

Pre-transplant optimization by Molecular Adsorbent Recirculating System in patients with severely decompensated chronic liver disease

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Background: The outcome of liver transplantation (LT) is influenced by the recipient's clinical condition. In a retrospective observational study, we evaluated the role of pre-LT Molecular Adsorbent Recirculating System (MARS) treatment in improving the clinical status and thereby the outcome of patients with chronic liver disease and severe hepatic decompensation. **Methods:** Between March 2002 and September 2006, 70 patients with end-stage chronic liver disease underwent living-donor LT (LDLT). Of these, 9 (13%) patients with severely decompensated liver function (serum bilirubin >350 $\mu\text{mol/L}$ [20 mg/dL] and/or hepatic encephalopathy \geq grade 2) received pre-LT MARS treatment. **Results:** The median MELD score was 33 (range, 26-47). A median of 2 (range, 1-6) sessions (8 hour/session) of MARS dialysis was performed per patient. MARS treatment was associated with reduction in serum bilirubin, creatinine and ammonia levels, and no procedure-related complications. **Conclusion:** Pre-LT MARS is well tolerated and results in reduction of jaundice and improvement in renal function, and may be useful in the management of patients with severe hepatic decompensation. [*Indian J Gastroenterol* 2007;26:110-112]

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The outcome of liver transplantation (LT) is significantly influenced by the recipient's perioperative condition. Patients with Model of End-stage Liver Disease (MELD) scores above 30 or erstwhile UNOS status 2a have been shown to have a significantly lower short-term graft and patient survival.^{1,2} It is possible that a better outcome can be achieved by pre-transplant optimization of the recipient.

Among the several liver support systems available, the Molecular Adsorbent Recirculating System (MARS) has been the most investigated. This treatment has been shown to result in improvement in serum bilirubin levels, encephalopathy and renal parameters, and possibly in systemic hemo-

dynamic function.^{3,4,5} It is also associated with a reduction in MELD score, through reduction in the serum levels of bilirubin and creatinine.⁶

In this retrospective observational study, we evaluated the role of pre-LT MARS treatment in patients with chronic liver disease and severe hepatic decompensation in improving the clinical condition and the outcome of LT.

Methods

Between March 2002 and September 2006, 82 living-donor LT (LDLT) were performed at our center; of these, 70 (85%) were for chronic liver disease. Pre-LT MARS dialysis had been performed in 9 of these 70 (13%) patients. Records of these 9 patients were retrieved.

These patients had been managed in a liver ICU and had received standard medical therapy (SMT)⁷ in addition to MARS dialysis. Our selection criteria for pre-LT MARS in these patients were: serum bilirubin >350 $\mu\text{mol/L}$ (20 mg/dL) and/or hepatic encephalopathy \geq grade 2. Informed consent for MARS treatment was obtained from the patient or next of kin.

MARS was performed through a standard double-lumen catheter for veno-venous access using the femoral vein. A standard hemodialysis machine (Gambro, Stockholm, Sweden) was coupled to the MARS monitor (Teraklin AG, Rostock, Germany). The MARS circuit was primed with 600 mL of 20% human albumin. Blood flow was set at 250 mL/min and a similar rate was used for the albumin flow rate. Dialysate flow was set at 500-750 mL/min. Dextrose (50%) was infused at a rate of 20 mL/h during MARS, with hourly blood glucose monitoring to prevent hypoglycemia. Heparin was not used. Albumin infusions were withheld temporarily as recommended.³ Inotropes were administered if necessary, to maintain a systolic BP of ≥ 100 mmHg.

Hemogram, coagulation profile, liver and renal function tests were repeated after every MARS

session. Serum bilirubin, creatinine and venous ammonia levels were measured before the first session and after the last session of MARS treatment. Patients with coagulopathy received platelets and fresh-frozen plasma; hence, coagulation parameters were not compared.

Results

The clinical characteristics of the 9 patients who received pre-LT MARS are summarized in the Table. The median pre-MARS MELD score was 33 (range, 26-47). The patients received 1 to 6 (median 2) sessions of MARS dialysis, each of 8 hours' duration. MARS treatment did not result in any overt complications.

Following MARS, serum bilirubin level decreased by median 85 (range 39 to 346) $\mu\text{mol/L}$ (4.97 [2.28 to 20.24] mg/dL), serum creatinine level decreased by 40 (-16 to 69) $\mu\text{mol/L}$ (0.45 [-0.18 to 0.78] mg/dL), and serum ammonia level decreased by 34 (22 to 79) $\mu\text{mol/L}$. Encephalopathy improved in four of 9 patients (#2, 4, 6 and 8).

The time duration from first MARS session till LDLT was 3-10 (median, 5) days. All patients underwent right-lobe LDLT. Eight of 9 patients survived following LDLT, and are alive and well at last follow up; the median duration of follow up of these 8 survivors was 27 (range, 6-59) months. One patient (#3) who had prior chest infection developed multi-organ failure with coagulopathy on postoperative day 2 and died on day 4; autopsy revealed bronchopneumonia and multiple infarcts in the kidneys, spleen and brain.

Discussion

In MARS treatment, blood is dialyzed across an albumin-impregnated high-flux polysulfone dialysis membrane with a pore size of 50 kDa, while a constant flow of albumin-rich (20%) dialysate is maintained. The dialysate takes up albumin-bound toxins, which are a main cause of end-organ dysfunction in liver failure, and removes these from blood.⁴ We withheld albumin infusions temporarily during MARS because bilirubin binds competitively to this albumin and thus withholding it may lead to improved bilirubin clearance with MARS.³ The amount of bilirubin removed is often regarded as a surrogate marker for efficacy of MARS.¹⁰ In this report, the median reduction in the serum levels of bilirubin, creatinine and ammonia was 85 $\mu\text{mol/L}$, 40 $\mu\text{mol/L}$ and 34 $\mu\text{mol/L}$, respectively. Four patients also had improvement in grades of encephalopathy. These results are consistent with other large studies on MARS, which have consistently shown improvement in these parameters^{3,5,10} and in the systemic hemodynamic function.⁴

Whether biochemical improvement after MARS serves as a bridge to recovery of native liver function and influences the outcome of liver disease is controversial. While a few early studies reported better outcome with MARS in comparison to SMT,^{3,4} these results have not been duplicated later.^{5,10}

In a randomized multi-center trial of 70 patients with cirrhosis with advanced grades of hepatic encephalopathy, patients receiving MARS treatment in addition to SMT had significant im-

Table: Clinical and biochemical characteristics at baseline and treatment details in 9 patients who underwent MARS before liver transplantation*

No.	Age / sex	Bilirubin [#]	Creatinine [#]	INR	Ammonia [#]	HE ^{8@}	MELD score ⁶	Child score ⁶	MARS [@]	Duration	Post-LT follow up (mo)
1	61 M	563	226	5.2	142	4	47	13	3	5	8 mo
2	58 F	608	138	2.3	128	3	33	13	2	3	9 mo
3	43 M	559	319	3.9	181	4	47	12	6	10	Died
4	42 M	483	90	1.9	70	2	26	12	1	3	24 mo
5	50 M	509	84	2.6	109	2	30	12	2	7	59 mo
6	62 M	231	138	2.4	148	3	30	13	1	5	33 mo
7	58 M	549	160	1.9	102	2	32	12	1	5	34 mo
8	46 M	997	173	2.5	102	3	38	13	4	5	31 mo
9	51 M	1126	211	1.8	84	2	37	13	2	3	6 mo

*Case #2 had HCV-related disease, #8 and 9 had cryptogenic cirrhosis, the rest had HBV-related disease. HE: grade of hepatic encephalopathy; Duration: duration in days between start of 1st MARS dialysis and LT; INR: international normalized ratio; HBV: hepatitis B virus; HCV: hepatitis C virus; POD: post-operative day; [#]data in $\mu\text{mol/L}$ (conversion of SI units: bilirubin - $\mu\text{mol/L} \times 0.0585 = \text{mg/dL}$, creatinine - $\mu\text{mol/L} \times 0.0113 = \text{mg/dL}$). @: data as number of sessions

provement in bilirubin, creatinine and ammonia levels as well as encephalopathy than those receiving SMT alone. There was however no difference in rate of LT or survival in the two groups. Thus, transplant-free survival rate at 6 months in the MARS group was <10%, similar to that predicted by the MELD score at the time of entry into the study.^{5,11} In a recent study from Hong Kong, none of the 12 patients with acute-on-chronic liver failure who were treated with MARS showed recovery of the native liver function. Two patients underwent LT and one survived, while the remaining 10 died within 30 days despite MARS and SMT.¹⁰

Patients with severe hepatic decompensation are critically ill and are at high risk of post-LT morbidity and mortality. MARS may stabilize their clinical condition and improve their outcome after LT by several mechanisms: clearing of protein-bound toxins, improving cholestasis (thereby accelerating regeneration of allograft liver), improving renal function, decreasing hepatic congestion, and improving systemic hemodynamics and tissue perfusion. In a study of 10 consecutive patients, all 3 patients who underwent MARS before LDLT survived, as compared to none of the 5 patients who received only MARS or of the 2 patients who underwent LDLT without MARS.¹²

The median MELD score in our patients was 33, which is associated with 90-day mortality of >80% without LT.⁶ Eight of our 9 patients survived. One patient died 4 days following LDLT due to coagulopathy and multi-organ failure; the duration between the first MARS session and LDLT in this patient was 9 days. Thus, the window of opportunity in patients with chronic liver disease and failed liver may be small, beyond which the outcome is dismal irrespective of interim liver support with MARS.

In conclusion, in our experience, MARS treatment was safe and well tolerated and resulted in reduction in jaundice with improvement in renal function and encephalopathy. Pre-LT MARS may help improve the outcome of LDLT in patients with decompensated liver function. However, in view of the inherent limitations of a retrospective study, a definitive conclusion about the real value

of pre-LT MARS is not possible and large prospective studies may be necessary.

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Received November 7, 2006. Received in final revised form March 7, 2007. Accepted March 17, 2007