APPLYING THE MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS) IN THE TREATMENT OF ACUTE LIVER FAILURE (ALF) CASE REPORT

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PRIMENA MARS (eng MOLECULAR ADSORBENT RECIRCULATING SYSTEM) U LEČENJU AKUTNE INSUFICIJENCIJE JETRE (AIJ) PRIKAZ SLUČAJA

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ABSTRACT

Acute liver failure (ALF) is a rare but life-threatening illness with multiple organ failure. The short-term mortality rate exceeded 80 % despite modern approaches in treatment. Drugs, infections by hepatic viruses and toxins are the most common causes of ALF. Progressive jaundice, coagulation disorder and hepatic encephalopathy are dominated as a clinical signs of the illness. We present a case of a 36-year-old Caucasian woman hospitalized in ICU due to yellow discoloration of the skin and sclera, severe disseminated coagulopathy and hemodynamic instability. ALF is developed due to Hepatitis B Virus infection, resulting in hepatic toxicity as well as coma. General condition rapidly improved after applying of Molecular Adsorbent Recirculating System (MARS), an extracorporeal liver support system based on albumin dialysis. It is relatively expensive treatment that is used for the patient with hepatic encephalopathy grade 3 or 4 in our institution. In conclusion, an early administration of MARS significantly reveals subjective and objective clinical improvement in the case we presented.

Keywords: *Hepatitis B, acute viral; Encephalopathy, hepatic; Treatment, early; Liver dialysis; Survival;*

SAŽETAK

Akutna insuficijencija jetre (AIJ) je retka, ali po život opasna bolest sa multiplmom disfunkcijom organa. Kratkoročni mortalitet je preko 80% uprkos modernim pristupima u lečenju. Lekovi, infekcije hepatotropnim virusima i toksini su najčešći uzroci ALF. U kliničkoj slici dominiraju progresivna žutica, poremećaj koagulacije i hepatična encefalopatija. Predstavljamo slučaj 36-godišnje žene hospitalizovane u JIL zbog žute boje kože i sklera, teške diseminirane koagulopatije i hemodinamske nestabilnosti. ALF je nastala tokom infekcije virusom hepatitisa B, koja je rezultirala insuficijencijom jetre i komom. Opšte stanje se brzo poboljšalo nakon primene sistema za recirkulaciju molekularnih adsorbenata (MARS), ekstrakorporealnog sistema za podršku jetre na bazi albuminske dijalize. To je relativno skupo lečenje koje se koristi za pacijenta sa hepatičnom encefalopatijom stadijuma tri ili četiri. U zaključku, rana primena MARS-a rezultirala je značajnim subjektivnim i objektivnim kliničkim poboljšanjem u prikazanom slučaju.

Ključne reči: *Hepatitis B, akutni virusni; hepatička encefalopatija; lečenje, dijaliza jetre, preživljavanje*

ABBREVIATIONS

ABP – Arterial Blood Pressure
MAP – Mean Arterial Pressure
GCS – Glasgow Coma Score
APACHE II – Acute Physiology and Chronic Health Evaluation score II
ALF – Acute liver failure
ICU – Intensive Care Unit
MARS – Molecular Adsorbent Recirculating System
HE – Hepatic encephalopathy
ARDS – Acute Respiratory Distress Syndrome
SMT – Standard Medical Therapy
SOFA - Sequential Organ Failure Assessment score
MELD – Model for End-stage Liver Disease
ACT – Activated clotting time
INR – International Normalized Ratio
ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
CVVHDF – Continuous venovenous hemodiafiltration
HRS – Hepatorenal syndrome
RRT - Renal Replacement Therapy
AFP – α (alpha)-fetoprotein
LPC - liver progenitor cells
MH – mature hepatocytes
IU/L – International Unit per liter

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INTRODUCTION

Acute liver failure (ALF) is a rare but life-threatening critical illness that occurs most often in patients who do not have preexisting liver disease (1). The predominant causes are acute viral infections (hepatitis A, B and E), acute alcoholism and gastrointestinal hemorrhage or drugs (1,2). In developing countries, ALF was registered in 0.5% to 1% of all of patients with viral hepatitis B with mortality rate of 70%. Standard therapeutic strategies include treatment of infections and hemorrhage as well as supportive treatment of remote organ dysfunction such as hepatic encephalopathy (HE), renal failure, coagulation disorder, circulatory dysfunction and acute respiratory distress syndrome (ARDS) (3).

Randomized controlled trials have shown different long term survival rates in applying any of the commercially available extracorporeal liver support systems (4-6)

The most frequently used system is the Molecular Adsorbent Recirculating System (MARS) that dialyses patient's blood against a high-flux albumin filter. MARS is an extracorporeal liver support system based on albumin dialysis (7). By removing albumin-bound toxins that cause HE liver regeneration can be facilitated and multi-organ failure can be prevented (8,9). Here, we present a case of a successful application of MARS therapy in a critically ill patient suffering from ALF due to hepatitis B virus infection, not suitable for liver transplantation.

CASE REPORT

A 36-year-old Caucasian woman was admitted to ward of the Department of infectious disease with fever, reduced exercise tolerance, muscle and joint pain, right hypochondriac pain and vomiting for six days. Physical examination revealed a communicative, but confused patient, disoriented-in-time with body temperature of 38.3°C and a respiratory rate of 23 per minute. The yellow discoloration of the skin and sclera as well as signs of severe dehydration and hemodynamic instability were registered with arterial blood pressure (ABP) of 100/60 mmHg with Mean Arterial Pressure (MAP) of 80 mmHg and heart rate of 98 per minute. Moreover, peripheral edema and essential tremor of hands were confirmed. A Glasgow coma score (GCS) of 12 and Acute Physiology and Chronic Health Evaluation score II (APACHE II) of 10 were calculated.

Baseline biochemical parameters on admission are shown in table 1 (column 2).

Serological analysis was total anti-HBc antibodies, anti-HBe antibodies and anti-HBs antibodies positive. No evidence of HBsAg and HBeAg were registered (Table 2).

Based on these findings, ALF based on hepatitis B virus infection and stage II of HE were diagnosed and standard medical therapy (SMT) was initiated.

Parenteral rehydration with 30 mL per kilo of 0.9% of sodium chloride solution and 50 mL per hour of 10% of glucose solution was administered. The existing coagulation disorder was treated with 10 mL per kilo of fresh frozen plasma (total of 250 mL administered every 6 hours), 7 units of cryoprecipitate (according to the modified guideline for the administration of cryoprecipitate, 1 unit is administered on every 10 kilos in order to achieve a raise of fibrinogen concentration by 100 mg per deciliter) and 10 mg per day of Vitamin K. Nucleoside analog reverse transcriptase inhibitor, Lamivudine, was administered in dose of 100 mg per day. A 40 mg per 12 hours of proton pump inhibitor, pantoprazole, with 50 mL per hour of concentrated Nutrison® were applied.

Table 1. Baseline biochemical parameters on admission and after SMT

Parameters, units	Value on admission	Value after SMT	Normal range
1	2	3	4
pH, arterial blood	7.19	7.29	7.32-7.42
Lactate, mg/dL	135.1	135.1	1.8-19.8
Sodium, mEq/L	132	132	135-145
Activated clotting time (ACT), s	53	196	25.0-35.0
International Normalized Ratio (INR)	8.4	5.7	< 1.1
Fibrinogen, mg/dL	140	62.5	200-500
Alanine aminotransferase (ALT), IU/L	8 110	4 510	0-40
Aspartate aminotransferase (AST), IU/L	2 471	1 363	0-40
Total bilirubin, mg/dL	11.3	10.1	0.3-1.1
Direct bilirubin, mg/dL	6.02	5.4	0.1-0.3

Table 2. Serological examination reveals acute immune response that follows acute Hepatitis B viral infection

Serological test	Days of admission to Department			
	1	2	9	17
HBsAg	-	-	-	-
HBeAg	-	-	-	-
Anti-HBe anti-bodies	+	+	+	+
Anti-HBc anti-bodies IgM class	+	+	+	+
Anti-HBc anti-bodies IgG class	+	+	+	+
Anti-HBs anti-bodies	+	+	+	+

Biochemical parameters after SMT are shown in table 1 (column 3).

Despite the applied SMT, the patient was referred to the ICU 48 hours after admission due to HE progression and hemodynamic instability. The ABP of 60/40 mmHg with MAP of 50 mmHg required administration of 5 μg per kilo per minute of dopamine supportive stimulation was registered. Heart rate of 110 per minute was confirmed. After initial treatment with dopamine, MAP of 80 mmHg with stabilized heart function was confirmed. Furthermore, 0.5 grams per kilo of 20% of Mannitol solution were infused every 8 hours in order to prevent renal failure due to circulatory collapse. All the time in ICU, diuresis was normal (2000 to 3000 mL per day). Stage IV of HE was confirmed and a GCS of 3 and the Sequential Organ Failure Assessment score (SOFA score) of 12 were calculated. The Model for End-stage Liver Disease score (MELD-Na) of 37 points was calculated with estimated 3-months mortality rate of 52.6%.

In order to screen intracranial expansive masses as the possible causing factors of consciousness disorder a contrast-enhanced cranial CT scan was performed. Here, no brain edema or focal lesions were registered. CT scan was negative for intracranial pathological processes. Therefore, increased intracranial pressure was excluded.

Immediately after admission to the ICU, the patient was sedated, put on a respiratory tube and a central venous catheter was placed due to further medication's administration and intensive monitoring. Due to the rapid progression to multiorgan failure following ALF the patient was placed on extracorporeal liver dialysis using the MARS system approximately 6 hours after admission to the ICU.

MARS treatment was conducted in combination with a conventional hemodialysis machine (Prismaflex® System, Gambro Lundia AB, Lund, Sweden) with a standard buffered dialysis solution for continuous venovenous hemodiafiltration (CVVHDF). MARS device (MARS flux, Gambro Lundia AB, Lund, Sweden) consisted of an albumin-impregnated, highly permeable dialyzer with 600 mL of 20% serum albumin that was used to guarantee the removal of the toxins from the dialysate side. The albumin-enriched fluid was regenerated by perfusion through an anion exchanger column and an uncoated charcoal column and dialyzer for dialysis. The blood flow of the dialysis machine and the albumin dialysate circuit were both held at a median rate of 150 mL/min (interquartile range [IQR], 100–150 mL/min) on the albumin-impregnated membrane and ultrafiltration rate of 50 mL/min was established. The median dialysate flow rate was set to 2000 mL/min. Regional anticoagulation was performed by infusion of 4% trisodium citrate solution. The median citrate infusion rate, necessary to maintain the postfilter ionized calcium between 0.2 and 0.4 mmol/L, was 3.1 mmol/L (interquartile range, 2.3–4 mmol/L) blood flow. The median calcium chloride substitution rate was 0.9 mmol/L (0.3–1.7 mmol/L) dialysate. Total serum calcium remained stable during molecular adsorbent recirculating system treatments.

Since the value of the ACT of 196 seconds was registered, there was no need to administer any systemic anticoagulants.

The system was performed every day over 8 hours.

Using the MARS therapy in presented case we wanted to reduce serum levels of laboratory parameters that were correlated with ALF and accompanied with neurological improvement.

Table 3. Patient's biochemical parameters before and after MARS

Parameters, units	MARS Treatment cycle							
	I		II		III		IV	
	before	after	before	after	before	after	before	after
pH, arterial blood	7.29	7.34	7.58	7.58	7.54	7.46	7.42	7.40
Lactate, mg/dL	135.1	108.1	69.4	51.3	40.5	22.5	26.1	16.2
Sodium, mEq/L	132	139	140	140	136	139	141	141
Activated clotting time (ACT), s	196	74.2	122.5	64.3	58.1	106.7	41	37.1
International Normalized Ratio (INR)	5.71	5.71	3.36	2.91	1.93	1.63	1.41	1.36
Fibrinogen, mg/dL	62.5	58.2	58.8	77.9	73.8	93.2	99.3	104
Alanine aminotransferase (ALT), IU/L	4 510	3 960	2 371	1781	1 560	1 086	817	780
Aspartate aminotransferase (AST), IU/L	1 363	987	434	331	332	188	139	125
Total bilirubin, mg/dL	10.1	8.3	7.19	6.2	5.8	5.2	4.7	5.5
Direct bilirubin, mg/dL	5.4	4.2	4.0	3.85	3.56	3.02	1.88	1.26
BUN, mmol/L	16.5	13.9	7.7	7.2	6.8	4.3	4.8	4.2
Creatinine, μmol/L	110	97	63	43	57	42	57	53
SOFA score	12	13	11	10	10	9	10	9
GCS score	3	3	4	8	10	12	14	14
MELD score (points)	37	35	27	25	21	18	16	16
MELD score (estimated 3-month mortality, %)	52.6	52.6	19.6	19.6	19.6	6.0	6.0	6.0

Table 4. Plasma levels of α-fetoprotein

	Days after admission to the Department					
	2	4	6	8	10	14
α-fetoprotein, ng/mL	4.83	151.33	229.09	284.02	334.76	172.06

After four cycles of liver dialysis with MARS, treatment was disrupted because blood analysis revealed objective clinical improvement.

Biochemical parameters before and after every MARS treatment cycle are shown in table 3.

When MARS treatment was initiated, the patient was in stage IV of HE and with only registered reaction after very rough stimuli. After the second treatment cycle with MARS, stage III of HE was registered. Patient opened eyes on demand but without any signs of other communication skills. After the treatment procedure had been finished, patient was somnolent with established verbal communication. It was stage II of HE that was characterized with impaired awareness, especially regarding *place, time* or personal identity. MELD-Na score of 16 points was calculated with estimated 3-month mortality of 6.0%. After treatment with MARS, both SOFA and MELD-Na scores were significantly (for 25% and 83,8%, respectively).

Plasma levels of α-fetoprotein as a marker of liver regeneration are shown in table 4.

The patient has experienced what is referred to as an *extubation* after 9 days from ICU admission. After 14 days in ICU, the patient was referred to ward of the Department and no signs of catheter-related fever or sepsis, bleeding or mild thrombocytopenia as potential adverse events of MARS treatment were registered. On the 21st day after admission the patient was discharged from University Clinical center with serum levels of total bilirubin of 1.0 mg per deciliter and direct bilirubin of 0.17 mg per deciliter.

DISCUSSION

Acute liver failure (ALF), the original term "fulminant hepatic failure, (FHF)", is defined as a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy (HE) within eight weeks of the first symptoms in the absence of pre-existing liver disease (1,10). Although it can occur from various causes, ALF results from massive necrosis of hepatocytes with appearance of progressive jaundice, HE and coagulation disorder of different degree. ALF is divided into hyper acute, acute and sub-acute forms according to the time between the onset of symptoms and the HE development. In hyper acute cases, this interval is a week or less and is commonly caused by viral infection (1,11). This interval provides clues to the cause of disease, but more likely complications and prognosis with supportive medical care (1,12). In reported case, hyper acute form of the disease was registered within the six days after initial symptoms were developed. This period is associated with a better survival prognosis.

Only 8% of almost all cases of ALF were originated from acute hepatitis B viral infections (13). This infection was a reasonable cause of ALF in our presented case. Very strong immune response on infection can also promote ALF and that was described in presented case.

After initial SMT had been administered, HE progressed rapidly in this case. We administered an endotracheal intubation and sedation for airway control in order to facilitate general care and control of oxygen. These procedures made liver transplantation impossible as surgery became contraindicated because of rapidly progression to multiorgan failure and dramatic deterioration of patient's medical condition. Therefore, the patient could not be a proper candidate for a liver transplantation and this intervention was not considered as a treatment option.

Kidney dysfunction with elevated plasma level of blood urea nitrogen (BUN) and creatinine did not indicate a hepatorenal syndrome (HRS) but the state of circulatory collapse and subsequent hemoconcentration. Therefore, Common Renal Replacement Therapy (RRT) was not considered as an appropriately treatment procedure in this case. Furthermore, RRT would only remove in-water soluble toxins but not albumin-conjugated. Recent studies also suggested that in patient with ALF and subsequent kidney dysfunction who are not candidates for liver transplantation (LT), RRT would not be beneficial (14,15). Moreover, RRT has not been shown to significantly alter outcomes in patients with ALF and kidney dysfunction in the absence of LT (16).

Although Molecular Adsorbent Recirculating System (MARS) is not recommended a standardized treatment option for ALF caused by acute Hepatitis B viral infections, MARS was introduced first time in our facility. It was done in order to stabilize the patient and to allow liver to recover from failure or to "bridge" patient to safer LT. Significant changes in plasma levels of several biochemical parameters were seen already after initial MARS administration compared to baseline (lactate, coagulation parameters, ALT, AST and bilirubin).

Low plasma level of α-fetoprotein (AFP) is one of the risk factor that promote poor survival prognosis in ALF (17). An increase in α-fetoprotein (AFP) following ALF is considered indicative of hepatic regeneration. Patients with ALF usually present with increased serum levels of AFP during hospitalization (18-20). AFP is thought to be secreted from liver progenitor cells (LPCs) as LPCs, but not mature hepatocytes (MHs) express AFP (20,21). Furthermore, an increase of serum level of AFP after admission in ICU is associated with the better prognosis of patients with ALF (18,20). Therefore, liver regeneration

is considered to play an important role in the recovery of the liver function and increasing the liver volume. In addition, AFP seems to be potent marker of better prognosis after ALF.

The safety profile of MARS is remarkable for an extracorporeal circuit. Transient no significant hyperbilirubinemia had been observed in presented case after the fourth treatment cycle, which was probably not due to MARS although the serum total and direct bilirubin levels on the discharge were normal. Bañares et al. also suggested that most studies had not reported any significant adverse effects, except for mild thrombocytopenia, which did not have any clinical implications (6). Sponholz et al. also demonstrated that the investigated albumin dialysis procedures were safe for temporary extracorporeal liver support (22).

CONCLUSION

We suggest that the MARS treatment can be the treatment option for patients in ICU with ALF associated with HE grade 3 or 4, especially in terms of the low likelihood of liver transplantation. It is significant method of treatment in developing countries where liver transplantation is impossible due to the lack of liver transplants. We also show that albumin dialysis with the MARS system is a safe procedure that provides support of organ failure (liver, kidney, and brain) in ALF. The MARS method allows the liver to regenerate completely after ALF. Despite the lack of large clinical trials on the use of MARS in treatment of ALF caused by viral infections, the literature reviews suggest that there are clinical and biological benefits from this treatment method. Furthermore, it can bypass liver failure patients to LT and reduce overall treatment expenditures.

Conflict of interest

The authors declare that they have no conflict of interest and financial support

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