Molecular Adsorbents Recirculating System (MARS): Evidence and Management Pitfalls

Dr. Alexander CHIU
MBChB, MRCP (UK), FHKCP, FHKAM (Med), FRCP (Edin)
Adult Intensive Care Unit, Queen Mary Hospital, Hong Kong

Prof. Sheung-tat FAN
MS, MD, PhD, DSc, FRCS (Glasg & Edin), FACS, FHKAM (Surg), FCSHK
Department of Surgery, The University of Hong Kong, Hong Kong

Evidence

Evidence relating to the efficacy of MARS can be categorized into three levels: biochemical efficacy, physiological improvement, and clinical benefits. The biochemical efficacy of MARS has been well proven. Toxins as removable by MARS documented in the literature include bilirubin, ammonia, aromatic amino acids, tryptophans, short-chain fatty acids, bile acids, GABA-like substances, nitric oxides and cytokines. Most of the toxins removable by MARS are implicated in the development of hepatic encephalopathy, portal hypertension or other inflammatory changes in liver failure. Amongst all, reduction of bilirubin, either total or direct, is the most consistent as demonstrated by all studies. It should be noted that bilirubin, at least in adult patients, is not a deadly toxin as such. Its use is mainly regarded as a surrogate marker for other hepatotoxins that are not routinely measured in daily clinical practice.

The physiological benefits demonstrated by the MARS system include lowering of intracranial pressure (ICP), reduction of portal pressure, and improvement of blood pressure and systemic vascular resistance. Reduction of ICP in liver failure by MARS was first reported in animal studies and subsequently also in a case report. Elevated ICP implies cerebral oedema which is one of the most common causes of death in patients with acute liver failure. Reduction of ICP implies that cerebral oedema is under control and the patient may be able to gain more time to bridge to transplantation.

In patients with liver failure, particularly those with cirrhosis, portal hypertension is a significant factor contributing to ascites formation, variceal bleeding and hepatorenal syndrome. MARS has been shown to be able to reduce the hepatic venous pressure gradient, an indirect measurement of portal pressure. This effect is not only observed during treatment, but sustained for up to 24 hours after MARS. The mechanism of reduction of portal pressure is unknown, but is believed to be mediated through removal of vasoactive substances like nitric oxide in the splanchnic circulation by MARS.

The haemodynamic benefits brought about by MARS in patients having liver failure include raised mean arterial pressure, increased systemic vascular resistance, and reduced cardiac output. Haemodynamic effect is particularly prominent in patients with cirrhosis during treatment. In patients with acute liver failure,
increased vascular tone could also be observed, but the result is not as sustained. These findings illustrate that MARS is haemodynamically well tolerated and would not cause hypotension as such. From our experience, however, we find transitory hypotension rather common at the beginning of treatment, and small doses of vasopressor are frequently needed to sustain blood pressure. We attribute this to release of cytokines secondary to platelet activation and change in rheology of blood circulating through the extracorporeal system.

The effects of MARS on two most common complications of liver failure have been studied. Mitzner et al. reported a significantly lower mortality rate in patients with type 1 hepatorenal syndrome treated with MARS compared with those having standard medical therapy. The major shortcoming of this study was that there were only 13 patients involved and in fact only one patient in the treatment survived beyond 30 days. Earlier studies of MARS on hepatic encephalopathy were mainly non-randomised studies and reported lower mortality in treatment groups. Hassanein et al. reported the use of MARS in patients with severe hepatic encephalopathy in a large-scale randomised controlled trial and concluded that the treatment was associated with earlier and more frequent improvement in encephalopathy grading. It should be noted, however, that the trial was not designed to address the impact of MARS on survival.

MARS is not without complications. The most common complication of MARS is platelet reduction. In our experience, the drop in platelet per treatment is around 5 to 10%, but it may be up to 20% in some cases. Though it might not seem significant in most patients with platelet count more than 100x10^9/L, it does raise concern in cirrhotic patients with splenomegaly in which they commonly have thrombocytopenia to start with and when repeated treatments are needed. We empirically give platelet transfusion before MARS to patients with platelet count less than 30x10^9/L. In our experience, four major bleeding episodes might have been related to MARS (2 intracranial bleeding, 1 variceal bleeding and 1 intra-abdominal bleeding after liver transplantation). However, given the inclination of developing these complications in such critical patients, it may be unjustifiable to attribute occurrences of these episodes to MARS. Worldwide, the opinion is that MARS treatment is safe and does not cause additional bleeding risk.

Other documented complications of MARS include hypoglycaemia during treatment, electrolyte disturbances, and non-cardiogenic pulmonary oedema. As MARS is one form of extracorporeal circuit, it shares the potential complications that extracorporeal circuits usually have, including catheter-related infection, haematoma and circuit thrombosis.

Anticoagulation in treatment by MARS is a difficult topic. In our unit, we have moved from no anticoagulation to the use of low molecular weight heparin, and then to heparin priming in which the system is flushed with heparin saline before use. Given the nature of the disease of patients treated, we have not used systemic anticoagulation, albeit it is claimed to be safe according to other centres’ experience. The coagulation profile of patients with liver failure varies significantly and represents the interplay between thrombocytopenia, platelet dysfunction and also reduced synthesis of clotting factors and antithrombin from liver. In order to develop a tailor-made anticoagulation strategy, some researchers have advocated the use of thromboelastography (TEG) to monitor these patients during treatment. We have also tried to apply this monitor in our practice, but because TEG interpretation is in itself open to a lot of debate, we feel that it is still a research tool rather than for routine clinical use. Circuit thrombosis is not necessarily due to inadequate anticoagulation. Circuit flow and turbulences, as well as position and properties of the dialysis catheter, could be contributing factors to inadequate anticoagulation.

Management Pitfalls

MARS is by no means a salvage treatment for liver failure. The most serious management pitfall is implementing MARS as a last resort hoping that the treatment can reverse the detrimental effects of liver failure at a time when the patient is already moribund. In our practice, we employ MARS as an early intervention to prevent deterioration, preferably when the patient is not too ill. We render MARS treatment to those showing rapid velocity but not high absolute value in biochemical deterioration, those with grade 2 hepatic encephalopathy, and those with hepatorenal syndrome with urine output still more than 0.5ml/kg/hr. We believe it is at these time points that MARS can alleviate organ damage and retard progression of the disease through hepatotoxin removal. On the contrary, if MARS treatment is rendered late in the course of liver failure, the benefit of hepatotoxin removal will become minimal amidst the overwhelming cascade of physiological damages brought about by multi-organ failure.

Another management pitfall is indiscriminate use of MARS for all patients with liver failure. In fact, MARS is not applicable to all patients; only a selected few can benefit from it. The selection criteria for MARS candidates in our unit are listed in Table 1. Based on these criteria, less than 25% of the patients admitted with liver failure to our intensive care unit are eligible for the treatment. Certain subgroups of patients, such as those with acute decompensated Wilson disease, have appeared to respond particularly well to MARS. Selection of suitable candidates and initiation of MARS at appropriate timing are the two most important factors to improve the success rate of MARS treatment.

The third management pitfall is utilising MARS as a means to reverse liver failure. Although native liver recovery with MARS has been reported in the literature and also occasionally encountered in our experience, it is unpredictable as to which patients will respond favourably. It is therefore inappropriate to commend the treatment as one which can promote liver recovery. In our centre, the sole objective of performing MARS is to stabilise patients’ conditions and to bridge them to transplantation. It should be clearly explained to patients who are undergoing MARS but not aiming for liver transplantation that the treatment would only
bring about short-term improvement to their conditions. Hopefully, recognition and appropriate future consideration of these management pitfalls will offer possibilities for further refinement of the use of MARS in patients with liver failure.

**Conclusion**

Since MARS was first launched into clinical application in year 2000, research materials published on this topic have exceeded 500, mostly descriptive studies with only a handful of randomised trials amongst them. Given the lack of concrete evidence to demonstrate the survival benefit of MARS, it is understandable that clinicians are skeptical to commit to such treatment which is expensive to run, has a complex operative procedure, and, most importantly, not without risk. It should be noted, however, that liver failure is a disease associated with high mortality and limited treatment options. Any suggestion or evidence, despite being observational or uncontrolled, should therefore not be overlooked and neglected casually. Moreover, the lack of conclusive result from randomised controlled trials could also be due to fallacies and limitations of study methodology. Heterogeneity of the disease, existence of confounding factors, e.g. availability of liver transplantation, and lack of reliable tools to prognosticate patients and to monitor treatment efficacy are all factors that need to be considered in the design of studies on MARS.

In summary, utilisation of MARS treatment requires a comprehensive understanding of its benefits and limitations if optimal outcome is to be achieved. Further studies to delineate and refine the clinical indications, timing of initiation and operative details are needed to give clinicians a better idea of how to implement such service in practice.

**Competing Interests:**

Nothing to declare.

**References**