

- Five multi-centre trials are on the way or planned in major indications (Europe and the USA)
- Definition of therapy protocols for the different indications is under way.

Equipment review

Martin Boyle, Jelica Kurtovic, David Bihari and Stephen Riordan

Introduction

The molecular adsorbents recirculating system (MARS) is a form of artificial liver support therapy that has been available for clinical use since 1998 and has been used in the treatment of more than 3300 patients (more than 16,000 single treatments) [10]. MARS became available in Australia in 2002. The Prince of Wales Hospital, Sydney, has a major clinical and research interest in the management of patients with liver failure and was interested to gain clinical experience with MARS therapy. Here we briefly review the principles of operation of the MARS device, the reported data on its possible efficacy and our own preliminary experience stemming from the introduction of this new technology into our clinical practice.

MARS consists of an albumin haemodialyser, a standard haemodialyser, an activated carbon adsorber and an anion exchanger. This circuit is filled with 600 ml of 20% human albumin solution. The albumin acts as a dialysate and is pumped through a hollow-fibre membrane haemodialyser (MARS Flux dialyser) countercurrent to the blood flow. Protein-bound toxins and water-soluble substances diffuse into the albumin solution. The albumin is then passed through another dialyser countercurrent to a standard buffered dialysis solution where diffusive clearance of water-soluble substances occurs. The albumin solution is then cleaned of its albumin-bound toxins by passage through an activated carbon adsorber and an anion exchanger [11].

The MARS Flux dialyser has a surface area of 2.1 m^2, a membrane thickness of 100 nm and a molecular cut-off of about 50 kDa. The irregularities in the membrane surface provide deep crypts, which act as binding sites for albumin when the circuit is primed with albumin solution. The albumin

molecules on the dialysis side of the membrane are in very close proximity to the surface of the membrane in contact with patient's blood. Albumin-bound toxins move by physicochemical interactions between the plasma, albumin molecules bound to the dialysis side of the membrane and the circulating albumin solution. A concentration gradient is maintained by circulation of the albumin solution and disposal of the albumin-bound toxins by passage through the activated charcoal and anion-exchange columns [12,13].

MARS therapy has been shown to result in a relative clearance of aromatic amino acids, leading to an improved profile of branched-chain to aromatic amino acids and the substantial removal of albumin-bound toxins such as fatty acids, bile acids, tryptophan and bilirubin. The removal rates of bilirubin and bile acids, for a single treatment, are about 28% and 55%, respectively [5,6,13–16]. The clearance of bilirubin has been shown to decline over time with relatively little clearance after about 6 hours of treatment, although there is some contradictory evidence showing clearance to be maintained at 5 hours [15,17]. Physiologically important proteins (such as albumin, α_1-glycoprotein, α_1-antitrypsin, α_2-macroglobulin, transferrin and thyroxin-binding globulin) and hormones (such as thyroxine and thyroid-stimulating hormone) are not significantly removed [12].

Albumin contains reversible binding sites for substances such as fatty acids, hormones, enzymes, dyes, trace metals and drugs [12,13,18,19]. Albumin has a vital role in the clearance from the body of substances that are toxic in the unbound state by reversible binding and transport to the liver, where they are metabolised and excreted into the biliary system or in a water-soluble form by means of the kidneys [13]. Albumin binds a number of substances that accumulate in liver failure and have been implicated in the development of hepato-renal syndrome, hepatic encephalopathy, haemodynamic instability, ongoing liver injury and inhibition of liver cell regeneration. It has been proposed that albumin binding sites for these putative toxins become saturated in patients with liver failure, consequent on decreased hepatic clearance, leading to an accumulation of unbound toxic substances and the development of organ dysfunction [13].

Rationale for MARS treatment in liver failure

In patients with liver failure it has been proposed that clearance of albumin-bound toxins would create an environment conducive to hepatocyte recovery and regeneration, thereby allowing time for any superimposed precipitant of hepatic decompensation, such as infection or gastrointestinal bleeding, to be reversed and to delay or even obviate the need for liver transplantation [13]. Such a treatment is vital if mortality from acute liver failure (ALF) and acute-on-chronic liver failure (AoCLF) is to be improved, given the worldwide shortage of donor organs and the fact that many patients listed for transplantation die while on waiting lists, even with priority listing [20].

Experience with MARS in AoCLF

MARS treatment has been shown in the AoCLF setting to significantly reduce plasma levels of the markers of albumin-bound toxins, bilirubin and bile acids. Ammonia, a water-soluble molecule, is also significantly cleared with MARS therapy, as are the indices of uraemia control (urea and creatinine) [5,6,13,15,16,21]. MARS has also been shown to clear nitric oxide effectively [22].

Improvements in haemodynamic stability as indicated by improved mean arterial pressure and a reduction in requirement for vasopressor agents have been reported, along with improvements in neurological state as measured by the hepatic encephalopathy grade and intracranial pressure [4,16,23,24]. Both in patients with AoCLF and in those with otherwise well-compensated cirrhosis, MARS has been reported to be used with some success in the treatment of intractable pruritus resulting from intrahepatic cholestasis [25].

Only two small, randomised controlled trials have assessed outcomes of MARS therapy compared with standard medical therapy in patients with AoCLF. The first assessed the effect of MARS in 13 patients with type I hepato-renal syndrome. Eight patients received MARS in addition to renal replacement and standard medical therapy, and five received renal replacement and standard medical therapy. The MARS group had a significant decrease in bilirubin level and an improved prothrombin activity, and the 30-day mortality was 75% and 100% in the MARS and standard medical therapy groups, respectively [6]. The second study assessed MARS in a group of 24 patients with AoCLF: 12 patients received MARS therapy and standard medical therapy, and the control group received standard medical therapy only. The primary outcome was a reduction and maintenance of serum bilirubin level to less than 15 mg dl^{-1}, while 30-day survival was a secondary endpoint. In comparison with pretreatment values, the bilirubin and bile acids decreased significantly in the MARS group but not in the controls. At 30 days, one of 12 patients receiving MARS had died, compared with 6 of 12 patients in the control group. At interim analysis, the trial was stopped on the recommendation of the institutional ethics committee, to allow protocol revision so patients deteriorating on standard medical therapy could have the opportunity to cross over to MARS treatment [5].

Use of MARS in ALF

The data regarding the use of MARS in ALF are sparse, consisting of small case series and case reports. No controlled experiences have been reported. As in the AoCLF setting, the use of MARS in ALF has been associated with improvements in serum bilirubin and ammonia levels, together with hepatic encephalopathy grade [26,27]. Several patients have been successfully bridged, over several days, to transplant [26–28]. MARS has been used in patients with a range of aetiologies of ALF, including not only that due to paracetamol overdose but other less common causes such

Table 1

Patient details

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	71	43	32	40	46
Gender	M	M	F	M	F
APACHE II	33	30	34	25	31
Primary diagnosis	AoCLF, 2° sepsis, grade 4 HE, HRS	Liver disease 2° to sepsis, ATN	Liver disease 2° to sepsis, ATN	AoCLF, 2° sepsis, grade 3 HE, HRS	AoCLF, 2° sepsis, grade 3 HE, HRS
Background	Cirrhosis (NASH)	Post-hemihepatectomy	Post-renal transplant	Cirrhosis (HCV, alcohol)	Cirrhosis (HCV)
Child–Pugh	Class C	N/A	N/A	Class C	Class C
Other treatment	Ventilated, CVVHD, inotropes	Ventilated, CVVHD, inotropes	Ventilated, CVVHD	Ventilated, CVVHD, inotropes	Ventilated, CVVHD, inotropes

AoCLF, acute-on-chronic liver failure; APACHE, Acute Physiology and Chronic Health Evaluation; CVVHD, continuous veno-venous haemodialysis; HCV, hepatitis C virus; HE, hepatic encephalopathy; HRS, hepato-renal syndrome; NASH, non-alcoholic steatohepatitis; N/A, not applicable (no pre-existing chronic liver disease).

as intoxication with *Amanita phalloides* [29,30]. MARS has also been used in the treatment of primary graft dysfunction after liver transplantation, with reports of success in bridging to retransplantation along with instances of recovery of graft function [27,28]. MARS has also been used to support patients who develop liver failure after hemi-hepatectomy [31,32].

The Prince of Wales Hospital experience with MARS

MARS became available for clinical use in Australia in 2002. Since December 2002 we have used MARS to treat five patients with severely impaired liver function, including three with AoCLF precipitated by sepsis and two with liver dysfunction due to sepsis in the absence of pre-existing chronic liver disease. Patients received MARS therapy in conjunction with parenteral antibiotics and full medical intensive care measures. Clinical details of these patients are presented in Table 1. Patients were selected for treatment with MARS on the basis of failed medical therapy, with an estimated mortality rate without intervention of more than 90%. Consequently, MARS therapy was introduced at an advanced stage of the clinical course in each case. Indeed, our five patients had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores than those reported in the available literature. All patients required mechanical ventilatory support and were in acute renal failure, caused by hepato-renal syndrome in three cases and sepsis-induced acute tubular necrosis in two. Renal replacement therapy with continuous veno-venous haemodialysis (CVVHD) was required in three patients. Four of our patients required vasopressor therapy (noradrenaline) to maintain a mean arterial pressure of at least 70 mmHg. One patient (patient 5) was on a waiting list for liver transplantation, and MARS was instituted with the aim of bridging the patient until complicating sepsis could be reversed and a donor liver

became available. Listing for transplantation was contra-indicated by uncontrolled sepsis in the remaining four patients.

Intensive care unit nursing staff set up the MARS (ASC BioTech Pty. Ltd., Sydney) circuit. These staff members were familiar with the setting up and management of continuous renal replacement therapy (CRRT). The set-up was accomplished with little difficulty but was time-consuming, taking about 2 hours to complete.

The planned duration of therapy in our patients ranged from 6 to 24 hours and was governed by haemodynamic status. The recommended treatment regimens in the literature include intermittent therapy over 6–8 hours in patients with a relatively stable haemodynamic profile and continuous therapy with circuit changes each 24 hours in unstable patients. The albumin pump speed was maintained at 150 ml min^{-1} unless circuit pressures were excessive, in which case the pump speed was reduced. CVVHD was used for all treatments with dialysate flow rates ranging from 8.3 to 25 ml min^{-1} depending on the need for uraemia control. Lactate-free dialysis fluid was used for all treatments.

Vascular access was gained with dual-lumen catheters placed in the femoral or subclavian veins. Blood pump speeds were set between 100 and 250 ml min^{-1} depending on the quality of the vascular access and circuit pressures. Anticoagulation of the extracorporeal circuit was achieved with heparin alone or epoprostenol at 5 ng kg^{-1} min^{-1} plus heparin. Heparin was adjusted to achieve an activated partial thromboplastin time of about 50–60 s in blood drawn from the patient. Only 6 of 12 treatments (50%) achieved the prescribed duration of treatment. The early failure of one circuit resulted from poor vascular access, whereas the others probably resulted from circuit clotting.

Table 2

Clinical and laboratory effects of MARS therapy

Parameter	Normal range	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
		Before	After	Before	After	Before	After	Before	After	Before	After
Noradrenaline, μg kg^{-1} min^{-1}		0.22	0.02	0.06	0.16	0	0	0.22	0.10	0.32	0.06
Creatinine	60–110 μM	307	142	132	239	171	234	241	144	164	107
Urea	2.9–7.1 mM	21	13	16	22	1	6	11	29	15	17
Ammonia	15–50 μM	67	47								
HE grade		4	3					3	1	3	2
Bilirubin	<25 μM	161	210	654	528	260	182	484	137	510	326
Bile acids	0–6 μM	75	75					27	16	202	67
AA/β-OH-But		4.2	6.8					1.3	8	4	4.5
PDR ICG	>16% min^{-1}	4.4	5.5	4.3	5.2	4.3	5.4	5.6	5.2		
Duration of treatment, h		24, 16		15, 13		5, 6		12, 16, 20		6, 6, 6	
Outcome		ICU D/C, died in ward		Died in ICU		ICU D/C, died in ward		D/C home		Died in ICU	

AA/β-OH-But, ratio of arterial acetoacetate to β-hydroxybutyrate (ketone body); D/C, discharged; HE, hepatic encephalopathy; ICU, intensive care unit; PDR ICG, plasma disappearance rate of indocyanine green (measured after an intravenous dose of 0.5 mg kg^{-1} body weight with a non-invasive transcutaneous probe [Pulsion Medical System AG, Munich]).

Clinical and biochemical data before and after MARS therapy, along with survival data, are presented in Table 2. Substantial reductions in the required dosage of nor-adrenaline were documented in three of the four patients who were vasopressor-dependent before MARS treatment. Conversely, the noradrenaline dose increased from 0.06 μg kg^{-1} min^{-1} to 0.16 μg kg^{-1} min^{-1} in the other patient (patient 2) in whom sepsis remained unresolved. Other clinical and laboratory effects were similarly variable, although improvement in hepatic encephalopathy grade was documented in all three patients who were encephalopathic before intervention. The serum creatinine level improved in all three patients with hepato-renal syndrome but not in the two with acute tubular necrosis. Patient 1 was the only patient to show no improvement in the serum level of bilirubin but did demonstrate improvements in urea, creatinine and ammonia, along with improvements in haemodynamic status and hepatic encephalopathy grade. Spur cell haemolytic anaemia, consequent on severe liver damage, contributed to hyper-bilirubinaemia in this patient and it is possible that the rate of production of bilirubin exceeded removal capacity, even with the MARS circuit. This explanation remains speculative because we did not measure clearance of bilirubin in the MARS dialysate. Nonetheless, a more marked increase in hyperbilirubinaemia followed the cessation of MARS therapy, lending weight to our hypothesis that at least some clearance of bilirubin probably occurred during MARS treatment. Patient 4 received the most MARS treatments, had the lowest severity of illness score, and showed reductions in creatinine, bilirubin and bile acids, and an improvement in the arterial ketone body ratio. This was the only patient who eventually survived to be discharged home.

Although our experience so far is only small, several qualitative observations as early adopters of MARS treatment in Australia are apparent. First, MARS treatment is a technically feasible therapeutic option for liver support in the general intensive-care setting. However, the set-up is labour intensive by comparison with CRRT. As with CRRT, vascular access seems to be a key factor in achieving the prescribed treatment dose. Vascular access in patient 4 was obtained by two double-lumen catheters. Both lumens of the internal jugular vein catheter and femoral vein catheter were used for outward blood flow and return blood flow respectively. This will be our standard practice in the future. Second, when haemodynamic status allows, we would favour shorter treatment times of 6–8 hours duration with albumin flow rates of at least 200 ml min^{-1} to reduce circuit failures resulting from clotting and to reduce the need for prolonged use of anti-coagulants. If patients are receiving CRRT, this can be maintained during MARS treatment and continued after it has been completed. Last, it is likely that MARS treatment was instituted too late in the clinical course of our patients for a realistic improvement in their chance of survival. Despite many thousand reported treatment applications over the past 6 years, selection criteria for MARS therapy remain ill-defined. This is due at least in part to the fact that most treatments have been delivered in an uncontrolled fashion and in many

diverse clinical settings and treatment centres. Outcome measures have similarly not been uniform. Further randomised controlled studies using standardised inclusion and exclusion criteria and outcome measures are urgently required so that those categories of liver failure patients who might benefit most from MARS therapy and those that can confidently be managed by medical means alone can be identified by the treating intensivist at a relatively early stage in their clinical course, thereby maximising the chance of a successful outcome.

Competing interests

Acknowledgement

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