THE IMPORTANCE OF EXTRACORPOREAL LIVER SUPPORT SYSTEMS IN THE TREATMENT OF HEPATORENAL SYNDROME

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ABSTRACT
Hepatorenal syndrome (HRS) is a functional irreversible renal failure that occurs in patients with advanced liver cirrhosis or acute hepatic failure. The mean characteristic of HRS is renal ischemia secondary to hypotension and profound renal cortical vasoconstriction as a consequence of activation of systemic and local vasoconstrictors. Pharmacological treatment of HRS, using mostly terlipressin, midodrine or octreotide, is focused on vasoconstriction of dilated splanchnic arterial beds leading to increase of systemic arterial pressure and renal perfusion pressure and suppression of endogenous vasoconstrictor systems. Nonpharmacological treatment of HRS includes transjugular intrahepatic portosystemic shunts, renal and liver support represented by modified methods of dialysis such as extracorporeal albumin dialysis (ECAD) and liver transplantation. The most frequently applied sort of albumin dialysis, MARS method (molecular adsorbent recirculating system), is based on dialysis across an albumin-impregnated membrane using 20% albumin in dialysate. Charcoal and anion exchange resins in the second circuit purify and regenerate the binding sites on albumins in dialysate. Not so often used method of Prometheus combines the fractional plasma separation and adsorption by polysulfone filters permeable for albumin and adsorbents that regenerate the filtered plasma. These kinds of renal and liver support showed better biochemical profile and haemodinamical and neurological improvement, and in trials with small number of patients longer survival was shown. For the time being, they are only buying time for the patients who are waiting for the liver transplantation as the only causal solution.

Key words: Hepatorenal syndrome, Liver support, Extracorporeal albumin dialysis, MARS method, Prometheus method, Liver transplantation

SAŽETAK
Hepatorenal sindrom (HRS) predstavlja funkcionalnu bubrenu insuficijenciju koja se javlja kod pacijenata sa uznemirenom cirozom jetre ili akutnom insuficijencijom jetre. Glavna karakteristka HRS je bubreni ishemij uzrokovan hipotenzijom i izraženom konstriciji kornih kromnih arterija bubrega koja predstavlja posledicu aktivacije sistematskih i lokalnih vazonaskonstritora. Nefarmakološko lečenje HRS obuhvata transjugularni portosystemski šant, bubrenu i jetrinu podršku. Najčešće korišćeni metod albuminske dijalize, MARS metoda (molecular adsorbent recirculating system), baziran je na dijalizi kroz albumin impregnisane membrane korišćene s koncentracijom albumina od 20%. Aktivni ugalj i jonosrednjica umesto u drugom kružnici dijalize služe u drugom kružnici dijalize. "Kupuju vreme" za bolesnike koji čekaju transplantaciju jetre kao jedino kauzalno rešenje. Pojedine reči: hepatorenalni sindrom, potpora jetrine funkcije, vantelesna albuminska dijaliza, MARS metoda, Prometeus metoda, transplantacija jetre

INTRODUCTION
The hepatorenal syndrome (HRS) is defined as the development of renal failure in patients with advanced liver cirrhosis or acute hepatic failure in the absence of any other identifiable cause of renal pathology (1-3). The diagnostic criteria for HRS have been revised by the International Ascites Club (2005) (4). HRS occurs in about 4% of patients admitted with decompensated cirrhosis, the cumulative probability being 39% at five years. Only 3.5% of patients spontaneously recover from HRS (2). Because of that, HRS has the worst prognosis among all complications of advanced liver cirrhosis and liver insufficiency. The survival is mostly influenced by the type of HRS. The expected median survival in type 1 is about 2 weeks, while the median survival of the patients with type 2 HRS is much longer, about 6 months (3). The type 1 is characterized by rapidly developing renal failure, defined by doubling the initial serum creatinine to a level greater than 225μmol/l, or a 50% reduction in initial 24h creatinine clearance to a value less than 20ml/min within two weeks (3, 4). Type 2 HRS usually occurs in patients with diuretic resistant ascites and is characterized by moderate renal failure with a creatinine clearance below 40ml/min (3). The high mortality of patients with HRS is mainly consequence of advanced liver insufficiency, but the patients in whom renal function improves after therapy survive longer than the patients who were not treated in that way (1-3). Since HRS represents just one of the complications of liver insufficiency, the full recovery could be achieved only by liver transplantation. The other treatment options postpone the lethal outcome or „buy” the time, improving the condition of the patients until the liver transplantation is performed. Possibly positive outcomes may also happen as liver regeneration in acute liver failure or spontaneous recovery of liver function in alcoholic hepatitis.
PATHOGENESIS OF HEPATORENAL SYNDROME AND THERAPEUTIC OPTIONS

The pathophysiological hallmark of HRS is reversible vasoconstriction of the renal circulation and mild systemic hypotension (1, 2, 7-9). A progressive decrease in renal perfusion occurs as cirrhosis progresses. That is why HRS represents a final step in a series of functional renal abnormalities that takes place as hepatic dysfunction and portal hypertension worsen. The kidneys are structurally normal and at least in the early part of the syndrome, tubular function is intact, as reflected by avid sodium retention and oliguria (1).

The precise mechanism of renal vasoconstriction is not fully understood, but may involve both increased vasoconstrictor and decreased vasodilator influences on renal circulation. The main vasoconstrictor systems (renin-angiotensin system, the sympathetic nervous system and arginine vasopressin) are activated as homeostatic response to improve underfilling of the arterial circulation which is the hallmark of advanced liver cirrhosis with portal hypertension (1, 2, 3, 7-9). Arterial underfilling is due to vasodilatation of the splanchnic circulation related to increased splanchnic production of vasodilator substances such as nitric oxide. In the early phase renal perfusion is maintained by increased renal production of vasodilators as prostaglandins and nitric oxide, but later this balance is destroyed as renal vasodilators production is decreased or resistance to their effects occur and activation and production of aforementioned vasoconstrictors is much higher (2). The splanchnic area escapes the effect of vasoconstrictors probably because of the greatly increased local production of vasodilators (2). Sepsis, spontaneous bacterial peritonitis, hypovolemia, gastrointestinal bleeding and the extensive use of diuretics could worsen liver function and exaggerate those haemodynamic changes in liver cirrhosis and represent the precipitating factors for the development of HRS (1, 2, 3, 7).

The crucial goals of managing and treatment of patients with hepatorenal syndrome are the avoidance and treatment of precipitating factors and optimization of haemodynamic changes which means improving of renal perfusion pressure and decreasing of vasoconstrictor action (1, 2, 3, 7). If precipitating factors are sought and treated, if patients do not respond by diuresis after receiving up to 1.5 liters of saline and albumine and if optimal paracentesis performed to decrease renal venous pressure does not improve parameters of renal function, than it is necessary to give systemic vasoconstrictors such as vasopressin analogues (ornipressin and terlipressin) or adrenergic agonists (norepinephrine, midodrine) or somatostatin analogue (octreotide) (1, 2). These drugs cause vasoconstriction of of dilated splanchnic arterial bed resulting in increase of systemic blood pressure and redistribution of the part of the splanchnic volume to the systemic arterial blood volume with consequent improved renal perfusion and glomerular filtration rate (1, 3, 4). A number of patients treated in that way is not so high, but evidence for beneficial effect of vasoconstrictor therapy for the treatment of HRS is steadily accumulating (5). Treatment with those vasoconstrictors and plasma expansion with albumin is beneficial and serves as a bridge to transplantation. Terlipressin not only improves renal function in majority of cases, but could also cause reversal of HRS in 57% to 78% of the patients (6). The other reports show that a significant number of responder patients relapsed after terlipressin withdrawal. Further studies are in progress to assess the link between terlipressin and survival in hepatorenal syndrome (10).

Nonpharmacological treatment of HRS includes tranjugular intrahepatic portosystemic shunts (TIPS), renal and liver support with modified dialysis methods (extracorporeal albumin dialysis-ECAD) and liver transplantation (3, 4). The insertion of TIPS, especially in cirrhotic patients with refractory ascites and some degree of renal dysfunction, returns a significant portion of the splanchnic volume into the systemic circulation. This leads to suppression of various vasoactive neurohormones, resulting in better renal perfusion and improvement in glomerular filtration (4). TIPS prolongs median survival in type 1 HRS between 2 months and 4 months (2). Unfortunately, there are no controlled studies comparing TIPS to other modalities of treatment, in particular vasoconstrictors plus albumin. It is interesting to note that when TIPS was placed after a period of vasoconstrictor therapy, renal function returned to normal levels (4).

RENAL AND LIVER SUPPORT WITH MODIFIED DIALYSIS METHODS

Renal replacement therapy (haemodialysis, haemofiltration, haemodiafiltration) is frequently used in patients who are on the waiting list for orthotopic liver transplantation, or if there is possibility for the recovery of liver function (1, 8). The potential benefit of that way of treatment was not unequivocally confirmed. On the contrary, renal replacement therapy just prolongs the process of dying because it can not compensate the lost liver function which is the main cause of HRS (1). The only acceptable indications for haemodialysis are fluid overload, acidosis and hyperkalaemia, but they are uncommon (1, 3, 4). Otherwise, the patients tolerate poorly intermittent haemodialysis because of frequent side-effects including arterial hypotension, bleeding and possible infections. In selected cases of anaarca, when there is a need to achieve negative fluid balance without hypotension, continuous arteriovenous or venovenous haemofiltration could be used.

Lately, the modified dialysis method, called extracorporeal albumin dialysis (ECAD), has been used more frequently as a liver support in which toxins bound by plasma proteins responsible for manifestations and complications in liver failure are removed using membranes and adsorbents (4). The premise is that albumin molecule has free binding sites which compete for toxins bound to proteins in the perfused blood (13, 14). Because most relevant toxins in liver failure are albumin bound, conventional haemodialysis/haemofiltration cannot effectively remove
them. While ammonia, protein breakdown products (aromatic amino acids, tryptophan indole, mercaptan, phenol) and endogenous benzodiazepine are implicated in the development of hepatic encephalopathy, nitric oxide and prostanoïd are important in the pathogenesis of circulatory dysfunction (11-14). Oxidative stress could cause increased capillary permeability and modulate cell death (13, 14). Majority of these toxins are water soluble and albumin-bound. Albumin, binding different molecules, acts as transporter and scavenger. It has a strong negative charge and binds weakly to bilirubin, fatty acids, nitric oxide, bile salts and by reduced sulphydrl groups binds reactive oxygen and nitrogen species especially superoxide, hydroxyl and peroxynitrite radicals. There have been attempts in earlier period to provide liver support using haemofiltration, plasma exchange and plasma perfusion using charcoal or polymer-based sorbents (11-13). Albumin bound toxic molecules are not effectively removed by these procedures and there are a lot of undesirable side-effects: bioincompatibility with complement activation and drops in fibrinogen and a loss of many hormones and active substances (hepatocyte growth factor, triiodthyronine, steroid hormones, insulin). There are two methods of extracorporeal albumin dialysis which were used in some hospitals. The first one is Prometheus (16). In order to avoid undesirable effects of direct contact of plasma and adsorbents, there have been developed specific membranes with a pore size large enough to allow albumin as toxin carrier to pass through, and to prevent the passage of substances of higher molecular mass such as IgM and fibrinogen (13, 16, 18). This method of fractionated plasma separation and adsorption represents a new type of albumin dialysis (16).

Albumin and bound toxins pass through the membrane and are then directly removed from the blood by special adsorber within the secondary circuit. The newly developed Prometheus system combines method of fractionated plasma separation and adsorption with high-flux haemodialysis (16). The pilot study designed to investigate safety, clinical use and efficiency of Prometheus system was approved by Ethics Committee of the Medical University Hanover and was conducted from October 2001 till May 2002 in 11 patients (16, 18). Nine patients had HRS and average Child-Pugh score was 12.2. Nine patients had two treatment sessions of at least 4h duration (two patients died after the first session because of complications caused by liver failure). The pricip of detoxication comprises two steps. First the blood is drawn into extracorporela circuit where it passes through an albumin-permeable polysulfon filter. In the secondary circuit the filtered plasma with the albumin-bound toxins flows through two adsorbers in a row (prometh 01 and prometh 02). The purified plasma is then returned to the blood side of the albumin filter. In order to eliminate water-soluble toxins, blood undergoes haemodialysis using high-flux dialyser, figure 1. The results of study showed significant decrease of bilirubin, bile acid, ammonia and creatinine concentrations. The laboratory parameters such as albumin, transaminases, international normalized ratio and trombocytes were not changed. An increase was noticed in leukocytes blood count without infection. The only serious complication during treatment was the drop of mean arterial pressure. The overall mortality during hospitalization (2 months) in this group of patients was 72%, that is not significantly different from the mortality rate observed in the control group of patients, not treated that way (from 51 to 85%) (16).

The name of second method of extracorporeal albumin dialysis is molecular adsorbents recirculation system (MARS). MARS has been more frequently used in the treatment of patients with advanced liver failure and HRS (11-15). It has been shown that albumin when attached to polymers has a higher affinity for albumin-bound toxins. MARS uses a hollow fiber dialysis module (Rostock, Germany) in which the blood from the patient is dialyzed across an albumin-impregnated membrane, while maintaining flow of dialysate containing albumin concentration of 20% in the extra-capillary compartment (12-14).

Albumin in dialysate is highly purified and has higher number of available binding sites for toxic substances. That creates the driving force for the mass transport of albumin-bound molecules that first detach from the albumin in blood, and then bind for lipophilic sites of the membrane, transport across the membrane and release into the dialysate where they bind with dialysate albumin (12, 14). The dialysate is then perfused over activated charcoal and anion-exchange resin to regenerate dialysate, while water-soluble substances are removed as in conventional haemofiltration (12-14). The volume of ultrafiltrate was replaced into the blood circuit proximal to the MARS membrane. The membrane is not permeable for albumin and other proteins such as hormones, coagulation factors and antithrombin III (12, 13). The only observed complication during MARS treatment was reduction of platelet count (11, 14). The components of MARS method are shown on the figure 2.
In the first prospective randomized controlled study conducted in two centers the influence of MARS method on the treatment of the patients with HRS was examined (17). All 13 patients were anuric or oliguric. Patients were randomized to standard medical therapy including haemodiafiltration or MARS treatment. MARS treatment resulted in a significant removal of bilirubin and decrease of creatinine with significant prolongation of survival time. The authors showed also efficacy of MARS treatment in the therapy of chronic liver disease complicated by cholestasis and HRS. MARS improved systemic chemodynamic status by increase of mean arterial pressure and vascular resistance, and also improved hepatic encephalopathy (11,12,13,14). It was shown that long-term MARS treatment was successful in supporting patients awaiting elective liver transplantation in case of decompensation of chronic liver disease. Ongoing prospective, randomized, controlled trials compare efficacy of MARS versus standard medical treatment in managing decompensated chronic liver disease to determine whether MARS can shorten the time of recovery and decrease morbidity and mortality (13,14,15).

There are still difficulties to compare MARS and Prometheus treatment because of the small number of the patients included in the study and the different time of the treatment. In reported studies, MARS was used 3 weeks and Prometheus only 2 days. The significant decrease of the level of substances not only water solved such as urea and creatinine, but also substances that are bound to albumin (bile salts and conjugated bilirubin) was achieved by Prometheus method (18, 19). In patients with liver failure caused by alcoholic hepatitis, the parameters of hyperkinetic circulation were much more decreased by MARS method than by Prometheus method (20). Currently there is not sufficient data to recommend the use of ECAD as a treatment for HRS. Randomized controlled trials comparing the efficacy and survival rate in ECAD versus vasoconstrictor therapy are needed but this will take a lot of efforts as ECAD is expensive and labor-intensive (4).

Except for aforementioned methods of artificial detoxification systems, there are efforts to develop biologic systems like whole organ perfusion and bioreactors with liver cells (21,22). Those extracorporeal liver support systems compensate synthetic (albumin, aminoacid, coagulation factors) and regulatory (precursors of CNS-transmitters) liver function, which are lost because of liver failure. The complex system of extracorporeal liver support combines the Cell Module as a specific bioreactor and the DetoxModule (21). Bioreactor comprises 3 capillary systems that enable plasma inflow and nutrients exchange, gas exchange (cell oxygenation/carbon dioxide removal) and removal of metabolites. The extracapillary space forms a cell compartment which is under conditions of capillary perfusion organised into liver tissue forming neosinusoidal structures and producing biomatrix. The DetoxModule enables removal of albumin-bound toxins and water-soluble toxins using albumin dialysis and venovenous haemofiltration. This concept, suggested as more efficacious way to bridge the period until liver transplantation or to get a time before the possible liver regeneration, is in the phase of pilot clinical investigation in the pilot study.

The only effective and permanent way of treatment of HRS and liver failure is orthotopic liver transplantation (1,3,4,8,9). The main problem in liver transplantation is a long waiting time and short time of survival. There are some reports that show one and four year survival rates of 71% and 60% respectively, for HRS patients, and 83% and 70% for non-HRS patients (23). However, 10% of patients are dialysis-dependent even after liver transplantation (1). Patients who had alcoholic hepatitis as a cause of liver failure complicated by the development of HRS had a lower chances for the resolution of HRS (24). Glomerular filtration rate is lower in patients who had HRS before transplantation (23). In order to explain those results, one should take into account nephrotoxic side effects of immunosuppressive drugs that are necessary as pharmacological treatment after liver transplantation (cyclosporine and FK506) and the persistence of hyperdinamic circulation after transplantation which potentiates the constriction of afferent arteriole (1,23). The majority of patients without HRS before liver transplantation had a decrease in GFR from 94 to 60ml/min one year after transplantation (1).

CONCLUSION

Hepatorenal syndrome (HRS) is a functional renal insufficiency that develops in terminal liver failure. Pathogenesis of this syndrome includes haemodynamic changes (decreased mean arterial pressure and renal perfusion pressure) and increased production of systemic and renal vasoactive substances with stimulation of renal sympathetic system. The usual medical pharmacological therapy is aimed at these pathophysiological disturbances. Currently, there is insufficient data to support the routine use of ECAD as a treatment for HRS, especially since ECAD is an expensive method. Firm recommendation for the use of ECAD will have to await the results of well-designed, randomized, controlled trials comparing ECAD with vasoconstrictor therapy, which is now regarded as the standard therapy for HRS.
Both types of treatment prolong survival time till liver transplantation or recovery of liver (function in the cases where that could happen), since the renal function directly depends on liver function. Standard HD treatment does not improve renal function. The only causal solution of this problem is orthotopic liver transplantation.

REFERENCES