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UPOTREBA “SINGLE PASS” ALBUMINSKE DIJALIZE U LEĈENJU
JETRENE INSUFICIJENCIJE- PRIKAZI BOLESNIKA

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Abstract

Introduction. A single pass albumin dialysis (SPAD) is a form of extracorporeal liver support system for the removal of albumin-bound toxins and water-soluble substances that accumulate in liver failure (LF). Case report. We present a retrospective case series of three patients hospitalized for LF and treated using the SPAD in the Clinical Center of Vojvodina, between 2018 and 2019. Of whom, two patients presenting with acute liver failure and one with acute-on-chronic liver failure. A total of 6 SPAD sessions were performed in each patient, resulting in decreased serum bilirubin and bile acid levels, and hepatic encephalopathy grade. On discharge from the hospital, liver function has been shown to improve in all the patients. Conclusion. SPAD removes the hepatotoxic substances without improvement of synthetic liver function, providing a supportive treatment for LF patients that do not respond to standard of care offering longer time for bridging to organ transplantation or spontaneous recovery of the liver function.

Key words: liver failure; liver, artificial; albumins; dialysis; liver regeneration.

Apstrakt

Uvod. “Single pass” albuminska dijaliza (SPAD) je vrsta ekstrakorporalne albuminske dijalize kojom se iz krvi uklanjaju toksini vezani za proteine i hidrosolubilne supstance kod bolesnika obolelih od jetrene insuficijencije. Prikaz bolesnika. Prikazali smo tri bolesnika obolela od jetrene insuficijencije lečena SPAD metodom u Kliničkom centru Vojvodine od 2018-2019. godine. Dvoje bolesnika je imalo akutnu insuficijenciju jetre, jedan akutizaciju hronične lezije jetre. Kod svakog bolesnika sprovedeno je 6 SPAD procedura, koje su dovele do redukcije serumskih bilirubina i žučnih kiselina, kao i stepena hepatične encefalopatie. Kod svih bolesnika došlo je do oporavka jetrene funkcije do početnog nivoa. Zaključak. SPAD predstavlja metodu ekstrakorporalne podrške jetrene funkcije kojom se omogućava uklanjanje hepatotoksičnih supstanci bez zamene sitetske funkcije jetre, omogućavajući stabilizaciju funkcije organa do spontane regeneracije ili transplantacije jetre.

Ključne reči: insuficijencija jetre; veštačka jetra; albumin; dijaliza; regeneracija jetre.
Introduction

There is a growing incidence of liver diseases in the world, 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 which can include 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 bridge therapy until the recovery to liver function or organ transplantation, extracorporeal liver support systems are used. Extracorporeal albumin dialysis (ECAD) is a mechanical, completely artificial support system which presents detoxification systems of many potential liver toxins that are using albumin as transport protein, such as hydrophobic bile acids, bilirubin, and serum nitric oxide even though it has not been shown to have 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 technique (Prometheus system) and the Single pass albumin dialysis (SPAD).

Case Report series

After being admitted to 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 normoglycaemic state, in addition to proton pump inhibitor (pantoprazole 40 mg per 12 hours) in 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, l-ornithine-l-aspartat was used for treating HE patients. 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 700ml/h for a seven-hour treatment) and 3% albumin (dialysate flow of 1000ml/h for a five-hour treatment) in the last two cases. Prior to initiation of SPAD, all the patients had double-lumen hemodialysis catheter inserted to the right internal jugular vein. Systemic anticoagulation was performed by infusion rates of unfractionated heparin. Blood sampling was performed within 30 minutes before the start and after the termination of the treatment.

First case: A 30-year-old male patient who 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 diffuse maculopapular rash with itching that did not resolve after taking antihistamines and became icteric. On physical examination, patient was afebrile, oriented, his arterial blood pressure (ABP) was 140/80mmHg, heart rate (HR) 80 beats per minute, respiratory rate (RR) of 16 breaths per minute, Glasgow Coma Scale score (GCS) of 15 and Acute Physiology and Chronic Health Evaluation (APACHE) II score 2. Abdominal ultrasonography and computed tomography (CT) showed hepatomegaly (17cm) with signs of hepatic steatosis. Gastroduodenoscopy revealed normal finding except chronic gastritic 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 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 regression of jaundice and significant bilirubin reduction. The characteristics of the present cases are given in Table 1 and 2.

Second case: A 49-year-old female patient who was admitted to hospital with fever, jaundice, and abdominal pain. Physical examination revealed patient to be oriented, without fever, with ABP of 109/53mmHg, HR 82/min, RR 18/min, painful sensation in the abdomen, GCS 15 and APACHE II 2. Diagnosis of acute LF caused by the hepatitis B virus was made. Additionally, SMT was initiated together with the nucleoside analogue reverse transcriptase inhibitor, Lamivudin, with a daily dose of 100mg. Despite the applied
SMT, on the fifth day of hospitalization HE has developed (stage II) with a worsening of coagulation disorder and 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 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 a diffuse cerebral edema without altered density in supratentorial and infratentorial region 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.

Third case: A 59-year-old female patient, who was hospitalized due to the 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. Also, she has been acquainted with the elevated aminotransferase levels for ten years, but not treated for that condition. Physical examination revealed a communicative but disoriented patient, without fiber, with ABP of 130/80mmHg, HR 100/min, RR 20/min, yellowish discoloration of the skin and sclera, painful sensation in the abdomen, GCS 15 and APACHE II 4. Diagnosis of an acute hepatitis A virus was confirmed by detection of IgM anti-HAV antibodies and a positive epidemiological data (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 the 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 improved hepatogram and normalization of the coagulation parameters.

Discussion
The use of the ECAD can contribute to an 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 the 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 have presented a series of 3 cases of hospitalized LF patients (1 male and 2 females) who had been treated with ECAD by modality of SPAD between 2018 and 2019. Two of our patients have had acute LF (ALF), although one patient has been diagnosed previously with the liver disease she has 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 which are more susceptible to develop an AoCLF in cases of HAV infection\(^9\).

According to the literature data, patients with ALF and AoCLF have been most frequently eligible for ECAD treatments, comprising three quarters of implemented ECAD\(^3\). The viral liver infection has been determined in two patients – ALF caused by the hepatitis B virus, and AoCLF caused by the hepatitis A virus. The treatment for LF caused by hepatitis B and C viruses, mainly by MARS, has been described in the literature, whilst Lee et al. have shown the case study of patients with ALF, caused by the hepatitis A, which has been successfully treated by the SPAD\(^3\),\(^8\). The use of lamivudine, potent inhibitor of hepatitis B virus (HBV) replication which causes rapid decline in serum HBV DNA levels, is indicated in patients with severe form of acute hepatitis B, but even then a small portion of patients with an overwhelming immune response to 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 have 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 has been the first case the SPAD was used for this indication\textsuperscript{10}.

The decrease in the bilirubin level has been verified, which correlates to the literature data regarding SPAD\textsuperscript{4,5,8,11}. Also, the meta-analysis, which has included ten randomized clinical trials (RCT), has shown that the use of the ECAD as opposed to the isolated application of SMT has achieved significant net decrease in a total serum bilirubin level of 8.0 mg/dl\textsuperscript{7}. A 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\textsuperscript{4,12}.

Schmuck \textit{et al.} have shown, in an \textit{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 1000ml/h\textsuperscript{11}. We have used 3% and 4% albumin dialysate solution, as well as 700ml/h and 1000ml/h dialysate flow rate; both albumin concentrations in dialysate solution and dialysate flow rates have proven successful in our case series.

Mild thrombocytopenia has been observed in one patient, whereas all other causes of thrombocytopenia have been excluded. Meta-analysis conducted by Tsiposis \textit{et al.} 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 other meta-analysis has shown that the use of ECAD was associated with increased risk of thrombocytopenia\textsuperscript{7,12}.

All the patients have been discharged from the hospital with liver function improved. The latest meta-analysis of Alshamsi \textit{et al.} that included patients with ALF and AoCLF showed that ECAD tend to reduce mortality in these patients\textsuperscript{12}.

\textbf{Conclusion}

To the best of our knowledge, this type of case series has not been presented in this region before. In conclusion, as one of the ECAD techniques, SPAD has the capacity to remove the hepatotoxic substances without improvement of synthetic liver function, providing a supportive treatment for patients with LF who do not respond to standard of care that 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 for evaluation of the efficacy and safety of the SPAD and other ECAD techniques used as “salvage” therapy in LF patients.

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**Table 1.**

| Biochemical parameters on admission and discharge from hospital |
|------------------|----------------|-------------|------------------|
|                  | Pts 1          | Pts 2       | Pts 3            |
| **Type of liver failure** | Acute          | Acute       | Acute-on-chronic |
| **Etiology of Liver Disease** | Drug intoxication | Viral (hepatitis B) | Viral (hepatitis A) |
| **Laboratory parameters** | Adm. | Disc. | Adm. | Disc. | Adm. | Disc. |
| AST [IU/l]        | 27             | 48          | >7000           | 77          | 7331 | 90 |
| ALT [IU/l]        | 71             | 167         | >7000           | 55          | 8808 | 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 10mg of Vitamin K which were administered at admission.

Abbreviations: 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.

**Table 2.**
Biochemical parameters before and after SPAD procedures

|                   | Pts 1 | Pts 2 | Pts 3 |
|-------------------|-------|-------|-------|
|                   | Before SPAD | After SPAD | Before SPAD | After SPAD | Before SPAD | After SPAD |
| Hgb [g/l]         | 158   | 147   | 122   | 90   | 126   | 132   |
| Plt [x10^9/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    |

Abbreviations: Hgb, hemoglobin; Plt, platelets; AST, Aspartate transaminase; ALT, Alanine aminotransferase; Pts, patient; SPAD, Single pass albumin dialysis.
Figure 1. - Total bilirubin levels during the SPAD sessions.

Figure 2. - Pathohistological findings of liver biopsy of the first patient (Haematoxylin and eosin stain; magnification x200).
Figure 3. - Endocranial CT scan of the second patient.