Catholic University Experience With Molecular Adsorbent Recycling System in Patients With Severe Liver Failure


ABSTRACT

Background and aim. Molecular adsorbent recycling system (MARS) treatment is able to remove both hydrosoluble and small- and medium-sized lipophilic toxins. MARS plays an important role in modifying liver failure complications, such as hepatorenal syndrome and hepatic encephalopathy. We sought to evaluate the clinical efficacy and safety of a MARS device in a consecutive series of hepatic failure patients.

Materials. Twenty patients with acute liver failure, transplantation failure, or acute on chronic liver failure fulfilled the inclusion criteria of total bilirubin ≥10 mg/dL and at least one of the following: hepatic encephalopathy (HE) II grade, hepatorenal syndrome (HRS) for chronic patients or total bilirubin ≥5 mg/dL and HE ≥I grade for acute patients.

Results. MARS was able to reduce cholestatic parameters and improve neurologic status and renal function parameters in all treated patients. We also observed an improvement in the 3-month survival rate compared to the expected outcome in patients with MELD scores between 20 and 29, as well as 30 and 39.

Conclusions. Based on these results, we confirm the safety and clinical efficacy of MARS treatment, with the best results in patients with MELD score of 20 to 29. Further studies are necessary to confirm whether this treatment is able to modify patient outcomes and prognosis.

LIVER FAILURE IS characterized by the development of hepatic encephalopathy (HE), jaundice, and coagulopathy. This disorder, which may rapidly progress to multorgan failure (MOF) and death can present as acute liver failure (ALF) or acute on chronic liver failure (AoCLF). ALF is characterized by the onset of coagulopathy and encephalopathy within 8 weeks from presentation of symptoms in an individual with no known underlying liver disease.1,2 Emergent liver transplantation offers the only chance of survival for patients with ALF.3,4 AoCLF refers to an acute liver function deterioration in a patient with previously compensated chronic liver disease caused by the effects of a precipitating event, such as sepsis or upper gastrointestinal bleeding.5 Often complicated by HE6,7 and hepatorenal syndrome,8–10 this pathology has a high mortality caused by MOF. Therefore, in this case orthotopic liver transplantation (OLT) remains the gold standard treatment; so both ALF and AoCLF need a liver support system either to give additional time for recovery of the liver or to serve as a bridge to transplant.

These devices should provide sufficient detoxification capacity without the negative side effects that arise from bioincompatibility and lack of selectivity. The molecular adsorbent recycling system (MARS) is a continuous hemofiltration module based on an albumin-impregnated permeable membrane, able to remove both protein-bound and water-soluble toxins in the low- and middle-molecular-weight range.11–19 These substances include bilirubin, bile...
acids, digoxin-like immunoreactive substances, indoles, phenols, mercaptans, endogenous benzodiazepine, aromatic amino acids, ammonia, and lactate, all of which play a role in hepatic failure.\textsuperscript{20–24} Recently it has been also shown that the MARS is able to significantly reduce the plasma renin levels with remarkable benefit for patients with ALF or AoCLF. Although the pathophysiologic basis of AoCLF and the effects of MARS are not completely known,\textsuperscript{25} previous studies have demonstrated the clearance of these molecules by MARS, leading to recovery from acute liver decompensation and/or providing a bridge to liver transplant.\textsuperscript{22–24,26} The aim of this study was to present our 3-year experience with MARS in terms of clinical efficacy, safety, and outcomes in patients with hepatic failure.

PATIENTS AND METHODS

Twenty patients (mean age 50.1 ± 14.8; 10 men, 4 women) were admitted to our intensive care unit (ICU) between May 2000 and May 2003 due to ALF, AoCLF, primary nonfunction (PNF), malfunction (MF) post-OLT, or chronic graft versus host disease (GVHD). These patients were divided into three groups: Group 1, 13 patients affected by AoCLF (mean age 49.7 years ± 17.7; M/F 8/5); Group 2, 4 patients with liver failure post-OLT, owing to PNF, MF or GVHD (mean age 49.2 years ± 14.5; M/F: 2/2); and Group 3: 3 patients with ALF (mean age 50.7 years ± 6.1, M/F: 0/3). A total of 72 MARS treatments were performed on the 20 patients, 11 of whom were awaiting OLT; the other 9 did not present criteria for OLT because of age >65 years or recent alcohol abuse. During the 3 days before treatment, the most important hematochemical and laboratory parameters were monitored and standard medical therapy (SMT) delivered in all 20 patients.

Despite standard medical therapy, all patients showed increasing cholestatic decompensation (total bilirubin >5 mg/dL), without evidence of extrahepatic origin, and presented with hepatorenal syndrome (HRS) and/or HE grades II. Exclusion criteria were age <18 and >70 years; hemodynamic instability (mean arterial pressure [MAP] < 60 mm Hg) despite vasopressor agent, pregnancy/lactation, cerebral hemorrhage, intractable or active gastrointestinal bleeding, severe cardiopulmonary disease (NYHA >2), HIV infection, disseminated intravascular coagulation, or neoplasia. Within the first 24 hours, the following evaluation scores were calculated: UNOS...
Hemodynamic parameters were continuously recorded using a right atrial catheter and an arterial catheter. Low-dose Norepinephrine (0.1 to 0.3 μg/kg/min) was used to keep a MAP above 60 mm Hg when the CVP was 8 to 12 cmH2O. Hemodialysis treatment (continuous venovenous hemodiafiltration and/or conventional hemodialysis) was performed when urinary output was <500 mL/day and diuretic therapy failed.

Liver biochemistry, coagulation tests, complete blood cell counts, serum electrolytes, ammonia, lactate, blood urea nitrogen (BUN), creatinine levels, bile acids, and arterial blood gases were determined daily as well as 1 hour before and 1 hour after each MARS treatment. The ratio of branched-chain acids (leucine, isoleucine, valine) to aromatic amino acids (phenylalanine, tyrosine), namely the Fischer ratio, was calculated at the beginning and end of each MARS treatment. The study was undertaken with the approval of the Ethics Committee; informed consent in writing was obtained from each patient or next of kin.

RESULTS

MARS therapy was well tolerated by all patients: 67 out of 72 (93%) treatments did not cause side effects. Among the other 5 patients (7%): MARS filter breakage with a decrease in hemoglobin up to 1.5 g/dL was observed in 1 patient; hematoma at CVC site placement in another; and a decrease in hemoglobin up to 1.5 g/dL was observed in 1 other 5 patients (7%). MARS filter breakage with a decrease in hemoglobin up to 1.5 g/dL was observed in 1 another 5 patients (7%).

DISCUSSION

In the last decade, several artificial systems have been proposed to support patients with liver failure until hepatic regeneration or OLT. At present, liver support devices include bioartificial systems and MARS. Because of the biological component, bioartificial systems should ensure complete metabolic support synthesis, detoxification and biochemical functions—while the MARS can only guarantee toxin clearance from the blood. The MARS has improved renal function parameters. In the two patients with intractable pruritus, MARS allowed complete control of symptoms, with a remarkable improvement in their quality of life.

Our experience confirms the good safety profile demonstrated in previous studies; no significant thrombocytopenia or other major complications or adverse events were observed during the procedure. Moreover, all patients were hemodynamically stable without any change in heart rate, mean arterial pressure on $SVO_2$ during or after each MARS treatment.

In our experience, the MARS treatment significantly reduces the plasma levels of bilirubin, biliary acids, ammonia, BUN, and creatinine. In all patients we observed an improvement or stabilization of HE, symptoms, with a remarkable improvement in their quality of life.

The decreased pruritus was maintained up to 90 days after treatment. By considering the outcome, in the first group (AoCLF) two patients (15%) showed a good recovery of hepatic function, while nine patients (70%) died and two (15%) were transplanted (Table 1). In the second group, (LTxF) two patients recovered hepatic function, and two patients died before transplant (Table 2). In the third group (ALF), one patient (33%) died before transplant because of severe respiratory failure, and the other two (67%) have been transplanted (Table 3). MELD scores calculated in patients of the first group and second group (AoCLF and LTxF) were compared to the expected survival rate within 90 days. Five patients with MELD score between 20 and 29 (24% expected survival rate) showed a 60% survival rate; seven patients with MELD score between 30 and 39 (17% expected survival rate) showed a 29% survival rate. In patients with MELD score > 40, the mortality rate within 90 days was 100%, as expected.

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<table>
<thead>
<tr>
<th>Patient</th>
<th>OLT</th>
<th>Outcome at 90 Days</th>
<th>Survival Time After MARS (d)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Yes</td>
<td>Alive (OLTx)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P2</td>
<td>No</td>
<td>Dead</td>
<td>7</td>
<td>MOF</td>
</tr>
<tr>
<td>P3</td>
<td>Yes</td>
<td>Alive (OLT)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P4</td>
<td>No</td>
<td>Dead</td>
<td>10</td>
<td>Septic shock</td>
</tr>
<tr>
<td>P5</td>
<td>No</td>
<td>Dead</td>
<td>31</td>
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</tr>
<tr>
<td>P6</td>
<td>No</td>
<td>Dead</td>
<td>17</td>
<td>GI bleeding</td>
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<tr>
<td>P7</td>
<td>No</td>
<td>Dead</td>
<td>10</td>
<td>MOF</td>
</tr>
<tr>
<td>P8</td>
<td>No</td>
<td>Alive (recovery)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P9</td>
<td>No</td>
<td>Dead</td>
<td>20</td>
<td>Cardiovascular failure</td>
</tr>
<tr>
<td>P10</td>
<td>No</td>
<td>Dead</td>
<td>11</td>
<td>MOF</td>
</tr>
<tr>
<td>P11</td>
<td>No</td>
<td>Dead</td>
<td>7</td>
<td>MOF</td>
</tr>
<tr>
<td>P12</td>
<td>No</td>
<td>Alive (recovery)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P13</td>
<td>No</td>
<td>Dead</td>
<td>2</td>
<td>Cardiac Failure</td>
</tr>
</tbody>
</table>

Table 1. Complications and Outcomes in Patients with AoCLF

Table 2. Complications and Outcome in Patients With LTxF
although not always related to reduction of the ammonia. Therefore it seems that the MARS may clear other substances involved in the pathogenesis of the HE.\(^{27,28}\) As regards the outcome, four patients, awaiting OLT have been successfully supported until transplantation. Four more patients experienced a good recovery of hepatic function (two patients waiting and two patients not awaiting OLT). Because of the small number of patients treated and the lack of a control group, we cannot provide a definitive judgement on the MARS effects.

Recent studies did not confirm a remarkable efficacy of MARS in patients with liver failure. In particular, a recent meta-analysis has shown that MARS treatment had no significant survival benefit compared with standard medical therapy.\(^{29}\) The most important limitation of MARS is the lack of synthetic activity, although some authors have described an improvement in synthetic function when evaluating plasma increase in clotting factors V and VII.\(^{30}\)

In conclusion, our data confirm the safety and clinical efficacy of MARS treatment. In our series the best results were observed among patients with MELD scores between 20 and 29. However, further controlled trials, conducted on strictly selected and stratified patients, are needed to define the subgroups of patients who could really benefit of MARS and the most appropriate timing of the intervention.

REFERENCES


Table 3. Complications and Outcome in Patients With ALF (Group 3)

<table>
<thead>
<tr>
<th>Patient</th>
<th>OLT</th>
<th>Outcome at 90 Days</th>
<th>Survival Time After MARS (d)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>P18</td>
<td>No</td>
<td>Dead</td>
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<tr>
<td>P19</td>
<td>Yes</td>
<td>Alive</td>
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<td>—</td>
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<tr>
<td>P20</td>
<td>Yes</td>
<td>Alive</td>
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<td>—</td>
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