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The use of a single-pass albumin dialysis (SPAD) to correct severe hyperbilirubinemia in Weil's disease: a case report

Primjena single-pass albuminske dijalize (SPAD) za korekciju teške hiperbilirubinemije u Weilovoj bolesti: prikaz bolesnika

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Case report

Liver failure, regardless of the cause, carries a high risk of morbidity and mortality. Many of the toxins that accumulate in liver failure are poorly water-soluble and are thus transported through the bloodstream bound to albumins. Renal replacement therapy does not significantly alter the concentration of bilirubin and other albumin-bound toxins in the serum. In patients with liver failure additional detoxification methods are needed. There are several artificial extracorporeal liver support systems based on the principle of albumin but their availability is limited due to high cost and requirement of operators with special training. There have been several reports of using SPAD (single pass albumin dialysis) as an effective alternative. The main advantage of this method is that it can be performed using conventional renal replacement therapy (RRT) devices. In this report, the authors report the use of SPAD to treat severe liver failure in a patient with Weil's disease.

Prikaz bolesnika

Zatajenje jetre, bez obzira na uzrok, sa sobom nosi visoki rizik morbiditeta i mortaliteta. Brojni toksini koji se nakupljaju tijekom zatajenja jetre slabo su topljivi u vodi i stoga se transportiraju u cirkulaciju vezani za albumine. Bubrežna nadomjesna terapija ne utječe značajnije na koncentraciju bilirubina i drugih toksina koji se vežu na albumine u serumu. U bolesnika s jetrenim zatajenjem potrebne su dodatne detoksikacijske metode. Postoji nekoliko umjetnih izvantjelesnih sustava za potporu jetri zasnovanih na albuminskom principu, ali je njihova dostupnost ograničena zbog visokih troškova i potrebe za posebnom edukacijom osoblja koje izvodi postupak. Do sada je opisano nekoliko slučajeva primjene SPAD-a (*single pass albumin dialysis*) kao učinkovita alternativa. Glavna prednost ove metoda je što se može provesti koristeći uređaj za konvencionalno nadomještanje bubrežne funkcije. U ovom prikazu, autori opisuju primjenu SPAD-a za liječenje teškog zatajenja jetre u bolesnika s Weilovom bolešću.

Introduction

Severe leptospirosis, also known as Weil's disease, is characterized by multiorgan involvement, including acute kidney injury and liver dysfunction. Liver failure, regardless of the cause, carries a high risk of morbidity and mortality [1]. Numerous toxins that are accumulated in liver failure are poorly water-soluble and are transported through the serum by being bound to albumin. Since it is impossible to monitor the concentrations of all possible albumin-bound toxins, the concentration of bilirubin is used as a surrogate. Although the management of Weil's disease often includes renal replacement therapy serum concentration of bilirubin and other albumin-bound toxins is not significantly altered by hemodyalisis [2]. In order to eliminate bilirubin and other albumin-bound toxins from the serum, additional detoxification methods are needed. There are several artificial extracorporeal liver support systems based on the principle of albumin, such as Molecular Adsorbents Recirculating Systems (MARS) and Fractionated Plasma Separation and Adsorption (FPSA), commercialized as Prometheus [3]. Both systems reduce hyperbilirubinemia and improve encephalopathy in patients with liver failure but both are expensive and require operators with special training. The use of single-pass albumin dialysis (SPAD) has been shown to be an effective method of eliminating bilirubin and other albumin-bind toxins in several studies in vitro and in vivo [4 – 6]. The main advantage of this method is that it can be performed using conventional renal replacement therapy (RRT) devices. SPAD dialyzes blood against albumin-rich dialysate in a single pass through the dialyzer. There

have been several reports of using SPAD in patients with liver disease, including acute and chronic liver failure [6]. In this report, the authors report a case of Weil's disease, in which SPAD was used to correct severe hyperbilirubinemia and improve encephalopathy.

Case report

A 67-year-old man was transferred to the University Hospital for Infectious Diseases Zagreb from the County General Hospital Cakovec, Croatia on October the 14th 2014. The illness had started 7 days prior to admission. The patient complained of general weakness, headache, severe muscle pain in the lower extremities, lumbar pain, inability to walk, decreased urine output, darker urine, diarrhea and vomiting. The patient assumed that he was afebrile but never measured his body temperature. History taking revealed that in 2009 he was treated for prostate adenocarcinoma. Radical prostatectomy and chemotherapy were performed. Follow-up showed no complications or recurrence of the original illness.

The patient lived on a small farm in a village in northern Croatia where he had been regularly exposed to rodents and a variety of domestic animals, including pigs. He reported occasional moderate alcohol consumption but denied having consumed mushrooms or any hepatotoxic drugs.

On admission the physical examination revealed jaundice, severe pain on palpation in all leg muscles and distended abdomen without hepatomegaly or tenderness in the right upper quadrant. There were multiple small lacerations on his fingers and palms. Muscle strength in both lower extremities was decreased. Laboratory examination was as followed: WBC 16.200 cells/μL, seg 92.7 %, ly 1.8%, Hgb 114 g/L, platelets 141 000 cells/μL, CRP 193.7 mg/L, lactate 1.55 mmol/L, bilirubin 416 μmol/L, conjugated bilirubin 336 μmol/L, urea 45.2 mmol/L, creatinine 875 μmol/L, Na 136 mmol/L, K 4.0 mmol/L, Cl 96 mmol/L, Ca 1.71 mmol/L, Mg 0.94 mmol/L, P 1.70 mmol/L, AST 80 U/L, ALT 64 U/L, GGT 189 U/L, ALP 176 U/L, serum amylase 194 U/L, CK 488 U/L, CK MB 42 U/L, LDH 442 U/L, total protein 43 g/L, albumin 23.4 g/L, INR 0.97, fibrinogen 8.2 g/L. Urinalysis showed: protein 3+, leukocytes 2+, erythrocytes 4+. The diagnosis of leptospirosis was confirmed on the day of admission by microscopic agglutination test and PCR. Microscopic agglutination was positive for L. icterohaemorrhagiae (1:1000) and L. australis (1:500). PCR was positive for leptospirosis.

Two blood culture sets were sterile. Serology tests for viral hepatitides (C, B, A, E), hemorrhagic fever with renal syndrome (Dobrava, Puumala) and syphilis were negative. HIV duo test was also negative.

Chest X-ray showed extensive bilateral infiltrates with sings of pulmonary congestion. Abdominal ultrasound showed moderate enlargement of liver and spleen. On October 16th the abdominal CT depicted diffuse intrahepatic lesions and a mildly enlarged liver. Due to anuria and markedly increased levels of urea and creatinine, renal replacement therapy was initiated immediately after admission. The patient was hemodynamically stable. Transesophageal echocardiography showed normal systolic function with 2nd stage diastolic dysfunction. Despite treatment, the patient gradually developed signs of encephalopathy over the course of the next three days, beginning with confusion and incoherent speech and eventually reaching stupor. The levels of bilirubin remained above 400 μmol/L with conjugated bilirubin between 80 and 85 percent throughout the first 3 days of hospitalization, reaching the maximum level of 730.9 μmol/L on the 4th day, at which point the first cycle of SPAD was initiated. SPAD was performed in CVVHDF mode using the same protocol as Seoung Woo Lee et al. Vascular access had been obtained with a dual lumen hemodialysis catheter via a femoral vein. Dialysate and replacement solutions were bicarbonate-buffered. 20 % albumin was mixed into the dialysate to reach albumin concentration of 2 %. SPAD was performed in four 4.5-hour sessions over the course of four days. After 4 sessions of SPAD serum bilirubin was 388.7 mmol/L. Over the course of the next 8 days serum bilirubin slowly decreased spontaneously, reaching 91.3 μmol/L on the 16th day of treatment. CVVHDF was performed for 18 days. From the 6th to the 11th day the patient required mechanical ventilation due to excessive lung hemorrhage caused by leptospirosis. Upon admission antimicrobial treatment was started with ceftriaxone. Due to increasing levels of bilirubin and concerns of the possibility that ceftriaxone could induce cholestasis, the drug was replaced with ampicillin-sulbactam on the 4th day. The course of treatment was further complicated by nosocomial sepsis of unknown origin and for that reason antimicrobial therapy had to be changed to imipenem and vancomycin on the 8th day. The patient received several erythrocyte and platelet transfusions due to normocytic anemia and severe thrombocytopenia. The patient was extubated on the 11th day. After discontinuation of sedation there were no signs of encephalopathy. LP was performed on the 7th day of treatment. Mild pleocytosis with lymphocytic predominance was noted (6 cells/cmm, 100 % lymphocytes, protein 150 mg/dl, glucose 4.2mmol/L, serum glucose 5.2 mmol/L).

Discussion

This report showed that SPAD was used efficiently to reduce serum bilirubin, a surrogate marker for albumin-bound toxins, and thus probably contribute to the resolution of encephalopathy in a patient with acute liver failure caused by a severe form of leptospirosis. SPAD was performed using a standard continuous renal replacement therapy (CRRT) machine, which is used in all ICU settings

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
L (10^6/ml)	16.2	9.9	13.7	14.7	16.3	26.2	24.6	32.9	22.8	19.7	15.9	8.4	6.5	7.8
Neu (%)	92.7	83.9	82.2	75.4	79.8	85.0	84.5		83.7	77	80.6	81.7	89.7	76
Plt (10^6/mL)	18	57	51	46	55	61	30	113	169	189	238	282	250	234
CRP (mg/L)	193		107		142	121	177	199	399		157			27
AST (U/L)	80	57		74	77	73	59	71	68	105	198	209	209	135
ALT (U/L)	64	59		47	46	79	32	62	53	58	103	130		71
BUN (mmol/L)	45.2	27.7	14.3	12.5	13.9	14.4	12.7	18.9	22.9	27.8	31.4	30.9		37.2
Cr (µmol/L)	875	486	280	219	205	208	179	284	314	341	332	290	256	352
PT Quick value	0.97	0.88	0.97	0.93	0.89	1.15	1.27	0.79			0.84	0.91	0.91	0.87
Bil. (µmol/L)	**416**	**451**		**730**	**631**	**616**	**463**	**338**	**329**	**269**	**249**	**182**		**115**
Bilc (µmol/L)	**336**	**425**		**604**	**515**	**415**	**335**	**274**	**225**	**157**	**141**	**101**		**57**

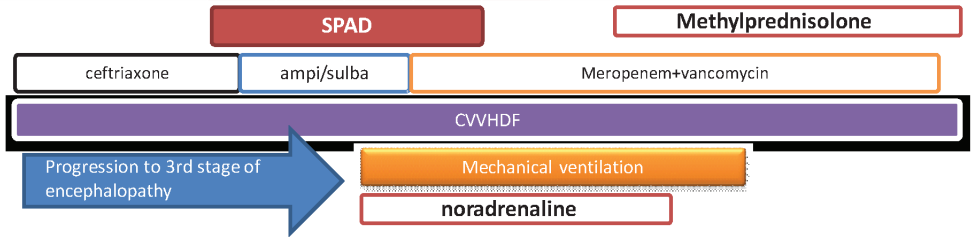

Figure 1. Treatment timeline since hospitalization

Slika 1. Vremenska crta liječenja nakon hospitalizacije

to treat patients with acute kidney failure. With CRRT machines being widely available and requiring no additional equipment or specialized personnel training in order to be used to remove albumin-bound toxins from blood, SPAD is an efficient and cost-effective potential alternative to MARS and similar specialized artificial extracorporeal liver support systems [5, 6]. Several studies have already demonstrated efficacy of SPAD in patients with acute liver failure (ALF) and acute-on-chronic liver failure (AoChLF) of various causes [6]. We demonstrated the first case of SPAD being successfully utilized in a patient with Weil's disease.

Despite liver damage and severe hyperbilirubinemia, the patient's serum concentration of NH3 was normal throughout the course of treatment. Although ammonia concentration in venous blood is usually elevated in liver disease and ammonia does contribute to the genesis of brain edema, a substantial role of ammonia in causing hepatic encephalopathy has not been demonstrated in human clinical studies [7]. In vitro SPAD and CVVHDF induced a significantly greater reduction of ammonia levels than MARS [4]. However, in vivo Boonsrirat et al. showed no significant difference between serum ammonia before and after treatment with SPAD in patients with liver failure [6].

An issue that deserves further research is that any method of removing albumin-bound toxins can cause unpredictable changes in albumin-bound drugs concentrations, which can lead to deleterious effects, especially in the ICU setting.

Larger prospective studies comparing SPAD to MARS and other artificial extracorporeal liver support systems are still needed. While it has been proven that artificial extracorporeal liver support systems remove albumin-bound toxins, studies are still conflicting regarding their ability to reduce mortality in patients with liver failure. It is often cited that without liver transplantation these systems don't reduce mortality and can be used only as a bridge therapy. While this is true for patients with irreversible liver failure, patients with transient liver dysfunction may benefit from these systems, as suggested in this case report and several other aforementioned studies.

In conclusion, despite the observed clinical and laboratory improvement with SPAD, whether this system could reduce mortality in patients with Weil's disease and other reversible causes of acute liver failure, remains to be determined by larger randomized studies. Finally, further research is necessary to establish the optimal technical settings for SPAD, including the concentration of human albumin in dialysate and blood and dialysate flow rates.

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