

Clinical Use of Kidney Replacement Therapy in Patients with Liver Failure: Case Report and Literature Review

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Abstract

Severe acute liver failure in adults is a condition that may lead to several complications such as cerebral edema and acute kidney injury requiring liver transplant. Few studies analyze the benefit of dialysis therapies for decreasing bilirubin and ammonia levels to achieve metabolic compensation. In Ecuador there are no case reports of treatment with combined hemoperfusion and online hemodiafiltration. We report the case of a patient who was diagnosed with fulminant hepatic failure due to acute alcoholic hepatitis and concomitant acute kidney injury. We include the clinical course after adding two sessions of combined hemoperfusion and online hemodiafiltration to the conventional treatment.

Keywords: Hemoperfusion; Hemodiafiltration; Acute liver failure

Introduction

Severe acute liver failure (SALF) and its metabolic consequences (due to hyperammonemia and hyperbilirubinemia) may be an important cause of cerebral edema and acute kidney injury (AKI) in adult patients. AKI complicate SALF in approximately 30 to 50% of patients [1,2]. The frequency may in fact be as high as 75%, due to etiologies that cause kidney damage independently, such as acetaminophen intoxication [3,4]. Once kidney damage has occurred, it is usually progressive and associates to poor prognosis if liver transplant is not performed immediately [5,6].

Hepatorenal syndrome (HRS) is one of the main causes of AKI in SALF patients and it is diagnosed by exclusion. Its pathophysiology is characterized by poor response to volume and refractory prerenal hyperazotemia, a consequence of systemic and splenic vasodilation with deep renal vasoconstriction without parenchymatous renal injury. Type 1 HRS is acute, quickly progressive and has worse short term prognosis; whereas type 2 HRS or chronic HRS displays a slower course [7,8].

The toxins in SALF that generate the most organic damage and thus worsen the prognosis of patients with kidney injury are bilirubin and ammonia. These patients have traditionally been treated with clinical measures. Because only a small number of patients with severe acute liver failure actually develop brain edema, few published trials assess the role of extracorporeal dialysis treatment for decreasing serum ammonia and bilirubin or as treatment for brain edema [9].

Currently, the best toxin removing treatment for SALF patients is Molecular Adsorbent Recirculant System (MARS). However, this

treatment is not available in Ecuador, so this patient was treated with a combination of resin hemoperfusion using neutral macroporous synthetic adsorption and online hemodiafiltration.

Case Presentation

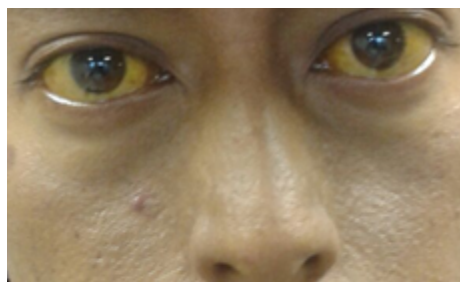
We present the case of a male 28 years old Hispanic patient with a history of alcohol abuse for 11 years, worsening in the past three months, up until 1 month prior to his hospitalization. He presented progressive jaundice, which was studied closely and was finally diagnosed as decompensated alcoholic cirrhosis associated with acute kidney injury and fulminant hepatitis due to alcohol intoxication. He was admitted due to lethargy, fatigue, itching, nausea and oliguria. On physical examination, the patient had generalized jaundice, lethargy, asterixis, ascitis and lower limb edema +++/+++. Laboratory tests are described in Table 1, in addition to PT= 28.6, INR: 2.43. Scales score: MELD score was 40 and Maddrey score of 73.4 indicating a poor prognosis. Medical treatment was initiated with: prednisone, ceftriaxone, pentoxifyline, ursodesoxycholic acid, human albumin, vitamin K, spironolactone, furosemide, terlipresine, lactulose and nutritional support. In spite of these measures, the patient's clinical status did not improve and bilirubin and nitrogen compound levels remained very elevated.

Integral management in nephrology and hepatology decided to carry out combined resin hemoperfusion and online hemodiafiltration for treatment of acute kidney injury, clearance of ammonia, bilirubin and other potentially nephrotoxic and neurotoxic substances in order to avoid greater cerebral complications. The patient was not a suitable candidate for liver transplant until a period of abstinence of at least 6 months was demonstrated, thus worsening the prognosis.

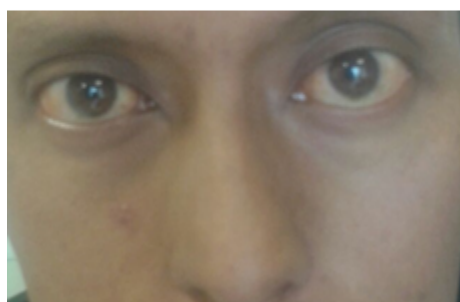
The patient underwent two sessions of intermittent hemoperfusion (Figures 1 and 2), three hours each, with a macroadsorbent resin, MG-250 filter plus high volume replacement on line hemodiafiltration (22 liters), pre-dilution, 300-400 ml/min and dialysate flow of 800 ml/min. After these sessions there was a significant decrease in total bilirubin levels, recovery of the acute kidney injury and clinical improvement and then he was transferred to the base hospital. In the ensuing five month follow-up patient improved the MELD score status, had no criteria for liver transplant and fully recovered from the kidney injury (Table 1).

Variable	Admission	Pre-treatment	Immediate post-treatment	Post-treatment (5 months)
Direct bilirubin (mg/dl)	26.47	31.61	9.8	0.94
Albumin (g/dl)	2.2	3.3	N/A	3.78
Creatinine (mg/dl)	3.4	1.6	0.5	1.2
Sodium (mmol/L)	135.9	135	130	138
Potassium (mmol/L)	3.37	5.07	3.05	4.66

Table 1: Laboratory test evolution (Source: Medical record - Hospital Metropolitano de Quito).



a)



b)

Figure 1: a) Patient before treatment. b) Patient after treatment.



a)



b)

Figure 2: a) Combined extracorporeal therapy. b) Evidence of bilirubin adsorption in the filter.

Discussion

Bilirubin is a highly toxic catabolic product, liposoluble and hydrosoluble in water solutions at a physiologic pH. In the blood, it forms a complex with albumin for its transportation and is bound by y and z of hepatocytes to be excreted in the bile jointly with the feces (90%), or as urobilinogen in urine [10]. When there are elevated concentrations of conjugated plasmatic bilirubin (intra or extrahepatic cholestasis), the kidney is responsible for 50 to 90% of its excretion. Non-conjugated bilirubin is toxic for many cells, levels above 20 mg/dl may result in brain damage [11].

The metabolism of ammonia depends on the enzyme activity of some organs, including bowels, muscles and kidney. It is eliminated via erythrocyte catabolism through conversion into urea in the liver and into glutamine in the liver, brain and skeletal muscles. The intestine is the site of greatest production of ammonia, and from there it reaches

the liver via portal circulation for its conversion into urea and water [12].

Even though abnormal levels of ammonia are not always associated with neurologic signs and symptoms, concentrations above 150 $\mu\text{mol/L}$ have shown a positive correlation with an increase of intracranial pressure and cerebral herniation [13]. Existing reports on the use of renal replacement therapy (RRT) for the decrease of blood ammonia in the treatment of cerebral edema are poorly executed, they do not specify the most appropriate dialysis techniques and do not establish criteria for initiating dialysis. In newborns with urea cycle disorders or congenital metabolism errors, there are small trials that showed that peritoneal dialysis, intermittent hemodialysis or continuous renal replacement therapies (CRRT) are effective for decreasing the levels of blood ammonia [14,15].

Liver failure due to many causes is a condition of difficult treatment with high mortality rates in spite of Intensive Care Unit management. The accumulation of albumin bound metabolites that are normally cleared by the liver, such as bilirubin and biliary acids, substantially contribute to the development of multiple organ dysfunction.

The MARS system is a cell-free method of liver extracorporeal assistance for selective removal of albumin bound substances, biliary acids, triptophan, mid-sized and short chain fatty acids, aromatic aminoacids and ammonia, resulting in a decrease of hepatic encephalopathy, an increase in the median arterial blood pressure and improvement of the function of the liver and kidney with a prolongation of the overall survival ($p < 0.05$) [16]. Currently, this type of treatment is not available in Ecuador, though resin hemoperfusion and online hemodiafiltration are accessible.

Hemoperfusion involves the passing of anticoagulant impregnated blood through a device, usually a column that contains adsorbent particles. It was introduced in 1940, refined between 1950 to 1970 and then applied in a clinical setting for the treatment of intoxications during the decades of 1970s and 1980s. In spite of its availability, it is rarely used [17-20].

There are several types of adsorbent particles used for hemoperfusion devices. The most commonly used are active charcoal and resin, with which several conditions can be treated, including intoxications and liver failure [17]. In hemoperfusion with resin, the adsorption capacity depends on molecular screening, tridimensional structure and the molecular group affinity of the resin and adsorbent material, as well as interactions of Vander Waals forces between molecular groups and the high adsorption. It is used for removing macromolecular toxins, especially those with lipophilic, hydrophobic groups or aromatic ring structures [21]. The resins are most useful and effective for the removal of liposoluble drugs, with drug clearance rates that exceeds those reached by charcoal hemoperfusion and are widely available in Europe and the United States market.

In most cases, in terms of clearance, the elimination of drugs is greater with hemoperfusion than hemodialysis, peritoneal dialysis or forced diuresis [22]. Broadly speaking, hemoperfusion is preferable to hemodialysis for the removal of chemicals that are liposoluble or with high protein binding, although its application has been limited due to the development of high flow dialysis membranes and procedures such as hemodiafiltration [23] (dialysis flows of 800 ml/min). The combined use of these two techniques may result in an improvement of patient's acid-base state, which is not achieved with hemoperfusion alone.

The procedure of hemoperfusion is simple; heparinization must be individualized, as it is in hemodialysis. The type and size of the filter will depend on the patient's body size and the toxic agent involved. The usual pump flows range from 200 to 300 ml/min, but if combined with hemodiafiltration it must increase to 400 ml/min and the dialysis flow to 800 ml/min. Duration of the procedure can range between two and four hours, depending on the serum levels of the toxic agent or patient's clinical status. Recycling of filter is not allowed due to toxic saturation of the resin.

Hemoperfusion must be used in cases of drug intoxication of poisons that may be removed more effectively than endogenous elimination by liver or kidney [24]. There is a substance rebound after their removal with this technique because of redistribution from tissues into the plasma. It may cause a new neurologic dysfunction and it is minimized with intermittent treatment in place of prolonged hemoperfusion.

The main side effects of hemoperfusion with resin are platelet depletion, which is corrected within 24 to 48 hours after the procedure, hypocalcemia, hypoglycemia, transient leukopenia and hypothermia. Hypotension is not frequent. In the authors' experience, patients who underwent hemoperfusion have not required corrections of above mentioned complications.

In Ecuador, there are no reports on the use of hemoperfusion in acute intoxications. This procedure has only been done with macroadsorbent resin as of 2014 by the authors' group.

In the case report, there was clinical improvement, eliminating the need for liver transplant by removing the toxins caused by liver injury, kidney injury and inflammatory products that are potentially harmful and may have led to coma or death. The laboratory tests that showed a decrease in bilirubin sufficed to conclude that the ammonia was also effectively removed due to its plasmatic profile and its smaller molecular size 9. The follow up of patient has shown a stable clinical status, with normal serum creatinine and bilirubin levels (Table 2).

Progressive deterioration in spite of intensive support therapy of intoxicated patient.
Severe intoxication with depression of brain function, hypoventilation, hypothermia and hypotension.
Development of coma's complications, such as pneumonia or septicemia, in intoxicated patients.
Alteration of normal drug excretion due to liver, renal or cardiac insufficiency.
Intoxication with agents delayed metabolic effects, such as bipyridyls (paraquat, diquat) or fungi.
Liver failure in which the extraction of liver toxins with hemoperfusion may prevent or delay hepatic coma and serve as a bridge for liver transplant [25-28].
End stage renal disease with aluminum intoxication.
To remove substances that predict cardiovascular mortality, with a medium molecular weight range (Beta 2 microglobulin, angiogenin, leptin, retinol and interleukin binding protein 18) dialysis patients [29,30].

Table 2: Indications of hemoperfusion.

Conclusion

Extracorporeal dialysis therapies in Ecuador are not considered for acute or fulminating liver failure treatment of any cause, and reference

to nephrologist is only carried out if there is concomitant acute kidney failure.

Combined hemoperfusion and online hemodiafiltration is a removal technique available in Ecuador for patients with hepatorenal syndrome and SALE.

The use of this technique may serve as coadjuvant treatment in patients with SALF with or without kidney failure, or who are in waiting list for liver transplant and present toxic levels of metabolic waste substances, improving their quality of life in this time period and reducing possible complications during the waiting period or until the liver condition is resolved.

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