Extracorporeal liver support for trauma-induced hepatic dysfunction

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Surgical management of trauma to the liver has persisted as a clinical challenge despite advances in management. Surgical intervention was initially the norm as described in 1986 by Feliciano et al.[1] in a 1,000-patient case series in which 881 patients received hepatorrhaphy, topical hemostatic agents, or drainage alone for management. An additional subset of 119 patients required more extensive intervention with resectional debridement, selective vascular ligation, or perihepatic packing, with 13.1% of all these patients developing hepatic necrosis and 10.5% mortality across all comers.

In 1993, Rotondo et al.[2] advocated the staged approach to liver injuries using "damage control" for penetrating abdominal trauma in which coagulopathy, acidosis, or hypothermia prevent pursuing primary surgical management and closure. In a 27-year span, a predominantly operative management plan for liver injury has evolved from attempting definitive management and closure on the first operation into a multidisciplinary staged approach sequencing surgical intervention, angioembolization, and continued resuscitation in the critical care unit as the patient's pathology dictates and physiology permits.

Major hepatic necrosis (MHN) is defined as any significant liver ischemia that requires specific intervention, such as lobectomy, nonanatomic resection, or serial debridements and/or drainage, for its management. Hepatic necrosis was found to be the most common reported complication, occurring in 14.9% (range, 0–43%) of embolized patients in a recent systematic review.[3] In 2009, a retrospective series of patients at the R Adams Cowley Shock Trauma Center showed an incidence of 42.2% of MHN across 71 patients who received therapeutic angioembolization within a group of 538 patients with high-grade liver injuries over a 5-year period.[4] This study accounts for 63% of the patients with hepatic necrosis reported in the systematic review.[3] Dabbs et al.[4] reported that there was no difference in mortality (14%) between those with high-grade liver injury who developed MHN and those who did not.

Practice patterns have evolved to use nonoperative management for low-grade liver injuries, and the natural history of MHN seems to be an acceptable complication of early hemostatic control with angioembolization in high-grade liver injuries. Yet, current understanding of MHN is limited to a binary outcome: a patient has it or does not. Quantification of the amount of viable liver is difficult to ascertain until the patient demonstrates symptoms of failure, such as hepatic encephalopathy, coagulopathy, and jaundice. Acute liver failure has shown considerable heterogeneity not only in part from the underlying cause but also in response to novel interventions such as extracorporeal liver support (ELS), suggesting that liver damage may in fact lie on a continuum.

Extracorporeal Liver Support

Management of chronic liver disease has included ELS (Fig. 1), such as, single-pass albumin dialysis (SPAD), Molecular Adsorbent Recirculating System (MARS, Baxter International Inc., Deerefield, IL), and Prometheus (Fresenius Medical Care, Bad Homburg, Germany). Albumin is used as a transporter in these systems to remove protein-bound substances from the blood. SPAD uses 2% to 5% albumin in solution, making one pass through the dialyzer, and then, the albumin is disposed of as effluent. Both the MARS and Prometheus allow for protein-bound substance removal by passing a 16% albumin dialysate (MARS) or separated plasma (Prometheus) through a series of filters and adsorbers. Both systems use continuous renal replacement therapy (CRRT) for water-soluble clearance in conjunction with charcoal and resin adsorbers for protein-bound clearance before returning the albumin for another pass to the dialyzer (MARS) or the plasma to the patient (Prometheus). The therapy is time limited because of the capacity of the adsorbers. Prometheus is currently not available in the United States, while MARS has Food and Drug Administration (FDA) approval for use in the treatment of drug overdose and poisonings as well as hepatic encephalopathy caused by decompensated chronic liver failure. Mitzner[5] provides an excellent review of these devices.

PATIENTS AND METHODS

We report our experience with the application of MARS in three separate cases of traumatic liver injury with development of MHN and who received MARS therapy since July 2013. MARS therapy was applied in patients demonstrating synthetic failure (e.g., coagulopathy), those with reduced detoxification (e.g., elevated ammonia), and/or those considered for liver transplantation. Three cases are included and described in the following section.

RESULTS

Case 1

The first case is an 18-year-old male following penetrating trauma to the abdomen. He underwent emergent exploratory

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Figure 1. A, SPAD performed using CVVHD pump on the left and continuous venovenous hemofiltration performed on the right. *B*, MARS.

laparotomy and was found to have a stellate liver laceration with active hemorrhage deep in the right lobe of the liver. There were also multiple ileal gunshot wounds and a through-and-through gunshot wound to the cecum. Clips and suture were used for hemostasis of the liver laceration. Packing was placed above and below the liver, and temporary closure was performed with vacuum-assisted closure dressing. Following damage-control surgery, he underwent angiography demonstrating large-volume active bleeding from a first-order right main hepatic artery branch that was treated with Gelfoam and coil embolization. On hospital Day 5, he developed fever, and a subsequent computed tomographic (CT) angiography of the abdomen showed hepatic necrosis.

Resectional debridement attempts were stalled by congestion of the liver secondary to volume overload refractory to diuresis. CRRT was initiated for volume management. The patient was placed on venovenous bypass to shunt around the liver and reduce hepatic congestion. Subsequently, the patient had a right hepatic lobectomy on hospital Day 9 and returned to the ICU (ICU) with an open abdomen. On hospital Day 11, his ammonia was 95 μmol/L with Grade 4 hepatic encephalopathy, had total bilirubin of 46.6 mg/dL, and deteriorated to a Child's Class C with international normalized ratio (INR) of 2.0, and a Model For End-Stage Liver Disease (MELD) score of 42. Hypertonic saline was administered to elevate his serum sodium in light of the hepatic encephalopathy. As he was coagulopathic and developed an upper gastrointestinal (GI) bleeding, a continuous infusion of plasma was initiated to correct his INR. Repeat CT scan revealed worsening necrosis of the liver remnant (Fig. 2).

Given the severity of hepatic dysfunction and MHN, SPAD was added to standard medical therapy (SMT). SPAD consisted of 500-mL/h to 1,000-mL/h 5% albumin on hospital Days 13, 14, 15, and 17 as albumin supplies allowed. Glasgow Coma Scale (GCS) score improved to a baseline of 11T following initiation of SPAD, the ammonia stabilized to 32 μmol/L to 53 μmol/L, and the total bilirubin decreased to 32 mg/dL. During this therapy, the supplies of 5% albumin were exhausted. MARS was obtained and begun on hospital Day 18 for 3 days to reduce the demand for albumin.

Following a washout and attempted closure of his abdomen on hospital Day 28, he developed abdominal compartment syndrome, his ammonia level increased to 192 μmol/L (Fig. 3), and the patient again became encephalopathic, with a rising INR, leukocytosis, fever, and elevated lactate of 9 mmol/L. His abdomen was reopened. The patient received three additional days of MARS therapy of 8 hours each. SMT was continued. His ammonia returned to previous levels of 22 μmol/L to 52 μmol/L, and his INR normalized.

The patient had an extended hospital course. Vicryl mesh was placed for abdominal closure. The patient had nosocomial

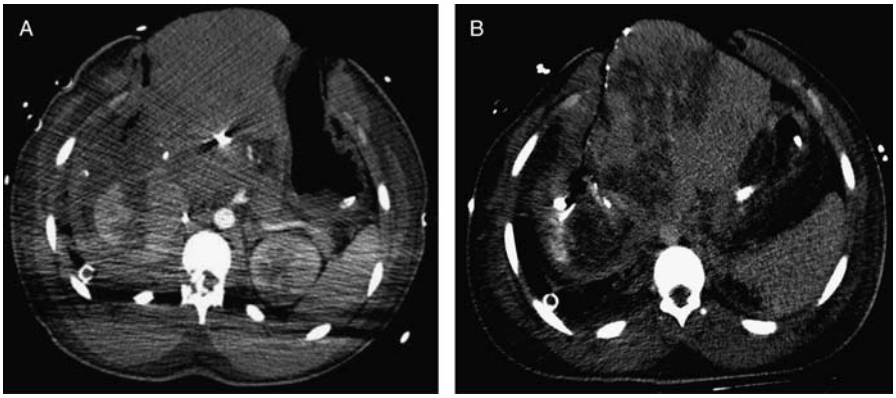

Figure 2. Case 1 CT scan of the abdomen. MHN demonstrated comparing Image A with Image B.

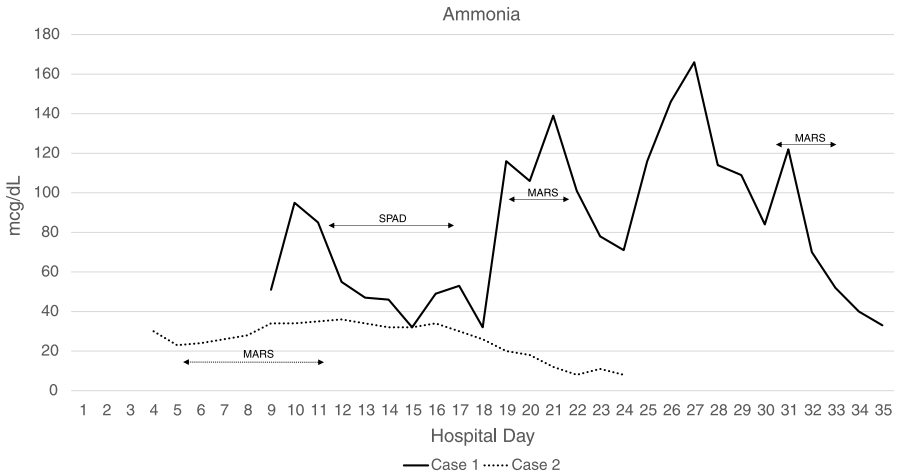

Figure 3. Ammonia levels for Cases 1 and 2. The patient in Case 1 was treated with SPAD followed by MARS therapy for 3 days on two separate occasions. The patient in Case 2 was treated with MARS starting on hospital Day 5 for a total of 6 days.

infections, developed an enterocutaneous fistula (ECF), and had an unrelated episode of cardiac tamponade causing cardiac arrest with successful resuscitation; however, he had no further hepatic complications. He was transferred for acute rehabilitation 4 months after his initial injury for his paraplegia. He returned for successful ECF closure and ventral hernia repair 10 months after his initial injury and is now living in an assisted living facility.

Case 2

A 28-year-old female from a motor vehicle collision versus a tractor-trailer sustained significant blunt abdominal trauma resulting in a Grade 4 liver injury necessitating damage-control surgery. She was found to have laceration to the right lobe of her liver, which extended all the way back to the vena cava. This was a stellate laceration, which involved the entirety of the lateral and posterior portion of the right lobe of the liver. She underwent major liver resection with packing and temporary abdominal closure. She subsequently developed significant postoperative liver dysfunction. Her other injuries included atlantooccipital dissociation, traumatic brain injury (with multiple blunt cerebrovascular injuries requiring intracranial pressure monitoring), and a Grade 4 renal laceration. She did not have angioembolization.

The patient developed acute kidney injury and was treated with CRRT. On hospital Day 5, she was coagulopathic (INR, 3.4) with hyperbilirubinemia of 4.9. Hepatology was consulted given the magnitude of her liver injury and failure. Biopsy of liver remnant showed extensive centrilobular hepatic necrosis (approximately 60%) and moderate microvesicular steatosis. MARS therapy was initiated for hepatic insufficiency in the setting of MHN for a total of five treatments. The patient's synthetic function improved, and her lactate level trended down; however, the bilirubin peaked at 44 and remained elevated beyond the treatment period. She had a cholecystectomy on subsequent abdominal washout, which was complicated by formation of an abscess. The patient had a complicated abdominal closure due to abscesses and loss of fascial domain. The patient remained in the ICU because of CRRT requirements, a prolonged ventilator wean, portal vein thrombosis, and bilateral pulmonary emboli. Her renal function returned, and she was transferred to acute rehabilitation 2 months following her injury. She is currently living with her mother and considering going back to work.

Case 3

A 61-year-old male who presented after a high-speed motor vehicle collision with additional deaths on scene. On arrival, his abdomen was distended with a positive Focused Assessment with Sonography for Trauma examination result and hypotension. He did respond to blood products and was taken to the operating room for damage-control stabilization with peritoneal packing and repair of Grade 2 splenic and Grade 3 liver laceration. There was a 4-cm deep laceration medially on the right lobe of the liver and a stellate laceration over the dome of the right lobe of the liver. There was additionally a linear laceration on the undersurface of the right lobe of the liver just lateral to the gallbladder fossa. There was a less than 1-mm superficial laceration in the left lobe of the liver. He underwent celiac arteriogram following damage-control surgery, which demonstrated a large area of hypoperfusion in the right and left hepatic lobes, consistent with the findings of hepatic laceration. Selective arteriogram of the right hepatic lobe demonstrated a truncated branch likely supplying Segment 8, which was embolized with two 3-mm coils. The left hepatic lobe demonstrated a truncated branch with persistent contrast opacification, which was embolized with three 4-mm coils.

In the ICU, he became profoundly hypotensive requiring vasopressors and hypoxemic because of the rapid development of adult respiratory distress syndrome and right ventricular decompensation. The patient was placed on veno-venous extracorporeal membrane oxygenation for hypoxemia and CRRT for volume management. Despite an open abdomen, the patient subsequently developed intra-abdominal hypertension. Reexploration on hospital Day 2 revealed extensive areas of focal necrosis of the liver parenchyma with the rest of the liver appearing extremely dusky and ischemic. Liver biopsy from three specimens (two from the left lobe and one from the right) demonstrated moderate steatosis throughout (approximately 50%) and hepatic necrosis in the left at approximately 10% to 30%. The patient was started on MARS therapy for liver dysfunction in the setting of MHN, receiving a total of 5 days of

therapy. Once the MARS treatment concluded, the patient regained synthetic function of his liver with resolution of severe coagulopathy, although he had persistent hyperbilirubinemia, which improved slowly. Extracorporeal membrane oxygenation was weaned, and he was decannulated. The patient's abdomen was eventually closed as intra-abdominal pressures permitted.

He had prolonged hospitalization secondary to deep vein thrombosis, acute kidney injury, and lower GI hemorrhage. Angiogram for GI bleeding demonstrated frank arterial extravasation from a right colic branch along the lateral wall of the ascending colon. The vessel was coiled, and repeat angiogram demonstrated no extravasation. He also developed an ECF and acute cholecystitis that was treated with percutaneous cholecystostomy tube. He was transferred to acute rehabilitation 3 months after his injury. He is awaiting staged repair of his traumatic abdominal hernia. He is currently home and has returned to his activities of daily living.

This case series reports three patients with high-grade traumatic liver injury requiring lobectomy on admission or developed MHN. This series illustrates a novel application of MARS for traumatic liver injury. These patients had 100% survival with recovery of liver function and no need for liver transplantation. Each of these patients received 8-hour sessions between 3 days and 6 consecutive days of MARS therapy. Most had concomitant acute kidney injury requiring CRRT; thus, we alternated 8 hours of MARS with 16 hours of CRRT using the same access site.

The physiologic data for the first 45 days of hospitalization (Table 1) showed initial hepatic insufficiency with a mean INR of 1.7, lactate of 5.5, aspartate aminotransferase (AST) of 1,311, alanine aminotransferase (ALT) of 785, and total bilirubin of 17.2. After ELS, the mean INR of 1.5, AST of 528, ALT of 336, and lactate of 2.5 were improved. Inferential statistics were not attempted because of the small sample. ALT

TABLE 1. Results of Liver Function Studies of the Cases

		Before ELS					During ELS					After ELS				
		Mean	Median	SD	Minimum	Maximum	Mean	Median	SD	Minimum	Maximum	Mean	Median	SD	Minimum	Maximum
All cases	INR	1.7	1.6	0.6	1.2	6.1	1.5	1.5	0.2	1.2	2.0	1.5	1.4	0.5	1.0	4.0
	Albumin	2.4	2.3	0.5	1.6	3.5	2.6	2.5	0.4	2.0	3.7	2.3	2.1	0.5	1.5	4.2
	ALT	1,369.6	1,148.0	511.2	235.0	2,253.0	486.1	375.0	348.3	133.0	1,457.0	336.4	212.0	332.3	71.0	1,600.0
	AST	1,369.6	1,185.0	794.6	225.0	3,885.0	535.4	402.5	434.5	122.0	2,094.0	527.7	450.0	461.4	64.0	2,840.0
	Total bilirubin	12.1	4.2	12.5	0.4	46.6	18.0	22.0	8.3	3.8	29.5	20.4	19.1	7.9	8.2	44.6
	Ammonia	54.2	40.5	34.5	19.0	99.0	80.7	69.0	43.1	32.0	192.0	37.1	25.0	33.2	8.0	142.0
	Lactate	5.5	4.5	3.3	1.3	14.4	3.7	3.2	1.8	1.7	10.7	2.5	2.3	0.9	1.2	6.4
	MAP	71.5	71.0	8.9	57.0	90.0	72.5	72.0	9.6	48.0	102.0	74.1	71.5	10.7	56.0	100.0
	Norepinephrine, μg/min	11.0	16.8	8.6	0.0	30.0	2.9	1.0	5.2	0.0	80.0	2.4	1.0	3.4	0.0	14.0
Case 1	Hospital days			0–13					14–32					33–45		
	INR	1.7	1.5	0.7	1.3	6.1	1.5	1.6	0.1	1.3	2.0	1.4	1.4	0.1	1.2	1.6
	Albumin	2.4	2.3	0.5	1.6	3.3	2.8	2.7	0.4	2.2	3.7	2.0	1.9	0.1	1.7	2.4
	ALT	785.3	387.0	825.1	235.0	1,734.0	289.1	148.0	240.8	133.0	759.0					
	AST	1,311.0	985.5	932.9	225.0	3,885.0	454.8	381.5	358.4	122.0	1,760.0	667.8	564.0	281.3	412.0	1,394.0
	Total bilirubin	17.2	21.0	13.6	0.4	46.6	23.2	23.6	3.2	15.1	29.5	19.1	19.1	2.9	12.7	25.1
	Ammonia	84.4	92.0	19.4	51.0	99.0	82.0	70.0	43.0	32.0	192.0	45.8	33.0	33.7	10.0	142.0
	Lactate	4.1	3.4	2.2	1.3	11.1	3.6	3.2	1.5	2.3	9.4	2.1	1.8	0.8	1.2	3.9
	MAP	63.7	62.0	6.5	57.0	80.0	70.2	69.0	9.2	50.0	102.0	69.2	68.5	7.7	56.0	92.0
	Norepinephrine, μg/min	2.5	3.0	1.4	1.0	5.0	2.0	2.0	2.1	0.0	10.0	2.3	3.0	1.2	0.0	4.0
Case 2	Hospital days			0–5					6–11					12–45		
	INR	2.0	1.9	0.5	1.5	3.4	1.4	1.4	0.1	1.3	1.7	1.5	1.4	0.2	1.2	2.3
	Albumin	2.5	2.5	0.4	1.7	3.1	2.3	2.3	0.1	2.1	2.6	2.8	2.7	0.5	2.2	4.2
	ALT	912.6	930.0	241.6	529.0	1,225.0	332.2	282.0	133.0	181.0	618.0	432.9	232.5	423.1	117.0	1,600.0
	AST	1,723.5	1,748.0	444.1	1,061.0	2,350.0	471.6	337.0	275.0	251.0	1,110.0	615.9	320.5	662.7	168.0	2,840.0
	Total bilirubin	3.8	3.7	0.5	3.2	4.9	5.6	4.8	1.7	3.8	9.8	28.0	26.2	8.4	10.4	44.6
	Ammonia	24.0	24.0	3.9	19.0	30.0						10.3	8.0	6.9	8.0	32.0
	Lactate	8.1	7.8	3.9	2.0	14.4	3.3	3.0	0.9	2.2	5.6	3.2	3.4	0.8	1.2	5.4
	MAP	80.3	78.0	7.2	68.0	90.0	80.0	81.0	7.6	60.0	96.0	75.0	72.5	11.6	60.0	99.0
Case 3	Hospital days			0–3					4–8					9–45		
	INR	1.7	1.6	0.3	1.2	2.3	1.5	1.5	0.2	1.2	1.7	1.7	1.4	0.7	1.0	4.0
	Albumin	2.5	2.4	0.4	2.0	3.5	2.3	2.3	0.3	2.0	3.0	2.1	2.2	0.3	1.5	2.9
	ALT	1,401.5	1,423.5	496.7	644.0	2,253.0	808.5	689.0	380.2	389.0	1,457.0	217.5	204.5	78.8	71.0	377.0
	AST	1,259.0	1,165.0	465.0	665.0	2,027.0	1,040.3	797.0	623.9	366.0	2,094.0	194.1	179.0	89.9	64.0	365.0
	Total bilirubin	4.0	2.6	3.0	0.8	9.7	7.2	7.0	1.7	4.9	10.2	13.1	11.7	3.9	8.2	21.3
	Lactate	7.7	7.8	2.8	3.7	12.5	4.7	2.9	3.4	1.7	10.7	2.1	2.0	0.7	1.3	6.4
	MAP	73.2	72.0	7.3	57.0	90.0	71.3	69.5	8.3	48.0	91.0	78.9	79.0	11.2	59.0	100.0
	Norepinephrine, μg/min	18.1	17.5	2.8	15.0	30.0	9.9	10.0	9.1	0.0	80.0	3.3	0.0	4.9	0.0	14.0

was not a routine measurement during the hospitalization of the patient in Case 1. Ammonia was measured in Cases 1 and 2. The patient in Case 1 had elevated ammonia levels consistent with hepatic encephalopathy, which normalized following institution of ELS and SMT. The patient in Case 2 did not have ammonia levels greater than the normal range; however, they were at the upper end of normal in the setting of traumatic brain injury (Fig. 3). These patients all had prolonged hospital courses over which hepatic synthetic function and clearance returned, although their bilirubin remained elevated well beyond the initial MARS treatment period (Fig. 4).

DISCUSSION

ELS has been used to bridge patients in liver failure to transplantation, although this use is not FDA approved. In vitro models comparing SPAD and MARS have shown them to be similar in clearance of bilirubin, ammonia, creatinine, and urea, with MARS clearing ammonia most efficiently in the continuous venovenous hemodiafiltration (CVVHDF) mode as compared with continuous venovenous hemodialysis (CVVHD) mode.[6] CVVHD and CVVHDF are modes of CRRT. CVVHD uses diffusion for solute clearance, while CVVHDF uses both convection and diffusion for solute clearance. Controlled trials with MARS in patients with cirrhosis have shown a 30-day survival benefit,[7] reduction in severity of hepatic encephalopathy,[8] and reduction in bilirubin and ammonia.[9] The largest and most recent trial of MARS in acute-on-chronic cirrhosis reaffirmed the improvements in creatinine, bilirubin, and encephalopathy but did not show a mortality benefit.[10] One uncontrolled pilot of MARS showed improvement in cerebral blood flow and hepatic encephalopathy among alcoholic patients with cirrhosis.[11]

A French prospective randomized control trial showed improved survival of those treated with MARS in acute liver failure compared with conventional therapy (85% vs. 76%), although these results were not statistically significant.[12] The study included all comers and subdivided further into acetaminophen related and nonacetaminophen causes of acute liver failure; however, the study was underpowered for subgroup analysis and thus could not identify further benefit. An earlier prospective randomized control trial in 2004 demonstrated safety and suggested that patient responses to MARS treatment may vary based on the cause of liver failure, although the study was insufficiently powered, as it was terminated early, to be able to draw definitive conclusions.[9] In another controlled trial of hyperacute liver injury from acetaminophen, hepatitis B virus, and disulfiram, MARS showed decreased oxygen consumption by 22% with associated improvements in mean arterial pressure (MAP), bilirubin, creatinine, and urea.[13]

Liver injury, whether acute or chronic, may be more heterogeneous than previously understood, and certain subgroups of previously studied populations may benefit from ELS. While the use of MARS has been FDA approved for the treatment of hepatic encephalopathy in acute-on-chronic liver failure, some expanded indications, and uses are still experimental. Our experience with MARS use while awaiting hepatic recovery in specific patient populations is in line with other proposed indications[14] such as fulminant liver failure, bridge to transplantation, or recovery during acute-on-chronic liver failure. In a study of patients with acute liver impairment, those with histopathologic specimens showing more than 50% hepatocellular necrosis compared with

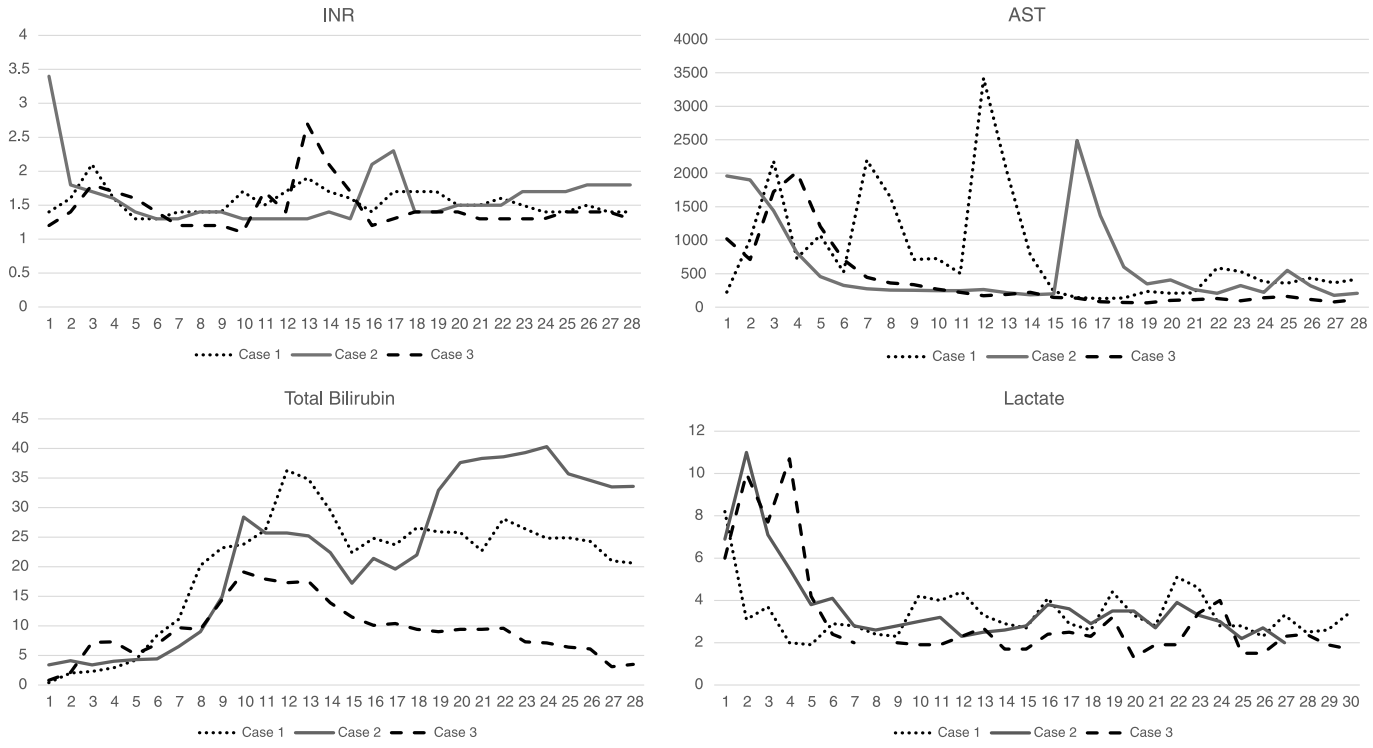

Figure 4. Trends of INR, AST, total bilirubin, and lactate.

those with less were associated with worse outcomes including mortality and trended with the MELD score.[15] They concluded that the degree of hepatocyte proliferative activity and hepatocyte loss were the most important independent predictors of outcome. Drawing physiologic parallels to other disease processes, similar to cerebral ischemia, there may be a "hepatic penumbra" or salvageable area of the liver that may benefit from "rest" provided by ELS. In a review of hepatic necrosis and regeneration, Weng et al.[16] postulate that hepatic necrosis activates liver progenitor cells (LPCs) and survival is determined by whether LPCs can provide enough functional hepatocytes to restore liver mass and function.

Hepatic insufficiency may occur along a continuum of disease and a spectrum of injury before frank failure and necrosis similar to the continuum of acute kidney injury and adult respiratory distress syndrome. Conceptually, clearance of toxins and restoration of biochemical homeostasis using ELS may provide an environment supportive of the remaining hepatocytes and LPCs. ELS offers improved hemodynamic and metabolic parameters in the setting of a dysfunctional liver and may be a means of augmenting perfusion to the liver penumbra. We have noted significant reductions in vasoactive requirements after starting MARS therapy in patients with liver failure outside of traumatic injury. Norepinephrine doses were reduced in Case 3 after initiating ELS. This may be a natural progression of illness but may also be related to reduction of inflammatory mediators and nitric oxide.

The management of liver injuries and MHN has been an evolving process. As best as the authors are aware, this is the first reported case series of patients with traumatic liver injury with necrosis in whom MARS was used to restore hepatic function and avoid transplantation. Our experience with these patients suggests a new treatment option in the road to recovery as well as a possible novel application for ELS in the trauma population. MARS may be considered in those patients with liver failure of a primary etiology, not secondary to multiple-organ dysfunction with significant biochemical imbalance. This is purely a conceptual hypothesis, as all studies to date have been insufficiently powered to illustrate a clear benefit and should not delay consultation for consideration of liver transplantation.

AUTHORSHIP

Z.G., D.S., and T.S. designed this study. Z.G. and P.T. reviewed the literature. Z.G. and P.T. collected the data, which Z.G., D.S., and P.T. analyzed. Z.G., P.T., D.S., and T.S. interpreted the data. Z.G., P.T., and D.S. wrote the manuscript. Z.G., P.T., D.S., and T.S. critically revised the manuscript for publication.

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