REVIEW

THERAPEUTIC MANAGEMENT OF HYPONATREMIA IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract*: Hyponatremia is frequently seen in patients with liver cirrhosis. The presence of hyponatremia in these patients has been shown to be associated with severe ascites, impaired kidney function, higher rates of hepatorenal syndrome, spontaneous bacterial peritonitis, and hepatic encephalopathy. The main physio pathological mechanisms involved in the occurrence of hyponatremia in patients with liver cirrhosis are systemic vasodilatation and increased secretion of antidiuretic hormone. The therapeutic management of these patients presents a series of particularities. At serum sodium values of less than 120 mEq/L or in presence of neurological symptoms associated with hyponatremia, water restriction of 1-1.5 L/day is recommended. The lack of response to this therapeutic measure, the drop in sodium values to less than 110 mEq/l, or severe hyponatremia in patients about to undergo liver transplant require the administration of hyperon saline. Other therapeutic measures that can contribute to the increase of serum sodium values include the correction of hypokalemia and the intravenous administration of albumin. The only situation in which vaptan can be administered orally remains severe hyponatremia in patients awaiting liver transplantation. Patients with liver cirrhosis and hyponatremia require careful monitoring due to the increased risk of complications and death.*

Keywords: hyponatremia, liver cirrhosis, treatment, prognosis.

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INTRODUCTION

Hyponatremia is the most frequent hydroelectrolytic disorder diagnosed among hospitalized patients [1]. Hyponatremia is defined by the reduction of serum sodium values below 135 mEq/L [2]. In patients with liver cirrhosis, hyponatremia is particularly defined by the decrease of serum sodium values below 130 mEq/L [3]. A study that followed 997 patients with cirrhosis reported the identification of serum sodium values ≤ 135 mmol/L in 49.4% of patients, ≤ 130 mmol/L in 21.6%, ≤ 125 mmol/L in 5.7%, and ≤120 mmol/L /L in 1.2% of patients [4]. Also, no large differences regarding serum sodium values ≤135 mmol/L were seen between inpatients and outpatients (57% vs 40%) [4]. The same authors identified a directly proportional relationship between hyponatremia and severe ascites, high frequency of spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome [4].

The pathophysiological mechanisms that lead to hyponatremia in patients with liver cirrhosis are complex. Among them are systemic vasodilation, activation of endogenous vasoconstrictors, water retention, and iatrogenic factors.

a. Systemic vasodilation

This is one of the most important factors responsible for the occurrence of hyponatremia in patients with cirrhosis and portal hypertension [1]. From a cardiovascular point of view, these patients develop hyperdynamic circulation characterized by an increase in cardiac output, a reduction in systemic vascular resistance (SVR), and finally, a decrease in mean arterial pressure [5]. The vascular territory in which SVR is most obviously reduced is the splanchnic territory. The pathophysiological mechanisms that can explain the predominantly splanchnic vasodilatation phenomenon are the opening of the portosystemic collaterals and the increase in the synthesis of circulatory vasodilators such as nitric oxide (NO), vasoactive intestinal peptides, platelet-activating factor, glucagon, substance P, prostaglandins and prostacyclins [6]. The most important stimuli for increasing NO synthesis are endotoxins and bacterial DNA that pass into the systemic circulation from the gastrointestinal tract. The large quantities of these stimuli at the systemic level are due to the increase in intestinal permeability and the less efficient clearance due to the opening of the portosystemic ports and defective reticuloendothelial cell function in patients with cirrhosis [7]. Systemic vasodilatation leads to the decrease of mean arterial pressure and secondary activation of endogenous vasoconstrictors and the synthesis of antidiuretic hormone (ADH). This hormone promotes water retention and secondary dilutional hyponatremia. The use of antihypertensive drugs in patients with cirrhosis further reduces the mean arterial pressure and thus can exacerbate hyponatremia.

b. Activation of endogenous vasoconstrictors

The systemic vasodilatation encountered in patients with liver cirrhosis and portal hypertension leads to a decrease in the effective circulating volume and secondary reduction in stretch at the renal and carotid baroreceptor. The result will be the activation of the neurohormonal mechanisms of sodium and water retention to restore tissue perfusion [1]. These include the sympathetic nervous system, the renin-angiotensin system and ADH. The activation of these systems leads to renal retention of water and sodium despite increased values of extracellular sodium stores, plasma volume, and increased cardiac output [1].

c. Water retention

The water excretion process is not affected in the compensated stages of liver cirrhosis. The progression of liver disease with the appearance of portal hypertension and ascites leads to water excretion abnormalities largely related to the increased release of ADH [8]. Tsuboi *et al.* demonstrated in a study on mice with liver cirrhosis that the use of a vasopressin receptor antagonist largely restores their ability to excrete water [9]. To a lesser extent, neurohormonal activation with renal vasoconstriction and reduction of renal blood flow also contributes to the reduction of water excretion [10]. According to data from specialized literature, the increase in ADH secretion and the degree of water retention is associated with the degree of hyponatremia and the severity of the liver disease. Thus, it has been demonstrated that patients with serum sodium levels of less than 130 mEq/L have a worse prognosis, and sodium values < 125 mEq/L may indicate the occurrence of the hepato-renal syndrome [11,12]. A study that followed 143 patients with liver cirrhosis identified a reduction in 1 year-survival rate among

patients with hyponatremia (22.5% vs 68.7%) [11]. Also, hyponatremia can be a prognostic factor for survival after liver transplantation [12]. Cardenas et al. followed 301 patients with acute on chronic liver failure (ACLF) and reported a reduction in survival rate after liver transplantation among patients who had associated hyponatremia compared to those with ACLF but without hyponatremia [12].

d. Iatrogenic factors

Some patients with liver cirrhosis, especially those with obesity in which the etiology of cirrhosis is non-alcoholic steatohepatitis, may also have arterial hypertension. Depending on the level of liver damage, patients with cirrhosis show a reduction in cytochrome P450 (CYP 450) activity with a secondary reduction in drug clearance and an increase in serum drug concentration [13]. In addition, in patients with cirrhosis, hepatic albumin production decreases by approximately 60-80% [14]. Therefore, it is necessary to reduce the dose of drugs that usually circulate linked to plasma proteins (warfarin, diazepam, phenytoin, digoxin, fluoxetine, and valproic acid) in order to decrease the risk of drug toxicity [15].

In patients with compensated liver cirrhosis, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) can be used, but careful monitoring of blood pressure values and avoidance of arterial hypotension is necessary [16]. Regarding CCBs, these drugs are metabolized mainly in the liver. Thus, in patients with cirrhosis, it is necessary to use the lowest possible doses of CCBs [13]. Antihypertensive therapy in association with systemic vasodilatation can contribute to the reduction of mean arterial pressure. Hypotension secondary to antihypertensive medication additionally increases the risk of hyponatremia and nitrogen retention syndrome as the liver disease progresses [13]. Nonselective beta-blockers (NSBBs) are usually used in patients with portal hypertension for variceal hemorrhage prophylaxis [17]. Inadequate doses may increase the risk of acute renal injury in patients with ascites, especially in those with baseline hypotension [18,19]

Clinical Manifestations

In patients with end-stage liver disease, it is difficult to differentiate the secondary symptoms of hyponatremia from those of the underlying disease. The symptoms seen in these patients are confusion, fatigue, dizziness, muscle cramps, or nausea [20]. Data on the impact of serum sodium correction on symptoms are limited. A study that followed 24 patients with liver cirrhosis and serum sodium < 130 mEq/L demonstrated a modest improvement in some cognitive tests by correcting the levels of this electrolyte [21].

Therapeutic management

Hyponatremia in patients with cirrhosis develops slowly, in parallel with the rate of progression of the liver disease. This hydroelectrolytic imbalance usually has no clinical manifestations until the moment when the sodium value drops below 120 mEq/L. Correction of hyponatremia does not improve the hemodynamic abnormalities secondary to the underlying liver disease. Also, according to data from the specialized literature, the correction of hyponatremia does not improve the morbidity or mortality of these patients [1]. Moreover, the rapid correction of sodium values, with > 9 mEq/L/24 h, increases the risk of osmotic demyelination syndrome (ODS) [22].

The indications for the correction of hyponatremia in patients with liver cirrhosis are currently represented by the decrease in serum sodium levels < 120 mEq/L or the association of neurological symptoms [1]. The therapeutic principles are presented in figure 1.

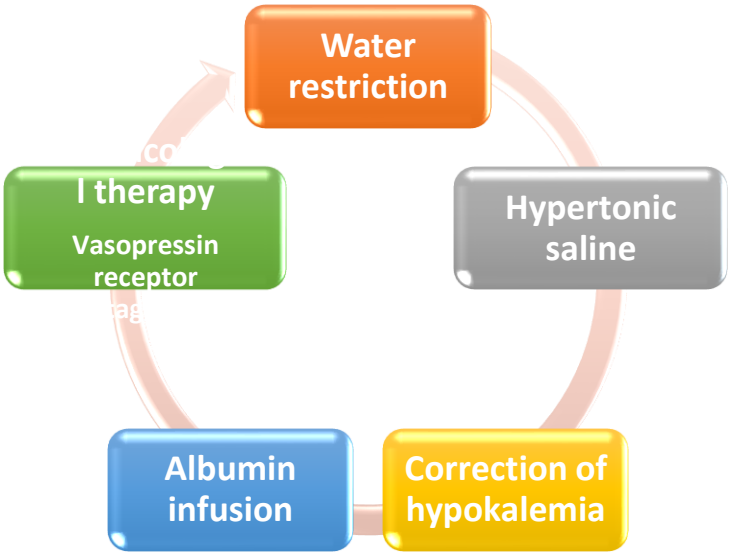

Figure 1. Therapeutic measures for correction of hyponatremia in patients with liver cirrhosis

1. Water restriction

In patients with liver cirrhosis, the mainstay of therapy for hyponatremia is fluid restriction. It is thus recommended to ingest 1-1.5 L of liquid per day to induce a negative water balance. Currently, this therapeutic measure is not recommended for asymptomatic patients with mild hyponatremia, because it has not proven any benefit. Therapeutic indications for fluid restriction remain:

- Serum sodium < 120 mEq/L
- Neurological symptoms possibly associated with hyponatremia [1,3].

Unfortunately, patients' adherence to water restriction is low [23,24]. The best indicator of adequate water restriction is the increase in serum sodium values in the first 24-48 hours [1,3]. The absence of change in plasma sodium concentration in the first 48-72 hours indicates the absence of the patient's adherence to water restriction or the need for a stricter restriction. It is also necessary to restrict sodium intake (2g/day), which must be continued after returning to normal fluid intake [1]. Current data from the literature recommend stopping the antihypertensive therapy (including both alpha blockers and beta blockers) when the systemic blood pressure drops below 90/60 mmHg [25,26].

2. Hypertonic saline solution (3% Na)

In patients with liver cirrhosis and dilutional hyponatremia, hypertonic saline solution is not usually used because it can lead to worsening ascites, edema, or even acute pulmonary edema [3]. In addition, rapid correction of hyponatremia may lead to ODS [3]. The only therapeutic indications for hypertonic saline remain:

- Symptomatic patients who do not respond to water restriction
- Serum sodium <110 mEq/L
- Patients with severe hyponatremia awaiting liver transplantation [23,27].

In patients with acute symptomatic hyponatremia (<24h), 100 ml of hypertonic saline 3% can be administered, as a bolus, in 15-30 minutes [28,29]. If the symptoms persist, the administration can be repeated (up to 300 ml) [28,29]. The goal of the treatment is to increase the serum sodium level by 4-6 mEq/L in the first 6 hours [28,29]. The risk of neurological complications by administering hypertonic saline in acute hyponatremia is lower than in chronic hyponatremia [3].

In patients with chronic symptomatic or severe hyponatremia (<110 mEq/L), hypertonic saline can be administered in continuous infusion at a rate of 15-30 ml/h [28,29]. Also, in patients receiving hypertonic saline, loop diuretics (not thiazide diuretics) can be associated to avoid progressive hypervolemia. Careful monitoring of renal function is necessary to avoid the occurrence or aggravation of nitrogen retention syndrome. An alternative to loop diuretic association is evacuation paracentesis. The objective of the treatment in patients with chronic hyponatremia consists in increasing the serum sodium value by a maximum of 8 mEq/L in 24 hours, to avoid ODS [28]. In the case of rapid overcorrection, desmopressin can be administered [23].

3. Correction of hypokalemia

The patient with liver cirrhosis can develop hypokalemia either through urinary loss of potassium secondary to diuretic therapy or through gastrointestinal loss in case of diarrhea or vomiting. Potassium is as active from an osmotic point of view as sodium, and the administration of potassium will tend to indirectly increase the serum concentration of sodium.

As potassium enters the cell, sodium moves extracellularly, with a secondary increase in serum concentrations [30]. Also, increased attention is needed to avoid rapid overcorrection of sodium and OTS, in case of additional potassium administration [31].

Hypokalemia can be associated with metabolic alkalosis, which can exacerbate hepatic encephalopathy. The mechanisms behind this phenomenon are the stimulation of renal ammonia synthesis by hypokalemia and the increase in the fraction of unionized ammonia in the plasma by alkalemia [32].

4. Albumin infusion

Albumin infusion can improve hyponatremia in patients with liver cirrhosis. The recommended dose is 1 g/kg body weight (maximum 100 g infused daily). The lack of improvement of the symptoms or the absence of the effect on the serum sodium values requires the interruption of albumin administration. A study that followed 1126 patients with liver cirrhosis and serum sodium levels < 130 mEq/L concluded that the administration of albumin was associated with a higher rate of resolution of hyponatremia independent of the initial values of serum sodium or creatinine (69% vs. 61%; p=0.008) [33].

5. Vasopressin receptor antagonist (vaptans)

Vasopressin receptors are V1a, V1b, and V2. V1a and V1b receptors mainly produce vasoconstriction and release of adrenocorticotropin. The antidiuretic effects of ADH are mainly mediated by V2 receptors at the level of the renal collecting ducts. The activation of these receptors determines the reabsorption of water. V2 receptor antagonists could produce pure aquaresis.

According to data from specialized literature, the administration of vaptans in patients with liver cirrhosis and hyponatremia can improve, in the short term, serum sodium levels, but increase the risk of mortality [34,35]. The oral agents (tolvaptan, lixivaptan, satavaptan) selectively block V2 receptors. Conivaptan, the intravenous agent, blocks both V2 and V1 receptors and may be associated with an additional increase in the risk of variceal bleeding [36]. The Food and Drug Administration (FDA) withdrew the recommendations on the use of tolvaptan and satavaptan in patients with liver cirrhosis and hyponatremia due to additional alteration of liver function and an increase in mortality rates [37,38]. An exception can be represented by patients with end-stage liver disease who are on the waiting list for a liver transplant [39]. In these patients, correction of hyponatremia is sought to avoid a rapid perioperative increase in serum sodium levels. Also, the

hepatotoxic effects of the drugs do not affect the morbidity-mortality rates in cases where liver transplantation is imminent [39].

Another vaptan, demeclocycline can increase free water excretion and correct hyponatremia. However, due to its nephrotoxic potential, its administration is not recommended in patients with liver cirrhosis [40].

Terlipressin acts mainly on V1 receptors, which explains its therapeutic utility in patients with portal hypertensive bleeding and hepatorenal syndrome. Also, terlipressin is a partial agonist of V2 receptors and can cause an acute reduction of serum sodium levels, usually reversible upon discontinuation of the treatment [41]. Thus, the use of terlipressin requires monitoring serum sodium levels.

Conclusions

In conclusion, hyponatremia is a hydroelectrolytic disorder frequently seen in patients with liver cirrhosis. Hyponatremia is an important prognostic factor and an independent risk factor for death among these patients. The presence of hyponatremia in patients with liver cirrhosis has been shown to be associated with severe ascites, impaired kidney function, higher rates of hepatorenal syndrome, spontaneous bacterial peritonitis, and hepatic encephalopathy [42]. The management of hyponatremia in patients with liver cirrhosis presents a series of particularities. The initiation of therapeutic measures is considered for patients with very low serum sodium levels and symptomatic patients. Thus, at serum sodium values of less than 120 mEq/L or in the presence of neurological symptoms associated with hyponatremia, water restriction (1-1.5 L/day) is recommended. In patients who do not respond to this measure, those with values <110 mEq/L or with severe hyponatremia awaiting liver transplantation, hypertonic saline (3% Na) can be administered. Also, in patients who associate hypokalemia, correction of serum potassium values is recommended. The administration of albumin up to 100 g per day, for the short term, can contribute to the improvement of hyponatremia. The use of vaptans in patients with hyponatremia and liver cirrhosis demonstrated a short-term improvement in the serum values of this electrolyte, but with increased mortality rates. The only therapeutic recommendation for vaptan remains severe hyponatremia in patients awaiting liver transplantation. Patients with liver cirrhosis and hyponatremia require careful monitoring due to the increased risk of complications and death.

Author Contributions:

G.G. and C.C.D. conceived the original draft preparation. G.C., G.G., and V-A.I. were responsible for conception and design of the review. VA.I., and F.G. were *responsible for the data acquisition. G.C., and G.G. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. G.C., G.G., C.C.D., F.G. and VA.I. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.*

Compliance with Ethics Requirements:

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