CASE REPORTS
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UDC: 616.36-08
DOI: https://doi.org/10.2298/VSP201116027A

The use of a single pass albumin dialysis for the management of liver failure

Upotreba jednoprotočne albuminske dijalize u lečenju insuficijencije jetre

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Abstract

Introduction. A single pass albumin dialysis (SPAD) is a form of extracorporeal liver support system for removing albumin-bound toxins and water-soluble substances that accumulate in liver failure (LF). **Case report.** We presented three patients hospitalized for LF and treated using the SPAD at the University Clinical Center of Vojvodina, Serbia, from 2018 to 2019. Two of the patients presented with acute LF and one with acute-on-chronic LF. A total of 6 SPAD sessions were performed on each patient, resulting in decreased serum bilirubin and bile acid levels and hepatic encephalopathy grade. On discharge from the hospital, the liver function was improved in all the patients. **Conclusion.** SPAD removes the hepatotoxic substances without improvement of synthetic liver function. It represents a supportive treatment for LF patients who do not respond to the standard of care, offering a longer time for bridging to organ transplantation or spontaneous recovery of the liver function.

Key words:
albumins; liver failure, acute; regeneration; renal dialysis; treatment outcome.

Apstrakt

Uvod. Jednoprotočna albuminska dijaliza (JPAD) je vrsta ekstrakorporalne dijalize kojom se iz krvi obolelih od insuficijencije jetre (IJ) uklanjaju toksini vezani za albumine i hidrosolubilne supstance. **Prikaz bolesnika.** Prikazali smo tri bolesnika sa IJ lečena JPAD metodom u Univerzitetskom kliničkom centru Vojvodine, Srbija od 2018. do 2019. godine. Dva bolesnika su imala akutnu IJ, a jedan akutizaciju hronične lezije jetre. Kod svakog bolesnika sprovedeno je 6 JPAD procedura, koje su dovele do smanjenja nivoa bilirubina i žučnih kiselina u serumu, kao i stepena hepatične encefalopatije. Na otpustu iz bolnice, kod svih bolesnika došlo je do oporavka funkcije jetre. **Zaključak.** JPAD vrši uklanjanje hepatotoksičnih supstanci, bez poboljšanja sintetske funkcije jetre. Koristi se kao suportivan tretman bolesnika sa IJ koji ne reaguju na standardni način lečenja i obezbeđuje stabilizaciju funkcije jetre do njenog spontanog oporavka ili transplantacije.

Ključne reči:
albumini; jetra, insuficijencija, akutna; regeneracija; dijaliza; lečenje, ishod.

Introduction

There is a growing incidence of liver diseases worldwide, accounting for approximately two million deaths per year. Liver failure (LF) is characterized by the lack of metabolic and regulatory functions, resulting in life-threatening complications, such as bleeding, impaired renal function, hepatic encephalopathy (HE) or brain edema, cardiovascular disorders, and immune dysfunction, which eventually may lead to multiple organ failure and death [1, 2]. It is important to identify patients who are not likely to progress after receiving standard medical therapy (SMT) and, accordingly, prepare them for the possibility of liver transplantation. In order to function as a bridge therapy until the recovery of liver function or organ transplantation, extracorporeal liver support systems are used. Extracorporeal albumin dialysis (ECAD) is a mechanical, completely artificial support system that presents detoxification systems of many potential liver toxins which use albumin as a transport protein, such as hydrophobic bile acids, bilirubin, and serum nitric oxide,

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even though it has not been shown to have an effect on synthetic liver function [3]. Several ECAD systems are in use, but the best-known and the most commonly used are the Molecular Adsorbent Recirculating System (MARS™), the Fractionated Plasma Separation and Adsorption System (Prometheus®), and the Single Pass Albumin Dialysis (SPAD).

Case report

After being admitted to the hospital, patients who were treated with SMT received parenteral fluids (0.9% of sodium chloride solution and 10% of glucose solution) for volume resuscitation and maintenance of normoglycemic state, in addition to proton pump inhibitor [pantoprazole 40 mg per 12 hours (hrs)] for stress ulcer prophylaxis, fresh frozen plasma (10 mL per kilogram of body weight) supplemented with 10 mg of vitamin K prior to the placement of central venous lines, and l-ornithine-l-aspartate for treating HE.

SPAD was performed with a machine for continuous renal replacement therapy (Multifiltrate, Fresenius Medical Care, Bad Homburg, Germany) using high-flux polysulfone membranes (Ultraflux® EMIC2 and AV1000S, Fresenius Medical Care). The standard dialysate solution (multiBIC, Fresenius Medical Care) was enriched with 20% human albumin (CSL Behring GMBH, Marburg, Germany) to a final concentration of 4% albumin in the first case [dialysate flow of 700 mL/h for a seven-h treatment] and 3% albumin (dialysate flow of 1,000 mL/h for a five-h treatment) in the last two cases. Prior to initiation of SPAD, all the patients had a double-lumen hemodialysis catheter inserted into the right internal jugular vein. Systemic anticoagulation was performed by infusion rates of unfractionated heparin. Blood sampling was performed within 30 min before the start and after the termination of the treatment.

Case 1

A 30-year-old male patient started taking anabolic steroids (stanazolol and oxymetholone) one month before the onset of the disease in order to increase his muscle mass. Two weeks prior to admission, the patient had a diffuse maculopapular rash with itching that did not resolve after taking antihistamines and became icteric. On physical examination, the patient was afebrile, oriented, his arterial blood pressure (ABP) was 140/80 mmHg, heart rate (HR) 80 beats per min, with respiratory rate (RR) of 16 breaths per min, Glasgow Coma Scale (GCS) score of 15, and Acute Physiology and Chronic Health Evaluation (APACHE) II score 2. Abdominal ultrasonography and computed tomography (CT) showed hepatomegaly (17 cm) with signs of hepatic steatosis. Gastroduodenoscopy revealed normal findings except for chronic gastric changes. Magnetic resonance cholangiopancreatography showed irregular contour of the bile ducts in the left and right lobes, and the first portion of the common hepatic duct of 7 mm in diameter, without signs of dilatation which could be a sign of edema. The ethylic, viral, metabolic, immunological, and neoplastic etiologies for the liver disease were excluded. Despite the applied SMT, LF persisted and six SPAD sessions were performed. Bilirubin levels during SPAD procedures of all patients are shown in Figure 1. After the SPAD treatment, a liver biopsy was performed, showing the intrahepatic cholestasis that could be caused by drug-induced acute toxic liver damage (Figure 2). The patient was discharged one month later with a regression of jaundice and significant bilirubin reduction. The characteristics of the present case are given in Tables 1 and 2.

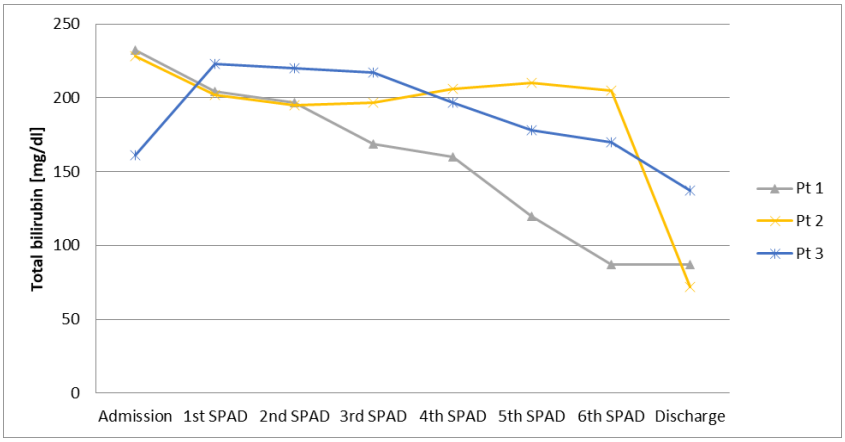


Fig. 1 – Total bilirubin levels during the single pass albumin dialysis (SPAD) sessions. Pt – patient.

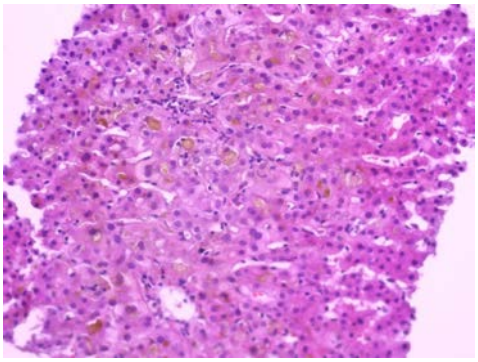


Fig. 2 – Pathohistological finding of liver biopsy of the first patient: the intrahepatic cholestasis (hematoxylin and eosin, ×200).

Table 1

Clinical characteristics of patients and their biochemical parameters on admission and discharge from hospital

Parameter	Pt. 1		Pt. 2		Pt. 3	
Type of liver failure	acute		acute		acute-on-chronic	
Etiology of liver disease	drug intoxication		viral (hepatitis B)		viral (hepatitis A)	
Laboratory finding	adm.	disc.	adm.	disc.	adm.	disc.
AST (IU/L)	27	48	> 7,000	77	7,331	90
ALT (IU/L)	71	167	> 7,000	55	8,808	106
GGT (IU/L)	46	65	62	41	281	282
total bilirubin (mg/dL)	232	87	228	72	161	137
direct bilirubin (mg/dL)	180	71	132	48	122	100
INR	1.5*	0.9	5.3	1.1	2.3	1.0
CRP (mg/dL)	1.5	1	27.6	4	16.2	23.2

***Value measured after two doses of fresh frozen plasma and 10 mg of vitamin K which were administered at admission.**

AST – aspartate transaminase; ALT – alanine aminotransferase; GGT – gamma-glutamyltransferase; INR – international normalized ratio; CRP – C-reactive protein; SPAD – single pass albumin dialysis; adm – admission; disc – discharge; Pt – patient.

Table 2

Biochemical parameters before the first and after the last single pass albumin dialysis (SPAD) procedures

Parameter	Pt. 1		Pt. 2		Pt. 3	
	before SPAD	after SPAD	before SPAD	after SPAD	before SPAD	after SPAD
Hgb (g/L)	158	147	122	90	126	132
Plt ($\times 10^{-9}$/L)	296	254	150	43	181	210
AST (IU/L)	71	167	102	58	4463	190
ALT (IU/L)	50	54	711	92	6893	1755
Total bilirubin (mg/dL)	232	87.2	202.6	193	183	178
Direct bilirubin (mg/dL)	180	71	104	106	141	134
Bile acids (μmol/L)	293	207	156	104	262	154
Albumin (mg/dL)	42	35	27	31	33	31
Urea (mmol/L)	5.8	6.7	2.5	4.4	3.5	8.4
Creatinine (μmol/L)	93	56	26	32	29	68

Hgb – hemoglobin; Plt – platelets; AST – aspartate transaminase; ALT – alanine aminotransferase; Pt – patient.

Case 2

A 49-year-old female patient was admitted to the hospital with fever, jaundice, and abdominal pain. Physical examination revealed the patient to be oriented, without fever, with ABP of 109/53 mmHg, HR 82/min, RR 18/min, painful sensation in the abdomen, GCS score 15, and APACHE II score 2. Diagnosis of acute LF caused by the hepatitis B virus (HBV) was made. Additionally, SMT was initiated together with the nucleoside analogue reverse transcriptase inhibitor, lamivudine, with a daily dose of 100 mg. Despite the applied SMT, on the fifth day of hospitalization, HE developed (stage II) with a worsening coagulation disorder and an increase in bilirubin and bile acid levels. The patient was transferred to the intensive care unit (ICU), and SPAD procedures were initiated. Preparation for the liver transplantation was carried out, but on the 10th day of hospitalization, HE progressed to stage IV, GCS score was 8, and the Model for End-stage Liver disease (MELD) score of 37 points was calculated. Mechanical ventilation was initiated, with the continuation of daily SPAD procedures. Given the performed endocranial CT scan, the signs of diffuse cerebral edema without altered density in the supratentorial and infratentorial regions have been shown (Figure 3). After 6 SPAD sessions, the treatment was discontinued due to the clinical improvement, but jaundice and elevated bilirubin values persisted. The patient was extubated on the 15th day of hospitalization. On the 20th day, she was referred to the Clinic for Infectious Diseases and, after 72 days of hospitalization, discharged with improved laboratory test results.

Case 3

A 59-year-old female patient was hospitalized due to nausea, vomiting, frequent diarrhea, and jaundice that occurred seven days before admission to the Clinic for Infectious Diseases. She has been treated for migraine with analgetics (ibuprofen, diclofenac) and Avamigran® (ergotamine, mecloxamine, camilofin, caffeine, propifenazone) for years. Moreover, she has been acquainted with the elevated aminotransferase levels for ten years but has not been treated for that condition. Physical examination revealed a communicative but disoriented patient, without fiber, with ABP of 130/80 mmHg, HR 100/min, RR 20/min, yellowish discol-

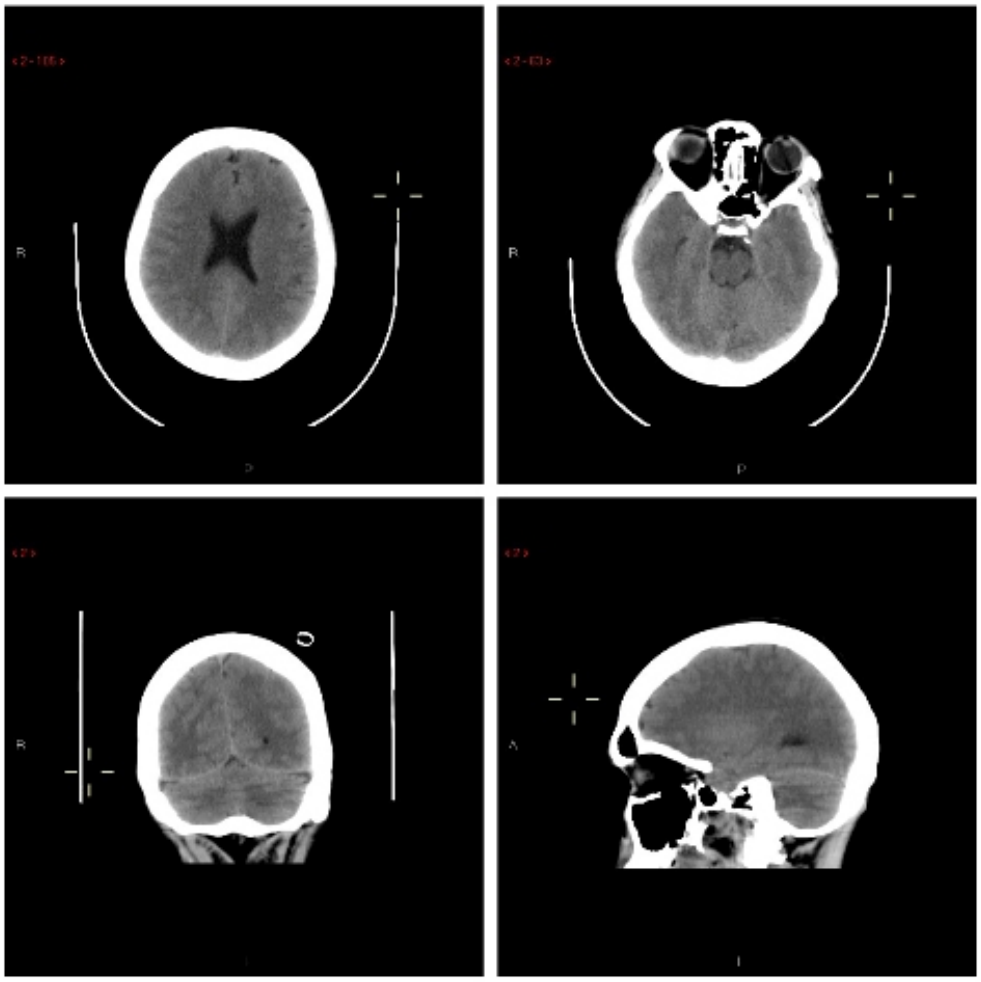


Fig. 3 – Endocranial computed tomography (CT) scan of the second patient shows the signs of a diffuse central edema without altered density in supratentorial and infratentorial regions.

oration of the skin and sclera, painful sensation in the abdomen, GCS score 15 and APACHE II score 4. Diagnosis of an acute hepatitis A virus (HAV) was confirmed by the detection of IgM anti-HAV antibodies and positive epidemiological data (the patient's husband was also diagnosed with acute hepatitis A and had positive IgM anti-HAV antibodies).

The patient was treated with SMT, but on the third day of hospitalization, HE progressed to stage III. Subsequently, she was transferred to ICU, where SPAD sessions were started. After 6 sessions, the HE withdrew, and she was transferred back to the Clinic for Infectious Diseases. Eventually, she was discharged after 37 days with an improved hepatogram and normalization of the coagulation parameters.

Discussion

The use of the ECAD can contribute to the effective removal of albumin-bound toxins, but these procedures cannot substitute the synthetic liver function [2]. Given the fact that the greatest clinical experience in the field of ECAD refers to MARS, SPAD has equal effectiveness in reducing the level of bilirubin as MARS, as well as the same safety profile, while MARS has shown the advantage in reducing the bile acid, creatinine, and urea [4]. Taking into account that the level of bilirubin represents the surrogate marker for protein-bound toxins and correlates positively with the patients' mortality, the greatest significance of the SPAD is in their removal [4–8].

We presented a series of three cases of hospitalized LF patients (1 male and 2 females) who were treated with ECAD by the modality of SPAD between 2018 and 2019. To the best of our knowledge, this type of case series has not been presented in this region before.

Two of our patients had acute LF (ALF), and although one patient was previously diagnosed with liver disease, she consequently developed acute-on-chronic LF (AoCLF). Given the uncertain etiology of the previous liver lesion, the diagnostic criteria for AoCLF remained uncertain without pathohistological findings of liver tissue in that patient. Moreover, prolonged use of migraine medications and elevations of aminotransferase levels in patient history suggested drug-or toxin-induced liver damage, while autoimmune hepatitis could not be ruled out. Less than 1% of acute HAV infections result in ALF, mostly in patients with pre-existing liver disease who are more susceptible to developing an AoCLF in cases of HAV infection [9].

According to the literature data, patients with ALF and AoCLF were frequently eligible for ECAD treatments, comprising three-quarters of implemented ECAD. The viral liver infection was determined in two patients – ALF caused by HBV and AoCLF caused by HAV. The treatment for LF caused by HBV and hepatitis C viruses, mainly by MARS, was described in literature [3], whilst Lee et al. [8] showed the case study of patients with ALF, caused by HAV, which was successfully treated by the SPAD. The use of lamivudine, a potent inhibitor of HBV replication that causes a rapid decline in serum HBV DNA levels, is indicated in patients with a severe form of acute HBV infection, but even then, a small portion of patients with an overwhelming immune response to the virus develop ALF with an expected poor prognosis without liver transplantation and transplant-free survival rates from 26% to 53% [9].

The cause of ALF in one of our cases was the use of anabolic steroids that include a 17-alpha alkyl group that has been linked to the development of jaundice. The literature describes four cases of successful MARS treatment of anabolic steroid-induced liver failure, but, according to our knowledge, this was the first case where the SPAD was used for this indication [10].

The decrease in the bilirubin level has been verified, which correlates to the literature data regarding SPAD [4, 5, 8, 11]. Furthermore, the meta-analysis, which has included ten randomized clinical trials, has shown that the use of the ECAD, as opposed to the isolated application of SMT, has achieved a significant net decrease in a total serum bilirubin level of 8.0 mg/dL [7]. Progressive jaundice and coagulation disorders have been dominant in all the patients, while HE was mild in one patient. A complete withdrawal of HE, including patients with the HE of III and IV grade, was noted after the SPAD treatment, and similar results of the SPAD effect have been presented in literature [4, 12].

Schmuck et al. [11] have shown in an *in vitro* model that optimal detoxification efficiency for albumin-bound substances (bilirubin and bile acids) can be reached with the 3% concentration of albumin in the dialysate and a flow rate of 1,000 mL/h. We used 3% and 4% albumin dialysate solution, as well as 700 mL/h and 1,000 mL/h dialysate flow rate; both albumin concentrations in dialysate solution and dialysate flow rates proved successful in our case series.

Mild thrombocytopenia has been observed in one patient, whereas all other causes of thrombocytopenia were excluded. A meta-analysis conducted by Tsiposis et al. [7] has determined that the application of ECAD has not led to a significant net decrease in the mean platelet count in patients treated by ECAD compared with patients treated with SMT, while another meta-analysis has shown that the use of ECAD was associated with increased risk of thrombocytopenia [12].

All the patients have been discharged from the hospital with liver function improved. The meta-analysis of Alshamsi et al. [12] that included patients with ALF and AoCLF showed that ECAD tended to reduce mortality in these patients.

Conclusion

As one of the ECAD techniques, SPAD has the capacity to remove the hepatotoxic substances without improvement of synthetic liver function. It provides supportive treatment for patients with LF who do not respond to the standard of care and can be used either as a bridge to transplant or for spontaneous recovery of the liver function. However, further prospective studies and meta-analyses are needed to evaluate the efficacy and safety of the SPAD and other ECAD techniques used as "salvage" therapy in LF patients.

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Received on November 16, 2020
Revised on March 7, 2021
Accepted on March 11, 2021
Online First March, 2021