

Acute liver failure and the molecular adsorbents recirculating system: Early experience in a tertiary care hospital in Mexico City

Nahum Méndez-Sánchez,¹ Norberto C. Chávez-Tapia,¹ Beatriz Espinoza,¹ Magali Herrera-Gomar,¹ Daniel Zamora-Valdés,¹ Misael Uribe¹

Abstract

Acute liver failure is a clinical condition associated with high mortality despite recent technological advances. Supportive devices such as the Molecular Adsorbents Recirculating System (MARS®) provide therapeutic strategies to add time to find an organ for orthotopic liver transplantation or to allow the native liver to recover sufficiently to make transplantation unnecessary. In this series of cases, we discuss our initial experiences with three patients with acute liver failure. One patient had high bilirubin levels caused by Epstein–Barr virus infection and responded well after three MARS sessions. In a second patient, MARS therapy was used to treat acute-on-chronic liver failure caused by chronic hepatitis B virus infection that had not been treated previously; because of severe hemodynamic compromise, only one MARS session was performed. The third patient had an initial diagnosis of acute liver failure and cryptogenic hepatitis, and was treated with five MARS sessions as a supportive measure until the definitive diagnosis (metastatic disease) was performed. In all patients, MARS therapy was well tolerated and induced only mild hypokalemia. In conclusion, although MARS therapy was an effective strategy for these cases of liver failure and greatly improved the biochemical variables, its impact on the mortality rate has not yet been determined.

Key words: Liver failure, cholestasis, molecular adsorbents recirculating system, Epstein-Barr virus, hypokalemia.

Introduction

The liver is a unique organ implicated in several physiological processes. One of its most important functions relates to the metabolic pathways involved in the biochemical modification and detoxification of substances absorbed in the digestive tract. However, many circumstances may cause serious changes in liver physiology. Acute liver failure was reported systematically in 1959 by Trey and Davison. Although acute liver failure can have many etiologies,^{3–8} the pathophysiological processes are similar. The most important clinical manifestations are hepatic encephalopathy caused by neurotoxins, brain edema, and impaired cerebral blood flow induced by the pathogenic pathways.^{9–11} In recent years, the mortality rate associated with acute liver failure has declined from 100% to 60–70%.¹² However, despite this decline in the mortality rate, cases can rapidly progress to coma and death. In most cases, the most useful treatment is orthotopic liver transplantation, but, unfortunately, this procedure is available in only ~30% of cases.¹³ The potential for rapid progression to death and the relatively high mortality rate have stimulated interest in developing liver-support devices to maintain the patient's life through the crisis and provide more time either to find an organ (“bridge”) for orthotopic liver transplantation or to allow the native liver to recover sufficiently and make transplantation unnecessary.¹⁴

Two basic approaches are under development: bioartificial devices, which use hepatocytes to perform the functions of the failing liver, and artificial devices, such as the Molecular Adsorbents Recirculating System (MARS®), which use the principles of albumin dialysis. Experience with MARS has not been reported previously in the Mexican population. We report our initial experiences with three patients with acute liver failure who received MARS therapy.

Patients

Patient 1. A 73-year-old man had complaints characterized by jaundice, dark urine, and white feces, but without other physical findings or other diseases. The liver functions tests showed moderately elevated levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin (25.95 mg/dL) (*Table I*). The serological analy-

¹ Liver Research Unit. Medica Sur Clinic & Foundation, Mexico City, Mexico.

Address for correspondence:
Nahum Méndez-Sánchez, M.D., Ph.D.
Departments of Biomedical Research, Gastroenterology & Liver Unit,
Medica Sur Clinic & Foundation, Puente de Piedra 150, Col. Toriello
Guerra, Mexico City, Mexico. Phone: (+525) 55606-6222, ext. 4215
Fax: (+525) 55666-4031 and 55606-1651;
E-mail: nmendez@medicasur.org.mx

ses for hepatitis A virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) were negative. Other causes of liver disease such as hemochromatosis and autoimmune hepatitis were excluded, and tests for antimitochondrial antibodies, antismooth muscle antibodies, antimicrosomal antibodies were negative. The viral capsid antigen test for Epstein–Barr virus (EBV) was positive. Abdominal ultrasound and MRI cholangiography demonstrated moderate bile duct dilatation. A percutaneous liver biopsy and immunohistochemical analysis (latency protein membrane) were performed, leading to a diagnosis of hepatitis associated with EBV infection. Because of increasing jaundice, the patient underwent three MARS therapy sessions. The only side effect reported was hypokalemia. No steroids or antiviral drugs were administered and the patient is now asymptomatic.

Patient 2. A 53-year-old man had cirrhosis due to chronic HBV infection and had not been treated previously. The clinical manifestations were acute hepatic encephalopathy and ascites. Paracentesis was performed and 4,000 cc of ascites fluid was removed and albumin replaced. Treatment for shock and inotropic support were necessary. One session of MARS therapy was started and was well tolerated. Hypokalemia was the only side effect associated with MARS therapy. The patient developed hepatorenal syndrome and died (*Table I*).

Patient 3. A 73-year-old man had previous bladder cancer treated with resection and chemotherapy based on platin. His main complaints were jaundice, hepatic encephalopathy, and abdominal pain. Serological analyses for hepatitis A virus, HBV, and HCV were negative (*Table I*), and MRI cholangiography showed bile duct dilatation. Supportive medical measures were started, and a percutaneous liver biopsy was performed. Five sessions of MARS therapy were performed before a definitive histopathological diagnosis was available. There were improvements in the liver function test and the grade of he-

patic encephalopathy. Metastatic bladder disease was diagnosed and the MARS therapy was stopped. The patient developed hepatorenal syndrome and died.

Discussion

We have reported our experience using MARS therapy to treat three patients with diverse cases of acute liver failure, ranging from disease caused by common infection (HBV) to severe atypical viral infection (EBV) and unsuspected metastatic disease. Despite these differences, all patients shared the same clinical entity: acute liver failure. We report the first application of MARS therapy to treat a patient with hepatic fulminant hepatitis associated with EBV infection. There are no recommendations for managing patients with acute liver failure associated with EBV infection, although some have used immunosuppressive agents, antiviral drugs, or steroid therapy, which may not be beneficial.^{15–17} Our case of EBV hepatitis was aggressive with high bilirubin levels (25.95 mg/dL) requiring MARS therapy to enhance liver recovery. In the first three hours of the MARS session, bilirubin levels declined significantly from 25.84 to 17.7 mg/dL. The support of MARS enabled the liver to recovery and a good outcome was obtained. We did not use steroid or antiviral therapy, and found that only this highly specialized supportive therapy was necessary.

The second patient had chronic liver disease associated with HBV and hepatic encephalopathy and ascites. In addition to MARS therapy, we found it necessary to provide inotropic support and mechanical ventilation because of the severe clinical status; however, hepatorenal syndrome developed. Chen et al.¹⁸ recently reported their experience with 52 liver failure patients with severe HBV infection who underwent intermittent MARS therapy for six to eight hours per session in addition to standard medical treatment. They showed decreases in the levels of serum bilirubin,

Table I. Main characteristics of patients under MARS therapy.

Variable	Patient 1	Patient 2	Patient 3
Diagnosis (etiology)	Severe colestasis (EBV)	Acute liver failure (HBV)	Acute liver failure (metastatic bladder cancer)
Sex	Male	Male	Male
Age (yr)	73	53	73
MARS sessions (#)	3	1	5
Prior MARS therapy bilirubin (mg/dL)	25.95	24.10	18.90
DB/IB (mg/dL)	13.23/10.72	12.56/11.60	10.2/8.70
PT (s)	13.1	22.7	25.0
Albumin (g/dL)	1.69	1.97	3.03
HE	–	++	+
Complications	Hypokalemia	Hypokalemia	Hypokalemia
Outcome	Survived	Died	Died
Cause of death	–	Multiorgan failure	Metastatic cancer

Abbreviations: MARS: Molecular Adsorbents Recirculating System; EBV, Epstein–Barr virus; HBV, Hepatitis B virus; DB, direct bilirubin; IB, indirect bilirubin; PT, prothrombin time (control 9.1–12.2 s); HE, hepatic encephalopathy.

ammonia, urea nitrogen, fragrant amino acids, endotoxin, IL-6, and TNF- α . Their most important finding was that patients who receive MARS therapy had a higher overall survival rate, indicating that MARS therapy could improve the survival rate in patients with liver failure.

The third patient was an interesting case who we initially considered to have cryptogenic acute liver failure. We performed MARS therapy because of the severe hepatic encephalopathy; however, we stopped the MARS therapy when the diagnosis from the biopsy was metastatic disease. Tan et al.¹⁹ used MARS therapy in patients critically ill with advanced malignancy but all subjects eventually died. However, they showed that MARS was well tolerated by these patients and improved their biochemical variables without major complications, but did not improve mortality rate. Faybik et al.²⁰ reported their use of MARS therapy in a patient with advanced malignancy of the pancreas and acute liver failure because of ischemic hepatitis and multi-organ failure resulting from prolonged hemorrhagic shock. In that case, MARS therapy was a good supportive measure and affected this individual patient's mortality.

MARS therapy is a well-tolerated and effective therapeutic strategy, although the outcomes appear to be inconclusive at present. Two recent randomized trials including acute-on-chronic liver failure patients²¹⁻²² showed that MARS therapy was associated with a high survival rate; for example, the mortality rate was 100% in the control group, and 62.5% at day 7 and 75% at day 30 in the MARS group. In acute pure liver failure, MARS therapy also appears to offer the possibility of enhanced liver recovery from an acute noxious stimulus.²³

The most common adverse effect associated with MARS therapy in our series was moderate hypokalemia; we did not observe any hematological reaction, the most common adverse reaction reported.¹⁸

Conclusion

MARS therapy is a well-tolerated and effective strategy that greatly improves biochemical variables in acute liver failure. However, its actual impact on mortality rate it is not clear at present. The procedure should be considered as a bridge to other more effective therapies or as a supportive care measure to treat acute liver failure.

References

1. Popper H, Schaffner F. *Progress in liver diseases*. Philadelphia; London: Saunders; 1990.
2. Rakela J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double-blinded, randomized trial of hydrocortisone in acute hepatic

- failure. The Acute Hepatic Failure Study Group. *Dig Dis Sci*. Sep 1991; 36(9): 1223-1228.
3. Schiodt FV, Atillasoy E, Shakil AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg*. Jan 1999; 5(1): 29-34.
4. Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transpl*. Mar 2000; 6(2):163-169.
5. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. Dec 17 2002; 137(12): 947-954.
6. Bernal W. Changing patterns of causation and the use of transplantation in the United kingdom. *Semin Liver Dis*. Aug 2003; 23(3): 227-237.
7. Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). *Gastroenterology*. Dec 1995; 109(6): 1907-1916.
8. Bihari DJ, Gimson AE, Williams R. Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. *Semin Liver Dis*. May 1986; 6(2): 119-128.
9. Aggarwal S, Kramer D, Yonas H, et al. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. *Hepatology*. Jan 1994; 19(1): 80-87.
10. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*. Mar 1999; 29(3): 648-653.
11. Lee WM. Acute liver failure in the United States. *Semin Liver Dis*. Aug 2003; 23(3): 217-226.
12. Baker A, Dhawan A, Devlin J, et al. Assessment of potential donors for living related liver transplantation. *Br J Surg*. Feb 1999; 86(2): 200-205.
13. Sen S, Williams R. New liver support devices in acute liver failure: a critical evaluation. *Semin Liver Dis*. Aug 2003; 23(3): 283-294.
14. Chiba T, Goto S, Yokosuka O, et al. Fatal chronic active Epstein-Barr virus infection mimicking autoimmune hepatitis. *Eur J Gastroenterol Hepatol*. Feb 2004; 16(2): 225-228.
15. Cacopardo B, Nunnari G, Mughini MT, Tosto S, Benanti F, Nigro L. Fatal hepatitis during Epstein-Barr virus reactivation. *Eur Rev Med Pharmacol Sci*. Jul-Aug 2003; 7(4): 107-109.
16. Palanduz A, Yildirmak Y, Telhan L, et al. Fulminant hepatic failure and autoimmune hemolytic anemia associated with Epstein-Barr virus infection. *J Infect*. Aug 2002; 45(2): 96-98.
17. Chen SB, Zhang LL, Shi YF, Yang XL, Wang ZH. [Application of molecular adsorbents recirculating system in the treatment for liver failure of hepatitis B]. *Zhonghua Gan Zang Bing Za Zhi*. Mar 2004; 12(3): 131-133.
18. Tan HK, Lim JS, Tan CK, et al. MARS therapy in critically ill patients with advanced malignancy: a clinical and technical report. *Liver Int*. 2003; 23 Suppl 3: 52-60.
19. Faybik P, Hetz H, Krenn CG, et al. Liver support in fulminant liver failure after hemorrhagic shock. *Wien Klin Wochenschr*. Sep 15 2003; 115(15-16): 595-598.
20. Mitzner SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. *Liver Transpl*. May 2000; 6(3): 277-286.
21. Heemann U, Treichel U, Loock J, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. *Hepatology*. Oct 2002; 36(4 Pt 1): 949-958.
22. Sen S, Jalan R. The role of the Molecular Adsorbents Recirculating System (MARS) in the management of liver failure. *Perfusion* 2004; 19 Suppl 1: S43-48.
23. Sen S, Mookerjee RP, Davies NA, Williams R, Jalan R. Review article: the molecular adsorbents recirculating system (MARS) in liver failure. *Aliment Pharmacol Ther*. Dec 2002; 16 Suppl 5: 32-38.