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Original Research Article

Observational Cross-Sectional Study to Assess the Dysnatremia in Patients with Chronic Liver Disease

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Conflict of interest: Nil

Abstract

Aim: To study the prevalence of hyponatremia in patients with chronic liver disease attending the outpatient department of a tertiary care hospital.

Methodology: An observational cross-sectional study was conducted in the department of medicine, Darbhanga Medical College and Hospital, Darbhanga, Bihar for one year .In this study, patients in the age group of 18 to 65 years were included irrespective of gender, diagnosed with chronic liver disease. A history, physical examination, biochemical markers, ultrasonography, and upper gastrointestinal endoscopy were used to identify cirrhosis. Child-Turcotte Pugh score (CPS) and model for end stage liver disease (MELD) score was calculated for all patients [16]. Those with serum sodium levels less than or equal to 130 meq/l were classified as group A, those with serum sodium levels between 131-135 meq/l as group B and those with serum sodium levels greater than or equal to 136 meq/l as group C. Descriptive analysis of quantitative parameters was expressed as means and standard deviation.

Results: In the present study, 100 patients were included. It was observed that 32% were in group A (≤ 130 mEq/l), 34% were in group B (131 to 135 mEq/l) and 34% were in group C (≥ 136 mEq/l). The age or gender of the patients was not associated with serum sodium levels. It was observed that patients from group A had jaundice ($p<0.05$) and altered sensorium ($p<0.05$) significantly more commonly as compared to those from group B and C. Serum sodium levels was not significantly associated with alcohol consumption. Among all examination findings, icterus ($p<0.05$) and clubbing ($p<0.05$) were found to be significantly more common among patients from group A, as compared to patients from group B or C. Pallor, pedal edema, signs of liver cell failure and organomegaly were not significantly associated with serum sodium levels in our study population. Hepatic encephalopathy ($p<0.01$), hepatorenal syndrome ($p<0.01$) and coagulopathy ($p<0.01$) were found to occur significantly more common among patients from group A, as compared to those in patients from group B or C. We also observed that mean direct bilirubin, alanine transaminase, aspartate transaminase and alkaline phosphatase were significantly higher among group A patients as compared to those from group B or C respectively. In addition, we observed that mean MELD (The Model for End-stage Liver Disease) score was significantly higher among group A patients (18.04±7.52) as compared to those with group B (13.24±5.02) and group C (12.04±4.72). We also observed that mean Child Pugh score (CPS) was significantly higher

among group A patients (10.04±2.82) as compared to those with group B (8.72±1.45) and group C (7.34±2.02). Overall, 12% of the patients expired.

Conclusion: Decompensated Chronic Liver Disease is associated with abnormal serum sodium concentration. Individuals with lower serum salt levels had a substantially higher MELD score and CPS. Furthermore, hepatic encephalopathy, hepatorenal syndrome, and coagulopathy were shown to be considerably more prevalent in individuals with blood sodium levels more than 136 mEq/l than in other patients.

Keywords: Hyponatremia, hypernatremia, cirrhosis, encephalopathy.

Introduction

Chronic liver diseases (CLDs) cause significant morbidity and mortality worldwide. Multiple etiological factors lead to a similar clinicopathological syndrome in CLDs, although the rates of progression and clinical course may be different [1]. Most of the increase in CLD mortality has been reported from the low- and low-middle-income countries (LMICs) of Asia and Africa. LMICs are experiencing a demographic and epidemiologic transition in disease burden. India is one of the epicenters of this change [2]. It may occur due to a wide variety of CLDs such as infections viral (HBV, HCV, and HDV), toxic (alcohol and arsenic), metabolic, biliary disorders, and vascular lesions like Budd-Chiari syndrome.

The normal range of serum sodium is 135-145 mEq/L. Its homeostasis is vital to the functioning of the cell. An imbalance in the regulation of total body water can lead to abnormal sodium levels. Decompensated chronic liver disease(DCLD) is associated with disturbance in water homeostasis leading to dysnatremias [3-7].

Hyponatremia is defined as concentration of sodium less than 135 mEq/L. It occurs when there is excess of water in relation to sodium. It is the most common electrolyte disorder in hospitalized patients and more so in DCLD patients [6-10]. A disturbance in total body water regulation leading to decreased clearance of solute free water and the consequent inability to match the urine output to the amount of water ingested leads to dilutional hyponatremia.

Hypernatremia is defined as concentration of sodium more than 145 mEq/L. It is associated with high mortality rate. Hypernatremia, though uncommon compared to hyponatremia in DCLD patients, occurs due to use of osmotic cathartics and Upper Gastro Intestinal (UGI) bleeding. If present, it is associated with increased mortality [11].

In cirrhosis, hyponatremia generally develops slowly and gradually. Therefore, the brain can adjust to hypoosmolality and hypotonicity of the extracellular fluid so that the incidence of neurological manifestations directly attributable to hyponatremia is relatively low. However, since hyponatremia occurs in the setting of end-stage liver disease, it is often difficult to define to what extent the clinical manifestations are due to reduced serum sodium concentration or to hepatic encephalopathy. The relationship between hyponatremia and severity of cirrhosis is further evidenced by its close association with the occurrence of complications: Indeed, the prevalence of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis is substantially higher in patients with serum sodium concentration ≤130 mmol/L than in those with higher levels. Studies indicate that hyponatremia is a key accomplice in the pathophysiology of

hepatic encephalopathy in cirrhosis and not just an innocent bystander [12].

Studies have shown that the severity of the hyponatremia is related to the severity of the chronic liver disease [13-15]. To the best of our knowledge, no study of hyponatremia in chronic liver disease has been conducted in our setting. The aim of this study is to study the prevalence of hyponatremia in patients with chronic liver disease attending the outpatient department of a tertiary care hospital.

Methodology:

An observational cross-sectional study was conducted in the department of medicine, Darbhanga Medical College and Hospital, Darbhanga, Bihar for one year In this study, patients in the age group of 18 to 65 years were included irrespective of gender, diagnosed with chronic liver disease. We also excluded patients aged less than 18 years, with comorbid cardiac failure, with co morbid chronic kidney disease and those taking drugs that alter serum sodium levels. The study protocol was approved by the Institutional Ethics Committee before commencement and a written informed consent was taken from all patients.

We acquired demographic information about the patients from their medical records. A history, physical examination, biochemical markers, ultrasonography, and upper gastrointestinal endoscopy were used to identify cirrhosis. Each patient's venous blood was taken and submitted to the institutional laboratory for analysis of serum electrolytes, liver function tests (LFTs), renal parameters, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalised ratio (INR). An automatic biochemical analyzer was used to test the biochemical indicators, while an automated haematology analyzer was used to measure the whole blood cell counts. Complications in the patients included hepatic encephalopathy, varices, hepatorenal syndrome, and infections. In addition, child-Turcotte Pugh score (CPS) and model for end stage liver disease (MELD) score was calculated for all patients [16].

Those with serum sodium levels less than or equal to 130 meq/l were classified as group A, those with serum sodium levels between 131-135 meq/l as group B and those with serum sodium levels greater than or equal to 136 meq/l as group C. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data were expressed as absolute number and percentage. Cross tables were generated and chi square test was used for testing of associations. One-way ANOVA was used for comparison of quantitative parameters, along with Bonferroni post-hoc test. A p value of <0.05 is considered statistically significant. All analysis were done using SPSS software, version 24.0.

Results:

In the present study, 100 patients were included. It was observed that 32% were in group A (≤ 130 mEq/l), 34% were in group B (131 to 135 mEq/l) and 34% were in group C (≥ 136 mEq/l). The age or gender of the patients was not associated with serum sodium levels.

Table 1: Basic demographic details between groups based on serum sodium levels.

Variables		Group A (≤ 130 mEq/l, n=32)	Group B (131-135 mEq/l, n=34)	Group C (≥ 136 mEq/l, n=34)	P value
Age (in years)	25-40 (28%)	9%	11%	8%	0.38
	41-60 (59%)	17%	19%	23%	
	61-80 (13%)	6%	4%	3%	
Gender	Males (81%)	27%	27%	27%	0.31
	Females (19%)	5%	7%	7%	

All patients had abdominal distension. It was observed that patients from group A had jaundice ($p<0.05$) and altered sensorium ($p<0.05$) significantly more commonly as compared to those from group B and C. Alcohol consumption was reported by 88% of the patients. Serum sodium levels was not significantly associated with alcohol consumption. Among all examination findings, icterus ($p<0.05$) and clubbing ($p<0.05$) were found to be significantly more common among patients from group A, as compared to patients from group B or C. Pallor, pedal edema, signs of liver cell failure and organomegaly were not significantly associated with serum sodium levels in our study population.

Table 2: Clinical presentation and examination findings between groups based on serum sodium levels.

Variables		Group A (≤ 130 mEq/l, n=32)	Group B (131-135 mEq/l, n=34)	Group C (≥ 136 mEq/l, n=34)	P value
Clinical Presentation	Abdominal distension (100%)	32%	34%	34%	-
	GI bleed (23%)	7%	8%	8%	0.2
	Jaundice (39%)	21%	11%	7%	<0.05
	Altered sensorium (30%)	17%	7%	6%	<0.05
	Alcohol (88%)	26%	30%	32%	0.47
Examination findings	Pallor (21%)	5%	7%	9%	0.65
	Icterus (45%)	21%	18%	6%	<0.05
	Clubbing (30%)	12%	14%	4%	<0.05
	Pedal edema (79%)	24%	26%	29%	0.57
	S/0 liver cell failure (94%)	27%	31%	36%	0.25
	Organomegaly (24%)	4%	12%	8%	0.18

Portal hypertension was observed in 77%, hepatic encephalopathy in 34%, hepatorenal syndrome in 24%, spontaneous bacterial peritonitis in 4% and coagulopathy in 20%. Of these, hepatic encephalopathy ($p<0.01$), hepatorenal syndrome ($p<0.01$) and coagulopathy ($p<0.01$) were found to occur significantly more common among patients from group A, as compared to those in patients from group B or C.

Table 3: Comparison of complication rate between groups based on serum sodium levels

Complications		Group A (≤ 130 mEq/l, n=32)	Group B (131 to 135 mEq/l, n=34)	Group C (≥ 136 mEq/l, n=34)	Total	P value*
Portal hypertension	N	22	25	30	77	0.16
Hepatic encephalopathy	N	19	9	6	34	<0.01
Hepatorenal syndrome	N	15	4	5	24	< 0.01
Spontaneous bacterial peritonitis	N	3	1	0	4	0.82
Coagulopathy	N	12	5	3	20	<0.01

We also observed that mean direct bilirubin, alanine transaminase, aspartate transaminase and alkaline phosphatase were significantly higher among group A patients as compared to those from group B or C respectively. In addition, we observed that mean MELD (The Model for End-stage Liver Disease) score was significantly higher among group A patients (18.04±7.52) as compared to those with group B (13.24±5.02) and group C (12.04±4.72). We also observed that mean Child Pugh score (CPS) was significantly higher among group A patients (10.04±2.82) as compared to those with group B (8.72±1.45) and group C (7.34±2.02). Overall, 12% of the patients expired. It was observed that mortality was 28.1% among group A patients, which was significantly higher than that of group B patients (11.1%) or group C patients (0%).

Table 4: Comparison of liver cirrhosis severity between groups based on serum sodium levels.

	Variables	Mean SD	P value*
MELD	Group A (n=32)	18.04±7.52	<0.01
	Group B (n=34)	13.24±5.02	
	Group C (n=34)	12.04±4.72	
CPS	Group A (n=32)	10.04±2.82	<0.01
	Group B (n=34)	8.72±1.45	
	Group C (n=34)	7.34±2.02	

Table 5: Comparison of mortality rate between groups based on serum sodium levels.

Outcome	Group A (≤ 130 mEq/l, n=32)	Group B (131 to 135 mEq/l, n=34)	Group C (≥ 136 mEq/l, n=34)	Total	P value*
Discharged	22	27	39	88	<0.05
Expired	9	3	0	12	

Discussion:

Chronic liver disease indicates a disease of the liver that causes progressive destruction and regeneration of its parenchyma leading on to fibrosis and cirrhosis. Chronic liver disease is said to be present when the disease process lasts for six months. It is important for the clinicians to differentiate patients of chronic liver disease into those who have compensated liver function and those who have decompensated liver function.

Hepatocellular injury due to various etiologies is followed by degeneration or necrosis of the hepatocyte. Necrosis leads to kupffer cell activation and macrophage immigration. T lymphocytes are also attracted. They are stimulated by IL-1. Fibroblasts are also attracted and transformed into myofibroblasts, which are responsible for increased synthesis of collagen and extra cellular matrix. The disease course of chronic liver disease is complicated when signs of decompensation develops. These complications occur in all cases regardless of the underlying etiology.

Hyponatremia is a frequent complication in patients with decompensated liver disease. It occurs due to the impaired free water clearance by renal tubules that leads to disproportionate retention of water when compared with sodium. This leads to reduction in serum sodium and hypoosmolality. Although hyponatremia in decompensated liver disease was described 50 years ago, interest in this area increased when studies done in 1980s indicated that hyponatremia is significant prognostic indicator. Recent studies also showed that presence of hyponatremia is associated not only with poor outcome in patients who has not undergone transplants but also in post transplant patients.

Hepatic encephalopathy, hepatorenal syndrome, and coagulopathy were shown to be considerably more prevalent in group A patients than in group B or C patients in the current study. In another study, Elkady et al [17] found that 91% of individuals with blood sodium levels less than 125 mEq/l had hepatic encephalopathy, and 50% had upper gastrointestinal haemorrhage, which was considerably higher than those with serum sodium levels greater than 125 mEq/l. Ascites were shown to be considerably less prevalent in individuals with blood sodium levels of 139 mEq/l, according to Umemura et al [18] (45 vs 65%). Jenq et al [19] found that a substantially larger proportion of individuals with sodium levels less than 135 mEq/l (52/67) developed hepatic encephalopathy than those with sodium levels more than 135 mEq/l (35/59). [11]

Meganathan and Kumar [20] established the prevalence of hyponatremia in cirrhosis and to investigate if hyponatremia predicts an increased rate and severity of complications in cirrhosis. They reported hyponatremia in 44%, normal serum sodium in 26%, and hypernatremia in 30% of the patients. In another study, Umemura et al [18], evaluated mortality in cirrhosis patients taking conventional diuretics and identified associations between serum sodium level and clinical characteristics. In their study, 26 of 171 patients (15.2%) had sodium values below the lower limit of the normal range (135 mEq/L) and eight of 171 patients (4.7%) had Na of 130mEq/L or less, which is the cutoff value commonly used to define hyponatremia.

In our study, we observed that mean MELD score was significantly higher among group A patients (18.04$\pm$7.52) as compared to those with group B (13.24$\pm$5.02) and group C (12.04$\pm$4.72). In another study by Meganathan and Kumar [20], the mean MELD score was 27.7±6.7 for patients with hyponatremia, which was significantly higher as compared to those with normal serum sodium levels and hypernatremia Elkady et al. [17], also reported the mean MELD score to be 18.19±5.3 among patients with serum sodium ≤125 mEq/L as compared to 16.17±6.2 in patients with serums odium more than 125 mEq/L

We also observed that mean Child Pugh score was significantly higher among group A patients (10.04$\pm$2.82) as compared to those with group B (8.72$\pm$1.45) and group C (7.34$\pm$2.02). In addition, Child-Pugh Class C was significantly more common in Group A patients (45.9%) as compared to those with Group B (25.6%) and Group C (11.4%). In a similar study by Jenq et al [19], CPS was significantly higher in patients with serum sodium level ≤135 mEq/L (12.4±2.3) as compared to those with serum sodium level >135 mEq/L (11.1±2.1).12 In the study by Kim et al [21], mean CPS was significantly higher in patients with hyponatremia (10.5±1.6) as compared to those with normal serum sodium level (9.8±1.7) and hypernatremia (8.7±1.6), P< 0.001.

A large study done on patients admitted for cirrhosis, has shown that the prevalence of hyponatremia to be 29.8% [22]. Low serum sodium levels were found to be an indicator of poor prognosis and short term in-hospital mortality. Low serum sodium levels were not found to be an independent predictor of mortality when compared with CPS [23]. Biggins et al showed that the ability of MELD score to predict three month waiting list mortality improved when serum sodium was added to it [24]. The mortality risk for patients with decompensated liver disease was found to be higher in patients with hyponatremia irrespective of the disease severity [25]. In this study also, 12% of the patients expired. It was observed that mortality was 28.1% among group A patients, which was significantly higher

than that of group B patients (11.1%) or group C patients (0%). [26]

Conclusion:

Decompensated Chronic Liver Disease is associated with abnormal serum sodium concentration. Hyponatremia is the most common abnormality in this study. Age and gender did not have any association with serum sodium levels. Individuals with lower serum salt levels had a substantially higher MELD score and CPS. Furthermore, hepatic encephalopathy, hepatorenal syndrome, and coagulopathy were shown to be considerably more prevalent in individuals with blood sodium levels more than 136 mEq/l than in other patients.

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