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Value of albumin dialysis therapy in severe liver insufficiency

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Abstract A blood purification system, molecular adsorbents re-circulating system (MARS), is based on the removal of both protein-bound and water-soluble substances and toxins in the liver. We treated a total of 88 patients within 2 years. Of these patients, 45 had acute liver failure (ALF), 31 had acute decompensation of chronic liver disease, eight had graft failure and four had miscellaneous conditions. Of the patients with ALF, 80% survived; in 23 patients their own liver recovered and 13 patients underwent successful transplantation. Only 23% of patients with acute-on-chronic liver failure survived. Most of them were not considered for transplantation due to their having liver failure from alcoholism and from not abstaining from drinking. MARS is a promising therapy for ALF, allowing the patient's own liver to recover or allowing enough time to find a liver graft. Best results were achieved in patients who had been intoxicated with a lethal dose of toxin. On the other hand, we did not observe much benefit in patients with severe acute-on-chronic liver failure (AcoChr) who did not undergo liver transplantation.

Keywords Albumin dialysis · Liver failure · Survival · MARS · Graft failure

Introduction

Temporary liver support is needed in various clinical situations when liver function fails. In decompensation of liver function many toxic substances are formed and accumulated, which may cause further liver damage. Liver failure can be caused by acute liver failure (ALF) without previous liver disease, by acute decompensation of chronic liver disease (acute-on-chronic, AcoChr), also after liver surgery and graft failure after liver transplantation. Mortality can be high in patients with ALF who did not undergo liver transplantation; mortality rates even up to 90% have been reported [1, 2, 3]. Despite modern intensive care; mortality is also high in patients with AcoChr [4, 5].

Liver transplantation has improved the prognosis of patients with acute and chronic liver disease. However, liver grafts are lacking and not all patients are considered suitable for liver transplantation. Therefore, there is a need for artificial liver support systems, which can help overcome the acute liver crisis, either allowing time for the native liver to recover or for a suitable liver graft to be found. The ideal liver support device should take care of the metabolic, synthesis and detoxification functions of the decompensated liver. Both mechanical (artificial) and cell-based bio-artificial liver support devices have been tried in the past. So far, the results have not been convincing and all the devices have had problems.

We used a blood purification system, molecular absorbents re-circulating system (MARS) [6, 7, 8], which is based on the removal of both albumin-bound and water-soluble substances and toxins, thus taking care of detoxification functions of the liver.

At present, MARS therapy is used in many centres; however, the indications for this therapy have not been clearly established. We assessed the first 88 patients who had shown indications of liver failure and who were treated with MARS. Our aim was to analyse critically the clinical benefit of MARS therapy in different liver failure groups.

Methods

We have used the MARS blood purification system since May 2001 in the ICU of the Department of Anaesthesiology and Intensive Care at the Surgical Hospital where the patients of the Transplantation and Liver Surgery Clinic are treated. The ethics committee of Helsinki University Hospital has approved MARS for the treatment of liver failure. Our unit has 20 years of experience in liver transplantation and also in assessing liver transplantation in acute and chronic end-stage liver disease. Furthermore, we treat half of the liver surgery patients in Finland.

Patients and indications of MARS therapy and listing criteria for liver transplantation

This study includes the first consecutive 88 patients who showed indications of liver failure and who were treated with MARS therapy in our ICU between May 2001 and May 2003. All patients had at least 6 months of follow-up. The indications for MARS therapies were divided into four groups; acute liver failure (ALF), acute decompensation of chronic liver disease (AcoChr), liver graft failure and miscellaneous indications.

In ALF patients, our main indication for starting MARS therapy was a deteriorating clinical condition with encephalopathy and low levels of coagulation factors. An exception was made for patients who had been intoxicated with a lethal dose of toxin; in these patients MARS therapy was started without our waiting for encephalopathy to develop. In patients with paracetamol intoxication, MARS therapy was also started if the ingested amount of paracetamol caused blood concentrations to increase above the critical point according to the Rumack–Matthew monogram. In patients with *Amanita* spp. mushroom poisoning, MARS therapy was started if the known amount of mushroom was lethal.

If the ALF patient fulfilled the Scandiatransplant criteria (includes all Nordic countries) for highly urgent liver transplantation [9] and had no contraindication for liver transplantation, the patient was listed. These patients fulfilled mainly King's College criteria, and, on some occasions, Clichy criteria were used to determine ALF. The Scandiatransplant allocation system gives priority to ALF patients. Although such patients have absolute priority for any donor liver for the next 72 h after having been listed, the mean waiting time is 4 days.

In patients with AcoChr the main indication for MARS therapy to be started was either hepato-renal syndrome type I or highly elevated serum bilirubin; some of them also had hepatic encephalopathy. Alcoholic patients who had not abstained from drinking were not listed. MARS therapy was also started for patients with chronic liver disease who were on the waiting list or with contraindication for liver transplantation, if they were rapidly deteriorating and needed intensive care treatment.

After liver transplantation MARS therapy was started in patients with primary non-functioning (PNF) graft or primary dysfunctioning (PDF) grafts. Furthermore, we treated a patient with MARS who had late graft failure but with contraindication for transplantation surgery.

Another four patients were treated with MARS therapy due to miscellaneous causes of liver failure. None of these patients was considered for liver transplantation.

MARS therapy

Albumin dialysis is a blood purification system that uses a double-sided, albumin impregnated, hollow-fibre dialysis membrane as a molecular adsorbent in a closed-loop dialysis circuit. MARS therapy removes both protein-bound and water-soluble substances of low- and middle-sized molecular weights.

The MARS treatment was conducted through a haemodialysis triple-lumen catheter inserted by the Seldinger technique in the internal jugular vein. The blood circuit was driven by a dialysis machine with a flow rate of 150 ml/min (Fresenius 4008E, Fresenius Medical Care, Germany or Gambro AK100, Gambro Instruments, Sweden). Blood was filtered with a specific non-albumin-permeable high-flux dialysis membrane (MARS-Flux, Teraklin, Rostock, Germany). A closed-loop dialysate circuit containing 600 ml of 20% human serum albumin (Finnish Red Cross, Blood Service, Helsinki, Finland) was driven by the pump of the MARS monitor with a flow rate of 150 ml/min. The albumin dialysate was recycled through a charcoal cartridge (diaMARS AC250) and a second cartridge with an anion-exchange resin (diaMARS IE250). Albumin dialysate circulated through the MARS dialysate compartment and subsequently was further filtered with another conventional dialysis membrane (dia Flux 1 s). In the conventional dialysate compartment, flow rate was maintained at 500 ml/min. In the dialysis machine the ultrafiltration rate was determined individually for every patient according to the clinical need to remove excessive water.

All patients were invasively monitored, and mean arterial pressure (MAP) was maintained above

65 mmHg and CVP above 5 mmHg, with adequate fluid loading and inotropic support (mainly noradrenaline) if needed. We measured haematological and coagulation parameters every six hours during the MARS treatment and determined neurological status every 2 h.

Policy to continue MARS therapy

The first patients with ALF were treated with an 8 h therapy session, which the goal had been in a previous study with AcoChr patients [6], and the same schedule was repeated on the next days. Very soon we changed our policy to use MARS therapy continuously for these acute patients. The target was to continue each therapy session for up to 22 h if there were no clotting problems. MARS therapy was continued up to transplantation or until the patient's condition was improving clinically and according to laboratory measurements. MARS therapy and intensive care were discontinued if there was irreversible organ damage.

Most of the chronic patients were not considered for liver transplantation because they had not abstained from drinking alcohol. In these patients the goal was to continue the same therapy session so long as there were no clotting problems. The next therapy session was started according to clinical response. For the chronic patients, MARS therapy was continued for as long as there was a need for intensive care treatment or if the patient underwent transplant surgery or was not eligible for transplant surgery.

Results

Between May 2001 and May 2003 altogether 88 cases with different aetiologies of liver failure were treated with MARS in our ICU (Table 1).

Overall survival was 58% but it varied in different subgroups between 23% and 80% (Table 2). The number of patients in each group who recovered without having undergone transplantation and who were still alive after successful liver transplantations is also presented in Table 2. In ALF 93% of the patients who underwent transplantation remained alive.

Table 1 Aetiology of liver failure

Cause	Number	Totals
Acute liver failure		45
Paracetamol intoxication	11	
Other toxic	12	
Unknown	18	
Other	4	
Acute decompensation of chronic liver disease		31
Alcohol	23	
Primary biliary cirrhosis and PSC	3	
Biliary atresia	1	
Autoimmune hepatitis	1	
Other	3	
Graft failure		8
Primary non-functioning	1	
Primary dysfunctioning	6	
Late graft failure	1	
Miscellaneous		4

The most common cause of ALF was intoxication with a lethal dose of toxin, in 23 patients. The native liver recovered in 17 out of 23 (74%) intoxicated patients and two successfully underwent transplant surgery. In patients with paracetamol intoxication ($n = 11$) the mean delay between ingestion of paracetamol to administration of *N*-acetyl-cysteine was 44 h (in one patient the delay was 5 h; in the rest of the patients the range was 20–96 h). Our first patient treated with MARS was intoxicated with paracetamol and died [7].

In the group with unknown aetiology of ALF three patients recovered with MARS without undergoing transplant surgery. Of 13 of the patients listed, 11 underwent transplant surgery, one recovered without undergoing liver transplantation and one died while

Table 2 Clinical data of MARS treated patients. *HE* hepatic encephalopathy, *HRS* hepatorenal syndrome, *Hyperbilirubinaemia* plasma bilirubin value above 200 μmol/l (reference values 5–25 μmol/l)

Parameter	Acute liver failure ($n = 45$)	AcoChr ($n = 31$)	Graft failure ($n = 8$)	Miscellaneous ($n = 4$)
Pre-treatment values				
Mean age (years)	46.6	50.3	42.4	50.3
HE grade 3–4	44%	42%	50%	50%
Need of mechanical ventilation	40%	45%	75%	100%
HRS	38%	61%	63%	100%
Hyperbilirubinaemia	62%	100%	38%	75%
Need of vasoactive support	42%	65%	38%	100%
Outcome data				
Mean number of MARS sessions	3.0	2.1	2.5	1.8
Alive per group	36/45 (80%)	7/31 (23%)	6/8 (75%)	1/4 (25%)
Transplanted alive	13	5	3	0
Native liver recovered	23	2	3	1

waiting, due to cardiac infarction. Of the 11 patients who underwent transplant surgery, ten with unknown aetiology remained alive (91%). Three patients with contraindication for liver transplantation all died.

In the ALF group there were four patients with other known aetiologies. They all recovered; one underwent transplantation (acute Budd–Chiari) and the other three did not undergo transplantation (two pregnancy induced one hepatitis A).

At the start of therapy 44% of ALF patients had grade 3–4 hepatic encephalopathy, mean grade 2.0, and it decreased to 1.1 ($P < 0.05$). Three patients without hepatic encephalopathy at the beginning of the MARS therapy underwent transplantation. In those three patients their clinical condition was worsening during MARS therapy and they all had encephalopathy at the time of transplantation. Five ALF patients with a hepatic encephalopathy grade 4 at the beginning of MARS therapy recovered without undergoing liver transplantation. Detailed laboratory parameters are presented in Table 3.

The majority of the patients with AcoChr had injured livers due to alcoholism 74% (23/31). Of the alcoholic patients, two underwent transplantation. Twenty-one alcoholic patients who did not abstain from drinking were not considered for liver transplantation, and only two of them survived. The median survival time after MARS treatment was 25 days in patients with acute decompensation of alcoholic liver disease. Of the eight remaining AcoChr patients, five underwent transplantation. One died 3 months after undergoing transplantation due to sepsis and fungal infection. The other died 8 days after transplant surgery due to haemorrhagic necrosis of the graft. Three of eight chronic patients who had an aetiology of liver failure other that of alcoholism died; one while waiting for a liver and two had contraindication for transplant surgery.

At the start of the MARS therapy 42% of AcoChr patients had hepatic encephalopathy grade 3-4. Mean grade of encephalopathy before MARS treatment in chronic patients was 2.1 and it decreased significantly to 1.5.

There were altogether eight graft failures. One was a PNF graft, six were primary dysfunctioning (PDF) and one was a late graft failure 5 months after transplantation, caused by tuberculous medication.

The only PNF graft was successfully re-transplanted in a patient after 4 days in a grade 4 coma. Of the six PDF grafts, two were caused by adipose liver and both recovered. Two other PDF grafts later developed chronic rejection with vanishing bile ducts, and both were successfully re-transplanted. In one patient PDF was caused by ischaemic graft damage due to cardiac arrest with resuscitation after revascularisation. That patient died after 12 days. One more PDF graft was lost. The late graft failure in one patient with contraindication for liver transplantation at that time recovered after four MARS therapy sessions.

Four patients had miscellaneous causes of liver failure: patient 1 had haemorrhagic pancreatitis, patient 2 had postoperative liver failure after hip arthroplasty and concomitant infectious problems, patient 3 had chronic hepatitis C and multiple trauma after a suicide attempt and patient 4 had myocarditis (diagnosed post-mortem). Of those four miscellaneous patients only the patient with haemorrhagic pancreatitis recovered.

Active bleeding is a contraindication for MARS treatment. Complications connected with MARS were rare and included a few venous-function related haematomas and mild thrombocytopenia. At the beginning of this programme a couple of patients had mucosal bleeding problems, which were later avoided, with intensive follow-up of coagulation factors and adjustment of anticoagulation treatment.

Table 3 Laboratory parameters of liver function. Data are presented as mean (range). *Pre* before MARS treatments,*Post* after MARS treatments, *Alat* alanine aminotransferase (reference values 10–45U/l), *Bil* bilirubin (reference values 5–25 μmol/l), *Crea* creatinine (reference values 50–90 μmol/l), *Urea* blood urea nitrogen (reference values 3–7 mmol/l) *INR* international normalized ratio (0.7–1.2 reference values), *Factor V* coagulation factor five (reference values 79%–129%)

Parameter	ALF ($n=45$)	AcoChr ($n=31$)	Graft failure ($n=8$)
Alat			
Pre	2,566 (13–12,500)	140 (10–897)	2,155 (38–9,460)
Post	670* (15–3,460)	106* (13–692)	5,460 (48–2,5120)
Bil			
Pre	308 (7–725)	473 (143–909)	320 (107–720)
Post	203* (9–460)	276* (132–530)	224 (76–348)
Crea			
Pre	160 (36–1,318)	194 (39–544)	183 (39–301)
Post	82* (17–585)	80* (20–449)	62 (23–107)
Urea			
Pre	8.3 (1–31.2)	18.0 (3.2–56.5)	8 (6.7–32.3)
Post	2.9* (0.5–15.5)	4.4* (1.4–18.2)	4.6 (1.3–10.0)
INR			
Pre	3.5(1.1–8)	2.6 (1–5.6)	2.1 (0.9–6.4)
Post	3.5(1.1–10)	3.0* (1.1–5.3)	2.0 (1.0–2.8)
Factor V (%)			
Pre	41 (5–139)	52 (8–142)	64 (7–114)
Post	54 (7–128)	35* (8–109)	60 (13–107)

*$P < 0.05$ as compared to pre-treatment value

Discussion

During a short time, MARS therapy has gained acceptance in intensive care treatment in the fields of hepatology, liver surgery and transplantation. This has happened despite there being a lack of adequate controlled studies, indicating a desperate need for liver

support devices. We have used MARS therapy in our ICU since May 2001 in patients with decompensated liver failure. The exact clinical conditions to warrant MARS therapy had not been established when we started our study. We analysed the possible advantages and disadvantages in different subgroups of patients with liver failure.

Most of the reports on MARS therapy included only a small number of patients. At present, our material includes the highest number of patients reported in one centre. The main cause of liver failure treated in our centre was ALF. There are no randomised controlled trials focusing on the survival of patients with ALF treated with MARS. One small controlled but non-randomised trial from the Copenhagen group on the effectiveness of one 6 h MARS therapy session showed a tendency for systemic haemodynamic values to normalise [10].

In our study the survival of patients with ALF, with their own livers recovering, was 51%, and the overall survival in ALF was 80%. The US Acute Liver Failure study group of 17 tertiary care centres recently published a 70% overall survival of ALF patients [11]. In that study, the most common cause of ALF was paracetamol intoxication (39% of cases), and only 17% were indeterminate cases. Our material was the opposite: 24% were paracetamol cases and 47% were unknown cases. There is a worldwide agreement that patients with acetaminophen aetiology have a better prognosis than those with unknown aetiology. In our study the best result of own-liver recovery (74%), was achieved in patients with ALF due to toxicity. In accordance with our findings there is a recent MARS study whereby four of six patients with mushroom poisoning recovered without undergoing transplant surgery [12]. Of our ALF patients with unknown aetiology most had to undergo transplant surgery, and the overall survival was 73% in this subgroup, but for the patients who underwent transplantation it was as high as 93%, which is clearly higher than the survival in our earlier series on ALF [9].

A few other groups have studied MARS therapy in ALF patients with different aetiologies, and only on a small number of patients, with different results [13, 14, 15, 16].

It seems that we can support vital organ functions during ALF with MARS in some patients. The best results are achieved in patients who have been poisoned, where the liver still has enough capacity to recover and liver transplantation is not necessarily needed. One explanation for our reasonably good results in these cases could be that therapy was immediately started at admission, before encephalopathy had possibly developed. Removal of toxins, which are formed in liver-cell damage, may have prevented further cell injury. We emphasise that all these patients without encephalopathy had ingested severe amounts of toxin. Therapy was started if the patient had ingested a lethal amount of toxin. In contrast, the majority of the patients with unknown aetiology of ALF had to undergo transplantation. The grade of necrosis in these explanted livers was high (median amount 80%, range up to 100%, data not shown) and in most cases without any signs of regeneration. If the liver cell damage was beyond the critical point whereby recovery was no longer possible, the best that could be achieved with MARS therapy was to gain enough time to find a liver graft for transplantation.

There are many papers on MARS therapy during end-stage liver disease, but only two are proper randomised trials on acute decompensation of chronic liver failure [6, 17]. Both were disclosed by the Ethics Committees due to better short-term survival in the MARS treated patients. The other papers on chronic patients are mostly case reports, based on small numbers of MARS-treated patients [15, 16, 18].

Follow-up times were short in most studies on MARS therapy for AcoChr. Follow-up time in both randomised studies was only 30 days. In both studies the survival in such a short interval was better than expected [6, 17]. There are other reports with a small number of patients who survived the acute phase but died within some weeks without undergoing transplant surgery [14, 18, 19]. In one study the mortality rate was 70%. and survival without a liver transplant only 8% [14].

In our study those with chronic liver disease due to alcoholism, who were not accepted to our transplant program, had a 38% (8/21) 30-day survival but the 180-day survival after starting MARS therapy was only 10%. Only two of the alcoholic patients are alive without having undergone transplantation, with a follow-up of 656 days and 206 days. In the randomised study, including mostly alcoholic patients, short-term survival was favourable for the MARS therapy, but the difference disappeared after 6 months [17]. With MARS therapy we can lighten symptoms, but, in most cases of chronic liver disease, the liver no longer has the capacity to regenerate, and these patients die without undergoing liver transplantation.

A longer life expectancy in patients with chronic disease could be achieved with MARS as a new mode of therapy. However, we do not know the real benefits of MARS therapy for alleviating chronic disease nor do we know which patient groups with chronic liver disease are best suited for MARS therapy.

In ALF patients on MARS therapy resolution of brain oedema and improvement of cerebral perfusion pressure have been described [18], and, also, hepatic encephalopathy has improved in AcoChr [13, 18, 20]. We also found improvement in hepatic encephalopathy in both acute and chronic liver disease groups. The mechanism for this improvement is not known. During liver failure accumulating toxins may have a role in the pathophysiology. Favourable effects of haemodynamics

have also been shown, both in acute and chronic cases [13, 18]. A recent study showed that MARS therapy improved haemodynamics (decreasing portal hypertension and ameliorating hyperdynamic circulation after three sessions, on average, lasting 6.5 h) in four patients with AcoChr liver failure; this was probably mediated by the clearance of vasoactive substances [21].

The kidney function improved especially in ALF patients, which may reflect a different pathophysiology behind the impairment of kidney failure. The patients with acute renal failure who received haemodialysis treatment daily had a better prognosis than those who were treated only when "needed" [22]. Along with MARS treatment we carry out continuous haemodialysis therapy, thus improving and accelerating the recovery of renal function. Some studies have shown improvement in hepato-renal syndrome with MARS therapy [6, 19].

The serum bilirubin level decreased significantly in our patients, as well as in other study groups [6, 13, 19]. In the randomised study on acute decompensation of liver disease, the indication for MARS therapy was hyperbilirubinaemia. We can very effectively decrease the serum bilirubin level with MARS therapy in most cases.

Occasionally after liver transplantation there is a need for artificial liver support in order to gain time for recovery or for retransplantation. Based on the MARS registry, 15% of MARS treatments have been given to patients with liver graft dysfunction [23]. In children, successful MARS therapy has been reported as a bridge to re-transplantation [24, 25]. Of our eight graft failures, six survived, half of them without retransplantation, and the other half were bridged to re-transplantation. In graft failures MARS therapy seems promising, providing time either for the liver to recover or for a suitable graft to be found.

Some other indications of favourable results with MARS therapy are in case reports on Wilson's disease, improving copper metabolism [26]. Patients with high bilirubin-related pruritus have also improved with MARS treatments [27].

MARS is a promising therapy for patients with ALF, allowing either their own liver/liver graft to recover or allowing time for a liver graft to be found. The best results were achieved in patients who had been intoxicated with a lethal dose of toxin. On the other hand, we did not observe much benefit in patients with severe acute-on-chronic liver failure, whereby MARS therapy can prolong life but without improvement in long-term survival without a transplanted liver.

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