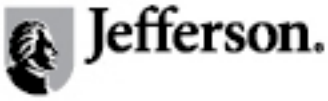

1-1-2017

Extracorporeal membrane oxygenation with multiple-organ failure: Can molecular adsorbent recirculating system therapy improve survival?

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EXTRACORPOREAL MEMBRANE OXYGENATION WITH MULTIPLE-ORGAN FAILURE: CAN MOLECULAR ADSORBENT RECIRCULATING SYSTEM THERAPY IMPROVE SURVIVAL?

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Short title: ECMO with MARS.

Total word count: xxx

Key words: ECMO; Multi organ failure; Liver failure; MARS.

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This paper was accepted for presentation at 36th Annual Meeting and Scientific Sessions, International Society of Hear and Lung Transplantation, April 2016, Washington DC.

Abstract

Background: Liver dialysis, molecular adsorbent recirculating system (MARS) particularly, has been used in liver failure to bridge to transplantation. We expanded the indication for MARS to patients with acute shock liver failure and cardiopulmonary failure on ECMO, aiming to improve survival to wean from ECMO.

Methods: An IRB approved, retrospective chart analysis of patients on ECMO between 2010 and 2015 found 28 patients who met the criteria for acute liver failure, diagnosed by hyperbilirubinemia (total bilirubin $\geq$ 10 mg/dl), or by elevated transaminase (alanine transaminase [ALT] >1000 IU/L). Among those, 14 patients underwent MARS treatment (Group M) and 14 patients were supported with optimal medical treatment without MARS (Group C). Patient characteristics, liver function and survival were compared between groups.

Results: Demographics, clinical risk factors, and pre-ECMO laboratory data were identical between the groups. MARS was utilized continuously for 8 ± 9 days in Group M. Total bilirubin, ALT, and international normalized ratio (INR) were improved significantly in Group M. There were no MARS-related complications. Survival to wean from ECMO for Group M was 64% (9/14) versus 21% (3/14) for Group C, p = 0.02. Death related to worsening liver dysfunction during ECMO was 40% (2/5 deaths) in Group M and 100% (11/11 deaths) in Group C, p=0.004. Thirty-day survival after ECMO was 43% (6/14) in Group M and 14% (2/14) in Group C, p=0.09.

Conclusions: MARS therapy on ECMO patients safely accelerated recovery of liver function and improved survival to wean from ECMO, without increasing complications.

Introduction

In cases of acute-on-chronic liver failure, liver dialysis, specifically the molecular adsorbent recirculating system (MARS) has been used to bridge patients to liver transplantation and is known to improve outcomes of liver transplantation. [1, 2] MARS therapy consists of filtering blood through a specialized albumin-containing dialysate to remove protein-bound toxins. Blood is filtered in-line through a charcoal column and an anion exchanger column before return. This system allows for the removal of molecules such as bile acids, bilirubin, and cytokines, as well as water-soluble toxins such as creatinine and ammonia. [3] By removing both protein-bound and water-soluble toxins, MARS facilitates liver recovery and also may prevent further deterioration of other organ systems. [4]

Overall ECMO mortality is reported to be 47%-61%, [5] and one of the primary causes of death for extracorporeal membrane oxygenation (ECMO) patients is refractory multiple-organ failure including acute liver failure. Acute liver failure (ALF) occurs in ~13-19% of the ECMO population. [6] In our institution, we expanded the indication for MARS to another patient population – cardiopulmonary failure patients requiring ECMO who have developed acute liver failure. This retrospective study was performed to evaluate the questions: can MARS improve acute liver failure on ECMO safely, and to evaluate the survival of the patients with or without MARS treatments on ECMO.

Methods

After approval from the institutional review board, medical records of consecutive ECMO patients between August 2010 and March 2015 were retrospectively reviewed to identify the incidence of liver dysfunction while on ECMO. The only exclusion criterion was any ECMO patient in whom treatment was deemed futile within the first 24 hours of cannulation. Veno-arterial ECMO (VA ECMO) was primarily used for refractory cardiac failure, [7] and veno-veno ECMO (VV ECMO) was primarily used for refractory respiratory failure, [8] detailed in the previous publications.

Among the 133 ECMO patients during the study period, 28 patients (21%) were found to have acute liver failure, defined as total bilirubin $\geq$ 10 mg/dl or alanine aminotransferase (ALT) $\geq$ 1000 IU/L. Further details for inclusion data are shown in Table 1. These patients were included if they met the

criteria for liver failure despite correction of an underlying process such as hemolysis or obstructive cholangitis. The rounding attending physician made the decision for the initiation of MARS. Of the 28 studied patients, 14 patients (Group M) underwent liver dialysis using MARS (Gambro, Lakewood, CO, USA), and 14 patients (Group C) were supported with optimal medical therapies. Medical therapies for Group C and Group M included maintenance of appropriate ECMO flow (body surface area x 2.2 L/min or above), lactulose treatment, nutrition support (via either enteral tube feeding or total parenteral nutrition), and avoidance of hepatotoxic medications, including statins and Amiodarone. In Group M, the MARS system was run with blood flow rates between 100 – 150 ml/min using a standard dual lumen dialysis catheter placed in the femoral vein, using a 25% albumin dialysate. Treatment was continued until recovery of liver function; specifically, total bilirubin returned to $\leq$ 7 mg/dl and/or ALT $\leq$ 500 IU/L, or the time of ECMO removal. No patient was placed on MARS with the intention to bridge to liver transplantation. The MARS circuit was maintained continuously, excepting for circuit changes needed every 24 hours. Anticoagulation was maintained for a PTT between 45-55 seconds for ECMO regardless the presence of MARS.

Primary study endpoints were survival to wean from ECMO and 30-day survival after ECMO decannulation. A secondary endpoint was the trend of liver function (total bilirubin, alanine aminotransferase [ALT], and international normalized ratio [INR]) during treatments. In addition, bleeding complications and disseminated intravascular coagulopathy (DIC) were monitored during ECMO.

Data were expressed as number with percent and mean with standard deviations. Statistical analysis consisted of two group comparisons between Group M and Group C using Student t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. A p-value less than 0.05 was considered to be significant.

Results

There were 14 patients in Group M and 14 patients in Group C. Baseline characteristics, pre-ECMO clinical risk factors, and laboratory data were compared and were similar between the two

groups (Table 2). Group C and Group M both include patients from overlapping timeframes – Group C was not from an era prior to availability of MARS therapy.

The laboratory values for the patients at the time criteria of acute liver failure were met are shown in Table 3. MARS therapy was initiated in mean of 5 ± 4 days after ECMO was started in Group M. The length of ECMO before the patients met the criteria for acute liver failure in Group C was 7 ± 6 days. The average length of MARS on ECMO was 8 ± 9 days (range 1 – 32 days). After 3 days, total bilirubin average for Group M (n=12) decreased by 5.1 ± 12 mg/dL, while Group C (n=9) average total bilirubin increased 2.6 ± 9 mg/dl ($p = 0.11$). By day 7, the average total bilirubin for Group M (n=11) had decreased by 7.9 ± 15 mg/dL, while in the same time period the average bilirubin for Group C had increased by 7.5 ± 6 mg/dL ($p = 0.01$). By day 3, ALT for Group M had decreased by 1310 ± 1851 IU/L while in Group C the ALT had increased by 320 ± 733 IU/L ($p = 0.01$). Similarly, by day 3, INR for Group M had decreased by 0.32 ± 0.5 while in Group C the INR had only decreased by 0.05 ± 0.4 IU/L ($p = 0.19$). These trends are shown in Figure 1. Furthermore, these trends continued for the duration of ECMO, as shown in Figure 2.

Bleeding complications while on ECMO, defined as bleeding that required invasive intervention, were 79% (n=11) in both groups. The most common etiologies were gastrointestinal bleeding, epistaxis, and cannula site bleeding; this breakdown was consistent across both groups. Incidence of disseminated intravascular coagulopathy (DIC) was 14% (n=2) for Group M vs. 21% (n=3) for Group C ($p = 0.62$). The causes of DIC were multifactorial, and did not appear to be related to MARS treatment. There was no MARS-related sepsis. There were no mechanical ECMO complications, such as flow competition, during MARS.

Survival to wean from ECMO was 64% (9/14) in Group M and 21% (3/14) in Group C, $p=0.02$ (Figure 3). Death related to worsening liver dysfunction was 40% (2/5 deaths) in Group M and 100% (11/11 deaths) in Group C ($p=0.004$). Of the patients to survive to wean off of ECMO, only 2 patients (22%) in Group M continued MARS treatment and in both of those cases, liver function was eventually normalized. Five patients (56%) in Group M weaned to a permanent mechanical circulatory support

device, versus only 1 patient (33%) in Group C (p=0.06). Thirty days survival after ECMO decannulation was 43% (6/14) in Group M and 14% (2/14) in Group C, p=0.09 (Figure 3). The patients in Group M who survived to wean off of ECMO all recovered liver function, therefore liver failure was not a contributing factor to their death.

Discussion

The research on MARS for patients with cardiopulmonary failure requiring ECMO is very sparse. Zitterman [9] used MARS for liver failure due to cardiogenic shock following cardiac surgery. The study involved 197 post-operative patients with a bilirubin > 6 mg/dl, of which 20 (10%) required ECMO. They reported many complications (gastrointestinal, respiratory, and infections) and had an in-hospital mortality rate of 66% (n=129) after MARS initiation. Total bilirubin did not decrease in their cohort overall, though the survivors did show a significant decrease compared with non-survivors. Based on APACHE II, SOFA, and SAPS II scores, they determined a predicted mortality of 100%, which improved to 34% (n=68) with MARS usage. [9] Survival within the ECMO population specifically was not discussed. In the only study specifically involving ECMO patients, Peek [10]reviewed their series of ECMO prior to the use of MARS and found that no ECMO patients at their institution survived once severe liver dysfunction (total bilirubin > 23 mg/dl) developed and only 10% survived if bilirubin was greater than 17 mg/dl. With this prior survival data, Peek et al. changed their indication to initiate MARS to include patients with bilirubin greater than 17 mg/dl. Using MARS with this indication, 2/5 (40%) of the patients survived, compared to a prediction of 100% mortality. [10]

While we were able to show that survival was improved in Group M versus Group C, it is equally important to note that complications from using the treatment did not arise. In the two cases of DIC within the treatment group, the causes were multifactorial, and did not appear to be related to MARS. One of the patients was an acetaminophen overdose who was never stabilized following cardiac arrest and ECMO, while the other was due to possible hemolysis after a prolonged course on ECMO requiring three different mechanical circulatory support devices. Complications occurring in the ICU course for both

groups were similar, and specifically, incidence of DIC was similar, with no indication MARS was the cause of any case of DIC.

In another study, Rittler[11] reviewed 5 patients after Whipple's operation or liver transplantation complicated with liver failure and gram-negative sepsis and/or fungemia. In that particular population with liver failure accompanied by sepsis, despite the use of MARS, no patients survived. They also reported significant bleeding side effects in this group, although they were using heparin to maintain PTT > 50 seconds to anti-coagulate the MARS system. They concluded that sepsis-related liver failure might not be an indication for MARS therapy. [11] In our study, sepsis was not the primary cause of shock liver, but 2 patients in Group M (14%) and 3 patients in Group C (21%) were septic during the study. The patients in Group M did not have any of the complications seen in the Rittler study. Those 2 patients in Group M survived, while none of the 3 septic patients in Group C survived to wean off of ECMO ($p = 0.03$).

Prior studies on the effectiveness of MARS in the acute-on-chronic liver failure population have found that treatment can improve hemodynamic status or have an effect on coagulation.[1,12] We found an improvement of INR while on MARS (Figures 1 & 2); however, we were not able to identify the hemodynamic improvement, maybe because hemodynamics were already supported by ECMO.

Our study supports that acute liver failure during ECMO can be supported with MARS and that once liver functions are normalized, no additional MARS are necessary. Additionally, the fact that five of the patients in Group M were implanted with ventricular assist devices points to recovery of end organ function, without any neurological deficits. Without recovery of liver function, these patients would not have been device candidates.

The decision to start MARS treatment was most often based upon increased total bilirubin. However, we found the Group M had significantly higher liver enzymes as well. Group M also met criteria for acute liver failure sooner after ECMO initiation (3 ± 3 days) than Group C (6 ± 7 days). By day 3 after inclusion, only 70% (10/14) of the patients in Group C were alive, dropping to 36% (5/14) survival by day 7. This is compared to 79% (11/14) survival to day 7 in Group M ($p=0.02$). This

illustrates that medical therapy alone is not enough to stop the progression from acute liver failure to death in this patient population. All patients in the treatment group showed total bilirubin that trended downward by day 3, and continued downward until MARS was stopped (Figure 2) - suggesting that liver function recovered.

The main limitation of this study was small sample size, retrospective, single center experience. The decision to initiate MARS therapy was a clinical judgment base on the attending physician's assessment at the bedside and thus the two groups were not randomized. This study does not address discharge survival data. Because many surviving patients in Group M went on to receive permanent mechanical circulatory support devices, they required a more prolonged hospital stay. Survival to discharge data in that group would have many other confounding variables from those other forms of mechanical support devices as well as from the prolonged hospital stay. Going forward, research is needed to further refine the appropriate patient selection criteria and to initiate optimal treatment guidelines, as well as to determine if MARS therapy increases survival to discharge.

Study Highlights

At this time, the use of MARS liver dialysis for acute-on-chronic liver failure to prolong survival until transplantation has been accepted. [1,2] However, the research on expanding the use of MARS to other patient populations has demonstrated mixed results, regarding both safety and efficacy. This study looked at a specific population – multiple-organ failure patients on ECMO with acute liver failure – in order to determine if MARS could improve survival to wean off ECMO. The results showed that without increasing complications, MARS could safely improve survival outcomes and accelerate liver recovery within this patient population. ECMO is widely used to support the patient while the heart and/or lungs recover, the results of this study indicate that the liver can recover in the same manner if the patient is supported with the MARS liver dialysis system.

Conclusion

The results of this study show that the MARS system for liver dialysis can safely and effectively be used for acute liver failure in cardiopulmonary failure patients who are being supported by ECMO in order to accelerate liver recovery. Survival benefit by MARS was clearly demonstrated, without any additional increase in complications.

Financial Conflict of Interest Disclosure

No conflicts of interest to disclose for any authors. No funding was received for this research.

Table 1: Inclusion Criteria for MARS on ECMO.

	Group M (N=14)	Group C (N=14)	P - value
Hyperbilirubinemia (>10mg/dl)	11	14	0.0668
Increased ALT (>1000 IU/L)	3	0	0.0668
Hyperbilirubinemia (>10mg/dl) and increased ALT (>1000 IU/L)	4	2	0.3570

ALT: alanine aminotransferase. Data expressed as number.

Table 2: Baseline Demographics and Indications for ECMO.

	Group M (n=14)	Group C (n=14)	P- value
Age (years)	44 ± 16	54 ± 13	0.0811
Male	5 (36%)	9 (64%)	0.1306
Body mass index (kg/m^2)	27 ± 6	28 ± 5	0.6359
Weight (kg)	76 ± 26	78 ± 21	0.8246
Clinical risk factors			
Smoker	5 (36%)	3 (21%)	0.4028
E-CPR	3 (21%)	2 (14%)	0.6217
Diabetes mellitus	4 (29%)	4 (29%)	1.0000
Coronary artery disease	4 (29%)	8 (57%)	0.1266
Acute myocardial infarction	3 (21%)	1 (7%)	0.2801
Primary respiratory failure	3 (21%)	4 (29%)	0.6625
Primary Diagnosis for ECMO			
Acute on chronic heart failure	4 (29%)	3 (21%)	0.6625
Malignant Arrhythmia	2 (14%)	0 (0%)	0.1422
Takotsubo Cardiomyopathy	0 (0%)	2 (14%)	0.1422
Bacterial Pneumonia	0 (0%)	1 (7%)	0.3085
Interstitial Pneumonitis	1 (7%)	0 (0%)	0.3085
Aspiration Pneumonia	0 (0%)	2 (14%)	0.1422
Viral Pneumonia	0 (0%)	1 (7%)	0.3085
Post-cardiotomy failure	5 (35%)	4 (29%)	0.6857
Acute Myocardial Infarction	2 (14%)	1 (7%)	0.5412
Pre ECMO laboratory data			
Creatinine (mg/dl)	1.7 ± 1	1.8 ± 0.99	0.7522
Total bilirubin (mg/dl)	2.9 ± 3.1	3.3 ± 3.2	0.7611
Aspartate aminotransferase (IU/L)	3198 ± 9997	784 ± 1610	0.3984
Alanine aminotransferase (IU/L)	770 ± 1884	351 ± 751	0.4642
Alkaline phosphatase (IU/L)	139 ± 100	107 ± 78	0.3704
Lactate (mg/dl)	7.4 ± 7.5	6.6 ± 5.2	0.7521
INR	1.99 ± 1.10	1.98 ± 0.89	0.9589
ECMO data			
Veno-arterial ECMO	11 (79%)	11 (79%)	1.0000
Veno-venous ECMO	3 (21%)	3 (21%)	1.0000
Length of ECMO (days)	17 ± 9	12 ± 10	0.1761
ECMO complications			
Bleeding	10 (71%)	11 (79%)	0.6625
Disseminated intravascular coagulopathy	2 (14%)	3 (21%)	0.6217

DIC: disseminated intravascular coagulopathy; E-CPR: extra-corporeal membrane oxygenation assisted cardiopulmonary resuscitation; ECMO: extra-corporeal membrane oxygenation; INR: international normalized ratio
Data are expressed as mean ± standard deviation or as number (percentage).

Table 3. Laboratory Data at Inclusion.

	Group M (N=14)	Group C (N=14)	P-value
Duration of ECMO before MARS in group M and before met criteria of acute liver failure in group C (days)	5 ± 4	7 ± 6	0.31
On CVVHD pre-MARS	6 (43%)	9 (64%)	0.2556
Creatinine (mg/dl)	1.3 ± 0.5	1.3 ± 0.7	1.0000
Bilirubin (mg/dl)	10.5 ± 3.3	11.8 ± 1.9	0.2128
Aspartate aminotransferase (IU/L)	9412 ± 13430	492 ± 698	0.0199
Alanine aminotransferase (IU/L)	2271 ± 2577	193 ± 210	0.0058
Alkaline phosphatase (IU/L)	162 ± 83	113 ± 47	0.0656
Lactate (mg/dl)	8.2 ± 8.0	6.8 ± 7.5	0.6369
INR	1.86 ± 0.57	1.52 ± 0.43	0.0865
MELD Score	29 ± 6	30 ± 5	0.6359

CVVHD: continuous veno-veno hemodialysis; ECMO: extra-corporeal membrane oxygenation; INR: international normalized ratio; MARS: molecular adsorbent recirculating system; MELD Score: Model for End-Stage Liver Disease Score.
Data expressed as mean ± standard deviation or as number (percentage).

Legends of Figures

Figure 1: 1a) Trends of total bilirubin; 1b) Trends of alanine aminotransferase (ALT); 1c) Trends of international normalized ratio (INR).

Figure 2: 2a) Trends of total bilirubin in Group M; 2b) Trends of alanine aminotransferase (ALT) in Group M; 2c) Trends of international normalized ratio (INR) in Group M.

Figure 3: Survival data.

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