Review Article

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REVIEW ARTICLE ON CLINICAL SIGNIFICANCE AND MANAGEMENT OF HYPONATREMIAINLIVER CIRRHOSIS

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Abstract

Hyponatremia is commonly observed in Liver cirrhosis patients, particularly in advanced stages with various complications and high mortality. The prevalence of hyponatremia in cirrhotic patients is approximately 50%., More frequently observed hyponatremia is hypervolemic hyponatremia, which occurs due to the overactivation of sodium and water retention mechanisms in response to effective arterial hypovolemia.Whereas hypovolemic hyponatremia typically results from excessive fluid loss, often due to diuretic therapy or diarrhea.In this review, we can figure out the relation between hyponatremia with clinical outcomes and management. Hyponatremia is a significant predictor of mortality and is associated with an increased risk of hepatorenal syndrome, altered mental status, infections, and poor post-transplantation outcomes. In treating hyponatremia, distinguishing between hypovolemic and hypervolemic types is essential.In hypervolemic hyponatremia,the management should be initiated only in the symptomatic patients. Prevents further declines in sodium levels by discontinuing diuretics and implementing fluid restriction. Currently, only albumin infusions can be routinely recommended, while other treatments such as vaptans, splanchnic vasoconstrictors, niravoline, or osmotic diuretics are reserved for specific scenarios, such as impending liver transplantation, or require careful indication.

Key Words: Hyponatremia, liver cirrhosis, mortality, fluid restriction, vaptanes, liver transplantation.

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Introduction

Hyponatremia is the most prevalent electrolyte disturbance in patients with advanced cirrhosis and is associated with a poor prognosis [1, 3]. The prevalence of hyponatremia in patients with liver cirrhosis ranges from 40% in outpatients to 57% in hospitalized individuals. Approximately 21.6% of patients exhibit serum sodium levels < 130 mmol/L. Serum sodium concentrations are independent of factors such as age, sex, or the etiology of cirrhosis , indicating that hyponatremia is a frequent complication in this population[3]. However, it has been demonstrated that even a mild decrease in sodium levels (130–134 mmol/L) is associated with a poorer prognosis compared to those with normal sodium concentrations[3]. Using a cutoff of 135 mmol/L, the prevalence of hyponatremia increases to nearly 50%. In contrast, the occurrence of severe hyponatremia, defined as a serum sodium concentration below 126 mmol/L, is infrequent, with a prevalence of 6% [3].

Pathophysiology

The process begins with cirrhosis, which is accompanied by portal hypertension and the release of vasodilator factors. These factors result in splanchnic arterial vasodilation, reducing the effective arterial blood volume. This condition is further exacerbated by cardiac function impairment. As a compensatory mechanism, the activation of vasoconstrictor systems occurs, including the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the non-osmotic hypersecretion of vasopressin. Vasopressin acts on kidney V2 receptors,

leading to increased tubular water reabsorption. This results in solute-free water retention, ultimately causing hypervolemic hyponatremia[2,4,5].

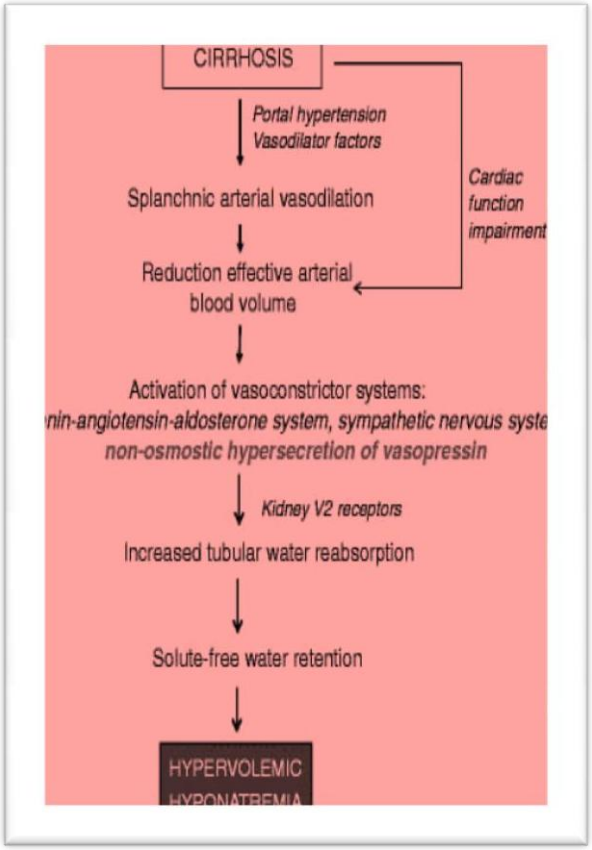

Figure 1: Schematic representation of pathophysiology of the hypervolemic hyponatremia in cirrhotic patients.

Clinical Manifestations

Hyponatremia in cirrhosis presents a complex interplay of systemicand neurological effects, largely influenced by the rate of sodium decline and its interaction with other metabolic abnormalities, such as hyperammonemia.

Clinical Features of Hyponatremia:

1. **Mild to Moderate Hyponatremia (Serum Sodium > 125 mEq/L):**
   - Often asymptomatic.
   - Symptoms, if present, are nonspecific and include: Headache, Anorexia, nausea and vomiting [7].
2. **Severe Hyponatremia (Serum Sodium < 120 mEq/L):**
   - Rapid decline in serum sodium can overwhelm the body's compensatory mechanisms.
   - Potential complications include:
   - Seizures, coma, and death [7,8].

Physiological Adaptation to Hyponatremia:

- **Gradual Onset:**
- The body adapts to slow reductions in extracellular osmolality through intracellular adjustments, particularly in the brain. Astrocytes decrease intracellular osmolality to limit cellular swelling [7].
- **Rapid Onset:**
  - Abrupt decreases in serum sodium disrupt this adaptation, leading to significant cerebral edema and neurological deterioration [6,9].

Interaction with Hyperammonemia:

- In cirrhosis, elevated ammonia levels exacerbate the effects of hyponatremia on the brain:
  - Ammonia enters astrocytes and is converted into glutamine byglutamine synthase.
  - Increased intracellular glutamine acts as an osmolyte, promoting water influx into astrocytes.
  - This leads to astrocyte swelling and brain edema, contributing to hepatic encephalopathy[6,9,10].

Clinical Implications

- Monitoring and management of serum sodium levels are critical to prevent neurological complications.
- Recognizing the interplay between hyponatremia and ammonia levels emphasizes the need for a comprehensive approach in managing cirrhotic patients, including strategies to reduce ammonia and maintain sodium balance.

Clinical Significance

Hypervolemic hyponatremia is a hallmark of hemodynamic derangements in cirrhosis, particularly after the disease progresses to decompensated stages. In compensated cirrhosis, sodium levels typically remain comparable to those observed in the general population[11]. However, hyponatremia in decompensated cirrhosis is a multifaceted issue that correlates with various pathophysiological markers and complications[12]. Moreover, sodium levels are directly correlated with impaired sympathovagal balance in cirrhosis[13]. There is a little evidence of a direct correlation between hyponatremia and variceal hemorrhage in the literature[14].

1. Hepatorenal syndrome

Severe renal vasoconstriction brought on by hemodynamic alterations in cirrhosis that hepatorenal syndrome(HRS) may also result from dilutional hyponatremia. In a research by Angeli et al., the prevalence of HRS was 6% in patients with sodium > 130mmol/L and 17% in those with sodium < 130mmol/L [3]. According to other research, patients with HRS had lower mean salt levels than those without HRS [15,16]. Patients with normal renal function are also at risk for developing HRS if their serum sodium levels are low [18].

2. Neurological symptoms:

For a variety of causes, brain functioning are disrupted in conjunction with liver disease. According to a recent explanation of hepatic encephalopathy(HE), a direct cause of HE is low-grade cerebral edema, which is brought on by the combined action of intracellular glutane,ammonium, and other neurotoxins in the context of an activated chronic inflammatory milieu. In this instance, alterations in plasma osmolality caused by hyponatremia may exacerbate the astrocyte swelling. Hyponatremia is confirmed by clinical data to be an independent predictor

of HE.In a study by Guevara et al., hyponatremia (serum sodium < 130 mmol/L) was associated with an adjusted hazard ratio of 8.36 for the development of HE, although the sample size was limited to 61 patients with multiple episodes and a high incidence of HE[17]. A study by Kim et al. reported a slightly lower odds ratio (OR) of 5.891 (95% CI: 1.49–23.3) for severe HE (grade III or above)[21]. Gines et al. observed a significantly increased risk of HE in cirrhotic patients treated with diuretics who also had hyponatremia (serum sodium < 135 mmol/L). The largest study to date, conducted in Denmark with 1,116 patients (302 of whom developed overt HE), demonstrated that for every 1 mmol/L decrease in serum sodium, the hazard of HE increased by 8%. The 1-year cumulative risk of HE was 57% in patients with serum sodium < 130 mmol/L, compared to only 6% in patients with serum sodium of 145 mmol/L[36].

The impact of hyponatremia and HE on cognitive and physical function has been evaluated in multiple studies. Wunsch et al. found a linear association between serum sodium levels and the physical component of the SF-36 questionnaire (regression coefficient 0.059, 95% CI: 0.024–0.093), independent of HE[19]. However, no such association was observed for the mental component. Ahluwalia et al. assessed cognitive function alongside health-related quality of life, noting that while cognitive abilities in patients with hyponatremia were superior to those with HE, their overall quality of life was lower[23]. Interestingly, improvement in hyponatremia has been linked to enhanced cognitive function, even in the absence of overt HE. Post-hoc analysis of two double-blind, randomized, parallel-group studies comparing satavaptan to placebo revealed that patients with improved natremia demonstrated significantly better performance on the more challenging "B" variant of the Trail-Making Test, with an improvement of approximately 12% compared to 4% in those without natremia improvement[22].

3. Infections:

Infections are identified in up to 50% of patients with liver cirrhosis, significantly increasing mortality in these patients by nearly fourfold. Observations by Kim et al. indicate a frequent association between hyponatremia and infections in cirrhotic patients, with an odds ratio (OR) of 2.562 (95% CI: 1.162–5.653). In addition to spontaneous bacterial peritonitis, hyponatremia is also linked to soft tissue and skin infections. A study by Pereira et al. reported that patients with such infections had significantly lower mean serum sodium levels (132 mmol/L vs. 135 mmol/L) and a higher prevalence of serum sodium < 130 mmol/L (40% vs. 25%) among infected individuals [24].

Lower sodium levels were further associated with increased mortality in infected patients and a heightened risk of subsequent kidney injury. Beyond its role as a concurrent finding, hyponatremia serves as an independent risk factor for the development of infections in cirrhotic patients. A multicenter study by Angeli et al. demonstrated that patients with serum sodium < 130 mmol/L had an OR of 2.36 (95% CI: 1.41–3.93) for developing spontaneous bacterial peritonitis within the following four weeks [3].

Management

The differentiation between hypovolemic and hypervolemic hyponatremia is crucial for implementing appropriate preventive strategies and therapeutic interventions.

Hypovolemic Hyponatremia

- Hypovolemic hyponatremia can be prevented by utilizing balanced crystalloids and avoiding diuretics can help to prevent further sodium loss [1,8].

Hypervolemic Hyponatremia

- The choice of treatment method depends on two key factors: the pathophysiology of hyponatremia and the rate of sodium decline. A distinct approach is required for acute hypovolemic hyponatremia resulting from excessive diuretic use, and a different strategy is needed for chronic hypervolemic (dilutional) hyponatremia in patients with sodium and fluid retention.
- Hypervolemic hyponatremia in cirrhosis is primarily a consequence rather than a cause of hemodynamic alterations in cirrhosis. Therefore, treatment should target the underlying liver disease. As a secondary approach, symptomatic treatment should focus on mitigating splanchnic vasodilation, enhancing solute-free water excretion, and preserving body sodium [3,4].

Diet and Lifestyle Changes:

- Fluid restriction to 1000 mL/day remains the first-line treatment for hypervolemic hyponatremia. The patients with liver cirrhosis often need to limit sodium intake to manage fluid retention and ascites[27,28].
- Expansion of effective blood volume through physical methods may also have beneficial effects on hyponatremia[29].

Pharmacological Treatment

The initial step should involve assessing the patient's current medical treatment. Medications known to reduce s-Na concentration include traditional diuretics (furosemide, spironolactone, thiazides), vasopressin analogs, and potentially non-selective beta-blockers (NSBB)[28].

1. Albumin Infusion:

While intravenous albumin infusion may prove beneficial, larger long-term studies are required to confirm its efficacy. A small randomized pilot study demonstrated an improvement in s-Na concentrations by 9 mmol/L in 24 patients admitted with an initial s-Na concentration of less than 130 mmol/L[30] .

2. Vaptanes :

Vaptan agents act by blocking vasopressin receptors in the renal collecting ducts responsible for water reabsorption. Studies in patients with hypervolemic dilutional hyponatremia demonstrated that tolvaptan

normalized s-Na concentrations to greater than 135 mEq/L in 41% of patients within 4 days and in 33% of patients by day 30. However, significant elevations in liver enzymes were observed in patients with autosomal dominant polycystic kidney disease, prompting the US Food and Drug Administration to issue a black box warning against the use of tolvaptan in patients with liver disease[31,32] . Furthermore, satavaptan was associated with increased mortality and subsequently withdrawn from development[1,31].

A meta-analysis evaluating the efficacy and safety of vaptans in patients with cirrhosis and hyponatremia found that vaptans improved s-Na concentrations and facilitated ascitic fluid mobilization but did not confer a survival benefit (relative risk: 1.06; 95% confidence interval: 0.90–1.26) [33]. Additionally, elevated blood urea nitrogen levels (>28.2 mg/dL or >29 mg/dL) and a creatinine concentration exceeding 0.98 mg/dL were identified as important independent predictors of reduced response to tolvaptan[34,35].

3. Hypertonic Saline and Liver Transplantation :

Correction with hypertonic saline may be considered in patients who are refractory to free water restriction, symptomatic patients experiencing seizures, those with profound hyponatremia (<110 mEq/L), or patients with s-Na levels below 120 mEq/L in the hours preceding liver transplantation [8,30]. However, due to the risk of exacerbating ascites and edema, hypertonic saline is not recommended for the long-term management of hypervolemic hyponatremia. Care must be taken to avoid overly rapid correction exceeding 8 mEq/L per 24 hours, as this may lead to osmotic demyelination syndrome[30] . Liver transplantation remains the only definitive treatment for advanced liver disease complicated by hyponatremia[30].

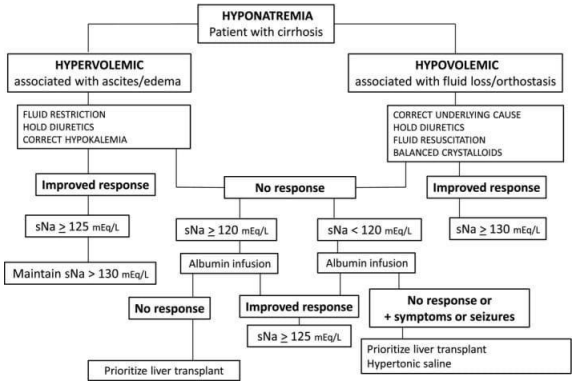

Figure-2: Algorithm depicting suggested management of hyponatremia in the patient with cirrhosis.

Conclusion

Hyponatremia in cirrhosis, according to the current understanding of pathophysiology, arises from significant hemodynamic alterations associated with advanced cirrhosis.It is not only a marker of poor prognosis but also exacerbates adverse outcomes by impairing quality of life and contributing to disturbances of consciousness in patients with hepatic encephalopathy. Although it is not usually advised, tomatic treatment with hypertonic saline, loop diuretics, or both may be explored in cases of extremely severe hyponatremia accompanied by severe consciousness disturbance. In addition to raising s-Na, albumin treatment lowers the risk of additional serious side effects such hepatorenal syndrome or infections without having any negative side effects. While vaptan treatment is quite effective in correcting hyponatremia, it has a negligible impact on symptoms (edema, ascites, consciousness, and quality of life) and the effect on mortality is completely absent.

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