Chapter 2

Management of Ascites Associated with Severe Hyponatremia

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Abstract

Advanced liver cirrhosis requiring hospitalization is frequently associated with electrolytic disturbances, the most common finding being serum hyponatremia. The goal of treatment in patients with decompensated liver cirrhosis complicated with severe hyponatremia is to normalize the increased amount of water in the body and to improve the sodium concentration. Fluid restriction is recommended at 1.5 L/day to prevent sodium depletion in the serum, but the lack of efficacy is probably due to a poor patient compliance. Discontinuation or adjustments of diuretic dosages are sometimes required. Albumin associated with vasoconstrictors as midodrine can increase the effective arterial blood volume and seems to improve the serum sodium concentration. A promising therapeutic option targeting the pathophysiological mechanism of hyponatremia consists of improving solute-free water excretion, which is markedly impaired in these patients. The use of agents such as k opioid agonists has been attempted, but has been dropped due to the severe side effects. Recently, a new therapeutic class called vaptans has taken an important place in the treatment of hypervolemic hyponatremia. The main side effects during the administration of these drugs in patients with liver cirrhosis are reversible after discontinuing therapy. Therefore, it is recommended to use vaptans for short periods of time.

Keywords: hypervolemia, hyponatremia, liver cirrhosis, fluid restriction, vasopressin receptor antagonists, vaptans

1. Introduction

Ascites is the most common complication of cirrhosis, approximately 60% of patients develop ascites within 10 years of disease progression. The mechanism of production is the development of portal hypertension and renal retention of sodium. This inability to excrete an adequate amount of sodium in the urine occurs due to arterial splanchnic vasodilatation. Therefore, arterial and pulmonary cardio vascular receptor activation occurs with homeostatic activation of vasoconstrictor and sodium retention systems, resulting in a decrease in the required arterial blood volume. Renal sodium retention increases the volume of extracellular fluid leading to ascites and edema [1–5].

At approximately 75% of patients from Western Europe and USA, the main cause of ascites is represented by cirrhosis. Other causes of ascites may be malignancy, heart failure, tuberculosis, pancreatic disease, or other causes.

Hyponatremia is one of the complications that occurs in end stage cirrhosis due to the impossibility of renal clearance of free water, which leads to a higher water retention than sodium with the occurrence of hyposomolarity, with an increase in mortality and morbidity. In the pathogenesis of hyponatremia, the main factor involved is hypersecretion of antidiuretic hormone (ADH). Hyponatremia is a risk factor for both hepatic encephalopathy and liver transplantation because it is associated with an increased frequency of complications and a short-term survival [6].

2. Definition

Patients with liver cirrhosis show two types of hyponatremia: hypovolemic and hypervolemic.

Hypervolemic hyponatremia is the most common form and is characterized by low levels of serum sodium and increased volume of extracellular fluid, ascites, and edema. It may appear secondary to bacterial infections, excessive hypotonic fluids or may occur spontaneously. Hypovolemic hyponatremia is less common, with low levels of sodium, without ascites and edema as a consequence of excessive diuretic administration.

Hyponatremia is defined when serum sodium levels fall below 130 mmol/L but according to the recent guidelines, reductions below 135 mmol/L should also be considered as hyponatremia [7].

3. Prevalence

A study made over an Asian population following 997 patients with cirrhosis and ascites over 28 days in 28 centers showed that hyponatremia is present in more than half of the patients [8].

4. Pathophysiology

The mechanism by which ascites fluid is formed is the excess water and sodium retention in the body. Several theories have been developed to understand pathophysiology, and in turn, it has been shown that much of it would arise as a result of portal hypertension. The three proposed theories are three distinct mechanisms named: filling, oversaturation, and peripheral arterial vasodilatation. The first theory of filling is determined by portal hypertension and decreased circulating volume that produces vascular fluid retention. Since cirrhotic patients have a higher percentage of hypervolemia than hypovolemia, the second overload theory is determined by the retention of water and sodium in the absence of volume exhaustion. And the third theory uses the first two theories. This indicates that vasodilation occurs as a result of portal hypertension and favors the increase in arterial blood volume. Also, several factors are involved in ascites fluid formation: hypoalbuminemia and oncotic low plasma pressure, elevated levels of epinephrine and norepinephrine.

The main mechanism of hyponatremia is represented by arterial vasodilation. By reducing effective blood volume, several neurohumoral systems such as the renin-angiotensin-aldosterone system and the sympathetic nervous system are stimulated and lead to the release of ADH.

Activation of those trigger systems causes sodium retention and may lead to renal vasoconstriction. Vasopressin 2 receptors affected by the ADH play an important role in rate of excretion of solute-free water. In the end, water excretion occurs with the appearance of serum dilution and hypo-osmolality [6].

Under normal circumstances, there is a synchronous increase in serum osmolarity and ADH secretion, and reabsorption of water occurs when activating the aquaporin channels in the renal collection tubes. In opposite, the inactivation of aquaporin channels occurs when a decrease in osmolarity appears, resulting in urine dilution as a mechanism in maintaining serum osmolarity. Thus, the good functioning of osmoreceptors in the anterior hypothalamus, the release of ADH and the mutual action between ADH and AQP-2 compete to adapt the release of free water.

ADH is secreted into the supraoptic and paraventricular nuclei of the hypothalamus and maintained in the posterior pituitary gland. Vasopressin secretion is stimulated by increased plasma osmolarity and hypovolemia. The release of ADH is conditioned by osmotic and nonosmotic stimulation. The osmoreceptors in the anterior hypothalamus, near the supraoptic nuclei mediate the osmotic pathway. These receptors detect intracellular water content in neurons and respond to changes in plasma osmolarity. The main nonosmotic pathway delivers an ADH release through the autonomic nervous system mediated by baroreceptors located in the atrium, ventricle, aortic arch, and carotid sinus. Through the parasympathetic pathway, these baroreceptors stimulate the hypothalamus to release ADH in response to hypovolemia [9].

Most patients with cirrhosis present low serum osmolarity and sodium levels, and it is expected to produce inhibition of ADH release if stimulation was achieved by osmoreceptors [10]. Because of the activation of the neurohumoral mechanisms that retain sodium, the levels of ADH, aldosterone, norepinephrine, and renin activity were significantly higher in patients with cirrhosis and ascites after the water loading test. Effective arterial uptake would result from a decrease in systemic vascular resistance and would result in nonosmotic stimulation due to baroreceptors of ADH and other vasoconstriction systems. These cause the activation of the neurohumoral mechanisms that produce sodium retention in order to restore the perfusion pressure [11].

It is suggested that hypoosmotic stimuli are suppressed by nonosmotic stimuli to suppress ADH release. That is why the body sacrifices osmolar homeostasis and releases ADH following nonosmotic stimulation of endogenous vasoconstrictors, and thus impairs vascular collapse by exhausting effective circulatory volume. It results in an inability to release sodium and water to replenish the circulation volume. All of these things happen despite the increase in cardiac output, plasma volume, and total body volume. To eliminate the extra amount of water, it is necessary to suppress adherence and the ability of the kidneys to remove water. The presence of nonosmotic adherence leads to the occurrence of a hyponatremia of dilution or hypervolemic hyponatremia. Therefore, in this category of patients, hyponatremia is only dilute and does not represent a sodium deficiency [12].

In a prospective cohort study of patients with ascites, it was demonstrated that the occurrence of hyponatremia is preceded by refractory ascites and subsequently by hepatorenal syndrome. Each of these steps was associated with a progressive Child Pugh score and Model for End Stage Liver Disease (MELD) indicating a worsening of liver function. Therefore, hyponatremia is an intermediate stage between ascites progression and hepatorenal syndrome [13].

5. Prognostic value

Hyponatremia in patients with cirrhosis is chronic, therefore, allows the brain to adapt to the hypo extracellular fluid osmolality. In conclusion, patients are less likely to have severe neurological symptoms. However, hyponatremia can aggravate cerebral edema and swollen astrocytes by adding to their dysfunction created by increased intracellular glutamine concentration, speeding up the appearance of hepatic encephalopathy [6].

Due to the severe restriction of fluid consumption, the quality of life of patients with cirrhosis and hyponatremia is poor [14]. Several studies have shown that the severity of hyponatremia and ascites is a prognostic factor of the disease [15, 16]. In one study, it was demonstrated that the serum sodium level prior to the occurrence of spontaneous bacterial peritonitis (SBP) was an independent predictor of renal insufficiency produced by SBP [17]. It is also a predictive marker with a higher sensitivity than serum creatinine to predict the occurrence of circulatory dysfunction resulting in renal insufficiency or death. Although patients with hyponatremia are susceptible to the hepatorenal syndrome, there is not only an increased level of ADH involved, but there is a decrease in glomerular filtration rate (GFR) and proximal sodium reabsorption [18].

Sodium concentration was included in the MELD model to indicate the need for liver transplantation and patient priority on waiting lists in order to improve prognosis [19]. It was found that the MELD-Na score indicated an anticipation of short-term mortality of transplant patient candidates much better than the initial MELD score [20].

6. Clinical presentation

Symptoms of hyponatremia are caused by the damage to the nervous system, with cerebral edema due to the migration of water from the intravascular space in the brain [21]. As a rapid adaptive mechanism, there is an increase in electrolytes in brain cells. As a slow adaptation mechanism, organic osmoliths are extruded. Finally, these mechanisms help return the water to the intravascular space and prevent brain edema [22].

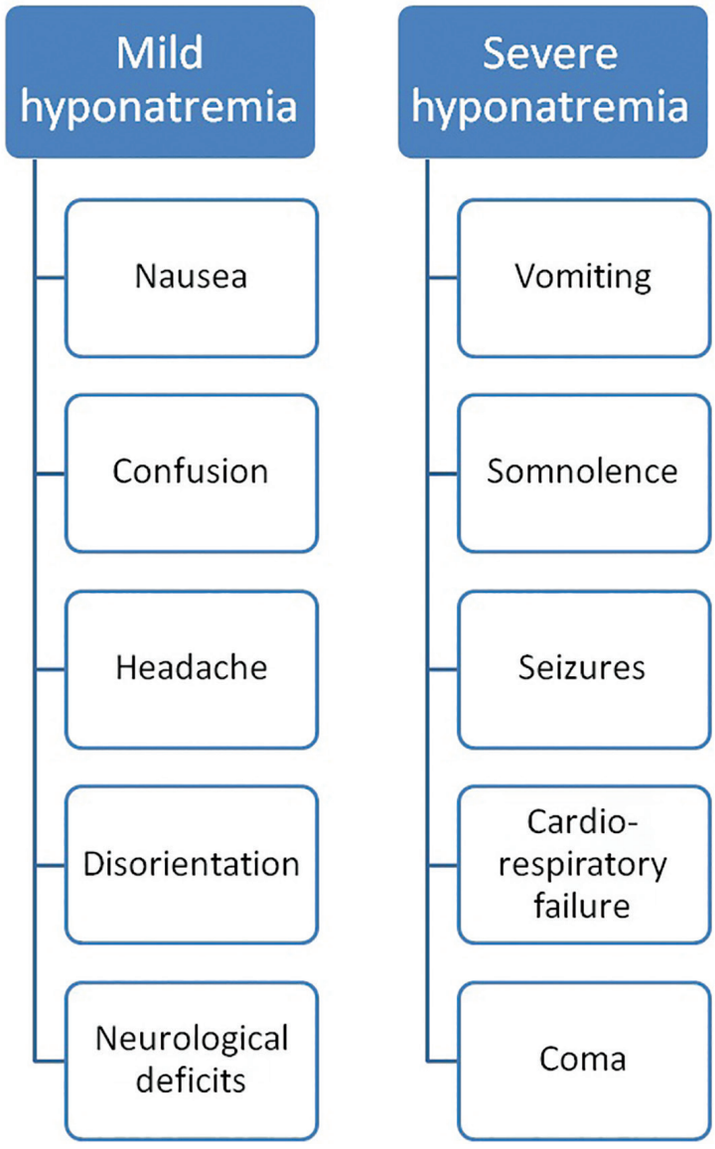

Figure 1. Clinical manifestations of hyponatremia.

In patients without hepatic impairment, hyponatremia manifests with: headache, disorientation, confusion, and neurological deficits. In contrast, in cirrhotic patients, hyponatremia develops slowly and at a value of 125 mEq/L is asymptomatic due to adaptive mechanisms. However, a rapid drop in sodium concentration may overcome adaptive mechanisms and serious symptoms may occur such as coma, seizures, brain-stern herniation, respiratory failure, and death [23] (**Figure 1**).

Hyponatremia usually occurs in the final stage of liver disease and is difficult to differentiate if the symptoms are within it or are part of liver encephalopathy occurrence. Both hyponatremia and hyperammonemia cause an alteration in brain metabolism of myoinositol [24].

Some theories show that hyponatremia can cause the appearance of a minimal cerebral edema that occurs by swelling of astrocytes and may cause the appearance of hepatic encephalopathy. This minimal brain edema occurs by increasing the concentration of glutamine resulting from the metabolism of ammonia and leads to a series of neurological changes to the appearance of hepatic encephalopathy [25].

7. Complications

Central pontine myelinolysis (CPM) is a complication of severe hyponatremia and occurs when its correction has been achieved very quickly. It is a neurological disorder that consists of a demyelination that occurs in a region called pons [26].

The mechanism by which this affection occurs is not fully known. One theory claims that this demyelination occurs by compressing fibrous structures as a result of cerebral edema arising from an osmotic fluctuation. Currently accepted theory supports the fact that brain cells adjust their osmolarity with certain osmolites, like inositol, betaine, and glutamine. In case of chronic hyponatremia, there is a decrease in these osmoliths in the brain, preventing fluid absorption [27, 28]. Clinical manifestations depend on the affected brain region, initially manifested by symptoms of hyponatremic encephalopathy such as nausea, vomiting, headache, confusion, and seizures. These symptoms can be reversed when adjusting the sodium concentration. Later signs of myelinolysis such as walking disturbances and respiratory dysfunction can occur [29]. Among the risk factors for this condition are: sodium concentration < 120 mEq/L for 48 hours, aggressive correction with saline solution and the occurrence of hypernatremia during treatment. If post liver transplant patients develop symptoms as confusion or weakness, CPM should be suspected because it may complicate a liver transplant [30].

Although the prognosis is poor with the occurrence of numerous neurological complications such as spastic quadriparesis and blocked syndrome, recovery is possible although it has a long duration [31].

Diagnosis can be done clinically and imagistically. The preferred imaging method is MRI, although lesions appear late and often initially may be normal [32]. The most common images are T2 weighted with hyperintense areas where demyelination was performed [33].

8. Management of hyponatremia

There are no data to recommend optimal serum sodium to initiate the treatment, but is generally recommended at a value of 130 mmol/L.

The identification and adjustment of excessive diuretic dosages and the addition of sodium are the main treatment requirements in the setting of hypovolemic hyponatremia. In case of hypervolemic hyponatremia, the most important issue is to decrease the amount of water to improve the sodium concentration.

When patients experience neurological symptoms due to hyponatremia or have a sodium concentration of less than 120 mEq/L, fluid restriction is indicated. In the case of mild and asymptomatic hyponatremia, fluid restriction is not indicated. Increasing sodium concentration in the first 24–48 hours is an important parameter that suggests an adequate fluid restriction. If this increase does not occur, either the restriction has to be more severe or the patient is not compliant. Fluid restriction is useful, but ineffective. Because the fluid restriction is severe, most patients cannot be compliant.

If patients have severe hyponatremia, there have been no responses to fluid restriction; it is indicated to administer the hypertonic saline. However, caution should be exercised in order not to cause a rapid increase in sodium concentration, which predisposes to the occurrence of numerous complications such as: central myelinolysis, quadriplegia, coma, or death [6].

The efficacy of using hypertonic sodium chloride in severe hypervolemic hyponatremia is partial, short-lived and aggravates ascites and edema. Instead, administration of albumin appears to have benefits, helps to increase the sodium concentration, but is not fully studied [34].

An important issue in patients with cirrhosis and hyponatremia is the correction of hypokalemia. Hypokalemia favors the appearance of hepatic encephalopathy because it increases the kidney synthesis of ammonium. By correcting it, there is also an increase in sodium concentration because both sodium and potassium are osmotically active [35].

In the past, the use of k-opiod agonist therapy has been attempted due to side effects [36]. According to recent studies, a new class of therapy, called vaptans, has been discovered in the treatment of hypervolemic hyponatremia. Vaptans selectively block the V2-receptors of AVP. They can be used in diseases like syndrome of inappropriate antidiuretic hormone secretion (SIADH), heart failure and cirrhosis, having the role of improving sodium concentration. The benefits of their administration over a short period of time are the increasing of urine volume and solute-free water excretion, and also, the improvement of the low serum sodium levels in 45–82% of patients [37] (**Figure 2**).

Hypernatremia, dehydration, renal impairment, and osmotic demyelination syndrome owing to a very rapid increase in serum sodium concentration could be the side effects of the administration of vaptans in patients with liver cirrhosis. Therefore, treatment should be initiated in the hospital and patients should be closely monitored to avoid hypernatremia.

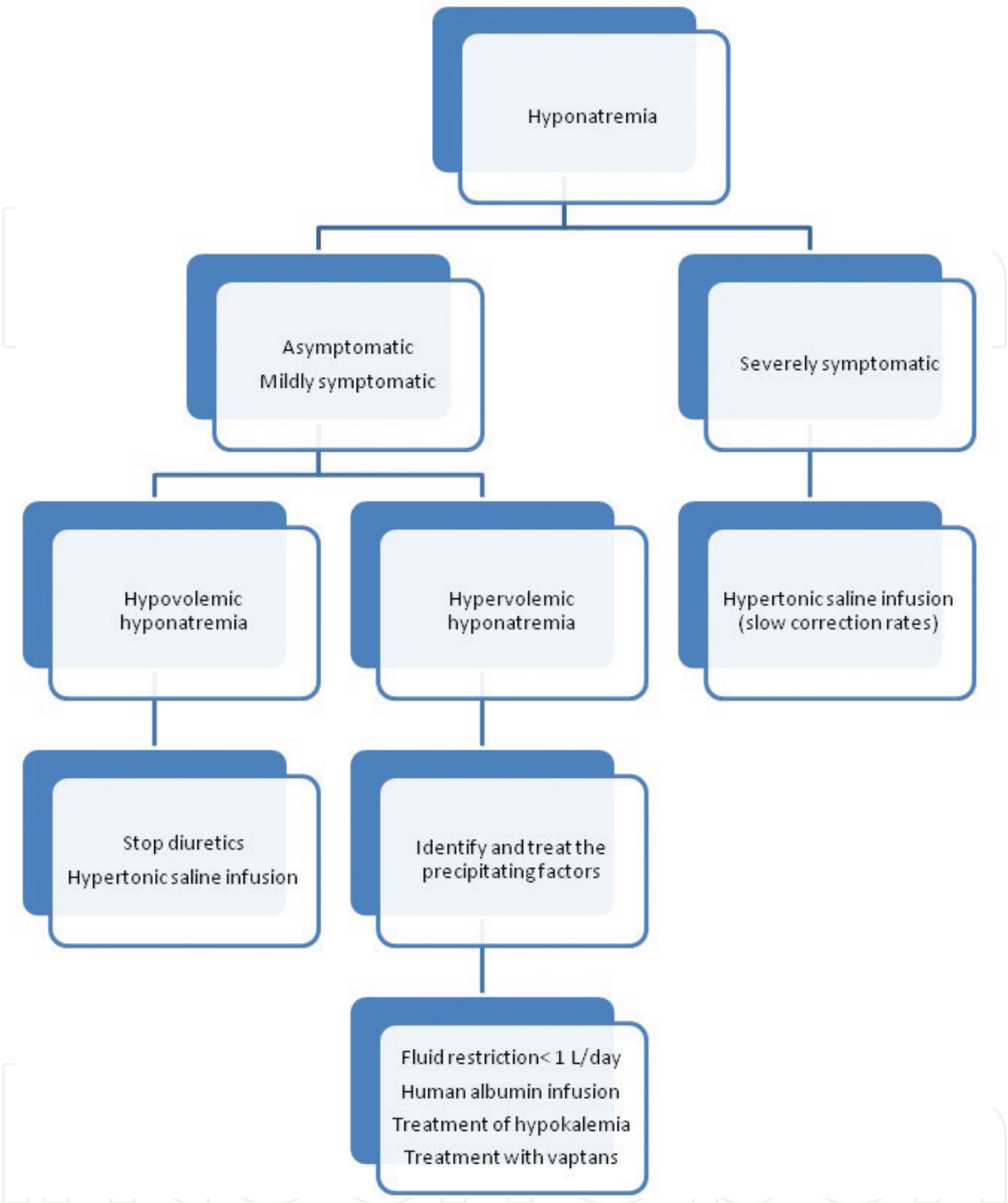

Figure 2. Management of hyponatremia.

Due to the risk of dehydration and hypernatremia, vaptans are also contraindicated in patients with an inappropriate consciousness state, unable to measure the volumes of fluid consumed.

The metabolism of vaptans is achieved in the liver by CYP3A enzymes. Therefore, CYP3A inhibitory drugs should be avoided because they increase the concentration of vaptans and may lead to the increase of serum sodium concentration. Also, drugs that are inducers of the CYP3A should be avoided because those drugs can reduce the concentration of vaptans.

Tolvaptan and conivaptan are recently approved in the USA for the treatment of severe hypervolemic hyponatremia from diseases such as cirrhosis, heart failure and SIADH. Treatment is started at a dose of 15 mg/day and can be increased progressively depending on the sodium concentration. In Europe, tolvaptan is authorized only for the treatment of SIADH. As an alternative option, conivaptan can be used to treat hypervolemic hyponatremia for short periods of time, especially when cirrhosis is associated with various conditions [38, 39].

Tolvaptan should be initiated without taking into account the period of meals, but initially it is advisable not to suppress the consumption of fluids to avoid rapid correction of sodium concentration. If, on completion of tolvaptan therapy, hyponatremia recurs, it should be corrected in a hospital unit. There may be no need for hospitalization, if treatment can be monitored to prevent excessive sodium concentration [40].

In randomized trials, the only side effects of tolvaptan treatment were gastrointestinal bleeding, but slightly increased incidence compared to placebo. It should be taken into account that the treatment was administered over a short period of time and new studies of the safety of long-term treatment are needed [41].

Treatment with conivaptan is contraindicated in patients who are allergic to constituents, in hyponatremia or hypovolaemia because it can induce from renal failure to shock. CYP3a4 inhibitors should not be administered concomitantly [42]. In general, the treatment was tolerated and adverse reactions were reported: local reactions (pain and erythema at the administration level), orthostatic hypotension, peripheral edema, headache, nausea, vomiting, urinary tract infections, and insomnia [43]. Effective treatment of hyponatremia should be initiated promptly to prevent irreversible neurological damage, but rapid correction may cause osmotic demyelination syndrome that can lead to death [44].

Domecycline favors the increase in free water excretion as an ADH antagonist, but cannot be used in cirrhosis due to nephrotoxicity [45].

The use of vasoconstrictors in hyponatremia is not tested, but studies of the hepatorenal syndrome have shown an improvement in sodium concentration [46].

The use of vasoconstrictors in hepatorenal syndrome has the following benefits: it improves the effective blood volume, vascular or systemic vasodilation, and renal perfusion. They are usually used in concomitant albumin administration. The most commonly used are: terlipressin, norepinephrine, vasopressin, and octeotrid, in combination with midodrine.

This combination can be used without supervision in a medical unit and is safe. Octreotide produces decreased splanchnic vasodilatation and midodrine improves renal perfusion and in combination with albumin improves kidney function, but there are still insufficient studies in this regard.

The octreotide is administered subcutaneously at the dose of 100 micrograms, 3 times per day, and the dose can be increased to 200 μg, 3 times per day. Midodrine is given orally 7.5 mg, 3 times per day and the dose can also be increased up to 12.5 mg, 3 times per day [47].

Treatment with terlipressin should be avoided in patients with cirrhosis, as it may cause severe hyponatremia, reversible upon discontinuation of treatment. Terlipresin acts on the vasopressin V1 receptor, but is also a partial vasopressin V2 receptor agonist. This is beneficial in the treatment of bleeding caused by portal hypertension, but also in hepatorenal syndrome [48].

By correcting hyponatremia in patients with cirrhosis, there are number of advantages: avoiding fluid restriction, administering effective doses of diuretics, especially in the treatment of refractory ascites, reducing the risk by developing hepatic encephalopathy, and improving the quality of life. It can also help reduce neurological complications after transplantation [49, 50].

9. Conclusions

Hyponatremia is a complication of cirrhosis, associated with an increased risk of mortality and morbidity in patients on the waiting list for a liver transplant. It also increases the risk of complications, such as hepatic encephalopathy, renal failure, and spontaneous bacterial peritonitis.

Hyponatremia occurred during cirrhosis evolution has as a pathophysiological mechanism arterial vasodilation that produces inadequate AVP secretion and a reduction in glomerular filtration rate with impairment of free water clearance. Clinical presentation does not differ from that of patients without hepatic impairment, but the symptoms of hyponatremia in cirrhosis are sometimes associated and difficult to differentiate from those in hepatic encephalopathy. As a dilutional hyponatremia, its treatment is not indicated if it is asymptomatic. Conversely, at a concentration of Na <120 mEq/L and on the occurrence of neurological symptoms, treatment can be initiated. An exception is the situation where patients are about to receive a liver transplant in a short time and the Na concentration is <130 mEq/L. In this case, its treatment is indicated to prevent the occurrence of serious neurological complications such as osmotic demyelination syndrome as a result of a rapid correction in the operating room. An important role is the differentiation of hypovolemic hyponatremia from the hypervolemic hyponatremia to initiate a suitable therapeutic scheme. In hypovolemic hyponatremia, it is necessary to identify the trigger factor and its treatment, usually discontinuation of diuretic treatment and administration of salt solution represents optimal methods in the correction of this. In hypervolemic hyponatremia, therapeutic methods are limited. Fluid restriction to about 1 L/day is important in improving Na concentration, but a small number of patients may be compliant with this therapy. Administration of saline solution in this case is only recommended if hyponatremia is severe because it usually favors the growth of ascites fluid and edema. Administration of albumin appears to be beneficial, but there is not enough data to confirm this.

A novelty in hyponatremic therapy is the treatment with vaptans. Treatment with tolvaptan should be given in the hospital to avoid a sudden increase in Na concentration, in oral administration, and with the possibility to increase the dose progressively to achieve the desired effects. Concomitant administration with vaptans of saline solution or fluid restriction is contraindicated to prevent osmotic demyelination syndrome. Medications that are inhibitors or inducers of CYP3A are also contraindicated. Conivaptan is given intravenously. Both

conivaptan and tolvaptan can be administered for a short period of time, and hyponatremia may reappear when the treatment is stopped. Although treatment with vaptans is effective in relieving hyponatremia, their use requires additional data.

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