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Study of Hyponatremia in Cirrhosis of Liver and Its Prognostic Value

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Abstract

Background/Aims: Dilutional hyponatremia associated with liver cirrhosis is caused by impaired free water clearance. Several studies have shown that serum sodium levels correlate with survival in cirrhotic patients. Low serum sodium concentration is an independent predictor of mortality in patients with cirrhosis, but its prevalence and clinical significance is unclear. Little is known regarding the relationship between the degree of dilutional hyponatremia and development of cirrhotic complications. The aim of this study was to study the prevalence of hyponatremia in cirrhosis and evaluate the association between the serum sodium levels, related complications in liver cirrhosis and its prognostic significance.

Methods: Data of patients with cirrhosis were collected prospectively. The prevalence of low serum sodium levels and its association with complications and prognostic significance in 100 patients were analyzed.

Results: The prevalence of dilutional hyponatremia, classified as serum sodium concentrations of 131 -135 meq/L and ≤130 meq/L, were 13%, 21% respectively. The serum sodium level was strongly associated with the severity of liver function impairment as assessed by Child-Pugh and MELD scores ($p<0.0001$). Patients with serum sodium levels less than 130 meq/L had higher frequency of grade III or higher hepatic encephalopathy and Hepatorenal syndrome but not gastrointestinal bleeding. Patients with serum sodium<130 meq/L had the greatest frequency of these complications, but the frequency was also increased in patients with mild reduction in serum sodium levels (131-135 meq/L).

Conclusions: Dilutional hyponatremia is frequent in cirrhotic patients and low serum sodium levels in cirrhosis are associated with complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome and high morbidity and mortality. Treatment of hyponatremia is important to prevent the possible complications of liver cirrhosis.

Keywords: Hyponatremia, Cirrhosis , Hepatic Encephalopathy , Hepatorenal Syndrome

Introduction

Hyponatremia is serum sodium less than 135 meq/L. Hyponatremia is the most common electrolyte disorder.[1] Its homeostasis is vital to the normal physiologic function of cells. A disturbance in body water homeostasis is a common feature of advanced

cirrhosis.[1] This is characterized by a higher rate of renal retention of water in relation to sodium due to a reduction in solute-free water clearance. The consequent inability to adjust the amount of water excreted in the urine to the amount of water ingested leads to dilutional hyponatremia. Dilutional hyponatremia, an excess of water in relation to the sodium in the extracellular fluid, is the most common electrolyte disorder in hospitalized patients and particularly so in patients with cirrhosis.[2,3,4]

Clinically significant hyponatremia is relatively uncommon and is nonspecific in its presentation; therefore, the physician must consider the diagnosis in patients presenting with vague constitutional symptoms or with altered level of consciousness. Identifying the etiology and risk factors for hyponatremia will help in reducing its incidence and minimize the complications associated with hyponatremia and improve the overall cost of health care. Cirrhotic patients with hyponatremia have a poor survival compared with that of patients without hyponatraemia.[5] According to several recent studies; hyponatremia occurring as a result of a reduced solute-free water clearance was a key prognostic factor in patients with liver cirrhosis when hyponatremia was incorporated into the MELD score[2,4,5]. There is a lack of Indian data on clinical spectrum of hyponatremia in cirrhosis and treatment strategies to be adopted in various clinical studies; therefore, we planned to undertake this prospective follow up study in patients with cirrhosis at our tertiary care centre.

Aims and Objectives

1. To study the prevalence of hyponatremia in cirrhosis.
2. To establish the association between hyponatremia and complications in cirrhosis
3. To establish its prognostic significance in cirrhosis.

Materials and Methods

Source of Data: The study was conducted on 100 consecutive cirrhotic patients admitted to Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow from December 2017 to November 2018.

Method of Collection of Data: Informed consent was obtained from all patients enrolled for the study. The data of the patients was collected in a well-designed proforma. The patients' demographics and the status of the patients at the time of inclusion (Inpatient or outpatient) as well as severity of cirrhosis were assessed according to Child-Pugh score. A total score from 5-6, 7-9 and 10-15 was classified as class A, B and C respectively.

The patients are selected based on clinical examinations, biochemical tests and ultrasound abdomen. The patients are followed over a period of one year with serum sodium levels measured at regular intervals of 3 months, 6 months and 1 year.Patients with cardiac failure, chronic kidney disease, patients on drugs like SSRI, TCA, MAO inhibitors, cytotoxic drugs etc. were excluded from study.

Statistical Methods: Descriptive statistical analysis has been carried out in the present study.

Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions:1.Dependent variables should be normally distributed,2.Samples drawn from the population should ber andom, Cases of the samples should be independent.

Observations and Results

This prospective study included 100 cirrhotic patients out of which 84 (84%) males and 16 (16%) females and the mean age of the patients was 44.89±10.27 years (range, 22-70 years). Table-1 shows the basic characteristic of cases in the study.

Table 1: Demography Details

S. No.	Parameter	N=100
1	Age (Years) (Mean±SD)	44.89 ±10.27
2	Sex: (Number) % Male Female	 84 (84%) 16 (16%)
3	Cause of cirrhosis: (Number) % Alcohol: HBV HCV: Other:	 52 (52%) 26 (26%) 12 (12%) 10 (10%)
4	MELD Score (Mean±SD)	22.77±8.262
5	Serum sodium: (meg/L) (Mean±SD) 1) <_130meq/L: 2) 131-135meq/L: 3) ≥136meq/L: (Number) (%)	 127.9±11.29 21(21%) 13 (13%) 66(66%)

The mean age of the patients was 44.89±10.27 years (range, 22-70 years) and consisted of 84 (84%) men and 16 (16%) women. Causative factors for liver cirrhosis included alcoholic liver disease (52 cases, 52%), chronic hepatitis B (26 cases, 26%), Chronic hepatitis C (12cases ,12%).The mean MELD score was 22.77± 8.262 (range, 9-46); and mean serum sodium concentration was127.9± 11.29 meq/L (range, 106-145 meq/L). Based on the diagnostic criteria for hyponatremia in patients, out of the 100 patients of liver cirrhosis21 (21%) patients had concurrent severe hyponatremia with serum sodium concentrations ≤130 meq/L. While, 13 (13%) patients had mild hyponatremia with serum sodium concentrations between 131-135 meq/L. However, 66(66%) patients had their serum sodium levels more than equal to the 136 meq/L.

Table 2: Characteristics of Patients According To Serum Sodium Concentration.

S. No.	Complications	≤130 meq/L n = 21	131-135 meq/L n =13	≥136 meq/L n =66	P value
1.	Age(years) (Mean ± SD)	45.47±10.28	45.75±11.93	44.09±9.640	0.7706£
2.	Sex: (Number)(%) M F	 29(85%) 5(15%)	 17(85%) 3(15%)	 38(83%) 8(17%)	0.9401@
3.	Cause of cirrhosis: (Number)(%) Alcohol: HBV : HCV: Other:	 15(71.42%) 3(14.28%) 1(4.7%) 2(9.52%)	 10(76.92%) 2 (15.38%) 1(7.69%) (0)	 27(40.90%) 21(31.81%) 10(15.15%) 8(12.12%)	0.0552@
4.	MELD score (Mean ± SD)	25.91±8.092	28.00±8.385	18.17±5.591	< 0.0001£
5.	Child-Pugh score	10.5±1.6	9.8± 1.7	7.8±1.6	<0.0001*
6.	Child-Pugh class Class A Class B Class C	 1 8 12	 1 5 7	 22 33 11	<0.0001

@ using Chi Square test; p value < 0.05- statistically significant (95 % Cl)

£ Using one way ANOVA. P value < 0.05, Significant (@95% CL).

*Using Mean±SD

Patients were classified according to level of serum sodium, 66(66%) belong to the group of serum sodium concentrations ≥136 meq/L. While, 21(21%) and 13(13%) patients were belong to serum sodium concentration group of≤130 meq/L and 131-135 meq/L respectively. Mean age in these three groups, ≤130 meq/L, 131-135 meq/L and ≥136 meq/L was 45.47±10.28, 45.75±11.93 and 44.09 ± 9.640 respectively, which were comparable and no statistical difference was found in these three groups (p value=0.7706). Frequency of gender and causative factor among these three groups were comparable and no statistical difference was found in this respect (p value, 0.9401, 0.0552 respectively).

To assess the association between serum sodium and patient characteristics and complications of cirrhosis, the patients were divided into three groups according to

serum sodium values. Serum sodium values were not associated with age, sex, or etiology of cirrhosis but were strongly associated with the severity of cirrhosis as assessed via Child-Pugh class (Table3). Low serum sodium had significantly high Child Pugh class compared to normal serum sodium. Among 21 patients with serum sodium < 130 meq/l, 12 were in class C Child-Pugh and 8 were in Class B (p=<0.001).

Mean MELD score in three groups, ≤130 meq/L, 131-135 meq/L and ≥136 meq/L was 25.91±8.092, 28.00±8.385, 18.17± 5.591 respectively. There was significant difference with respect to MELD score in three groups (p value=< 0.0001).

Table: 3 clinical presentation of patients at the time of admission.

S.No.	Presentation	N=100 (Number)(%)
1.	Abdominal Distension	100(100%)
2.	Lower Limb Swelling	99(99%)
3.	Jaundice	60(60%)
4.	Altered Sensorium	34(34%)
5.	Gastrointestinal Bleeding	24(24%)
6.	Seizures	1(1%)

All 100 patients presented to hospital with abdominal distension, jaundice was seen in 60(60%) patients 99 patients had lower limb swelling.Altered sensorium and gastrointestinal bleeding were present in 34 (34%) and 24(24%) of patients respectively. Only one patient with liver cirrhosis was having concurrent seizures at the time of hospital admission.

Table:4 Frequency of complications.

S. No.	Complications	N=100 (Number)(%)
1	Ascites	98(98%)
2	Hepatic Encephalopathy	34(34%)
3	GI Bleeding	24(24%)
4	Coagulopathy	9(9%)
5	Hepatorenal Syndrome	9(9%)

Out of the 100 patients of cirrhosis, 98(98%) patients had ascites, 34(34%) hepatic encephalopathy and GI bleeding in 24(24%) patients. Coagulopathy and hepatorenal syndrome was present in 9(9%) patients each.

Table 5: Mortality According To Serum Sodium Concentration.

	≤130 eq/L n = 21	131-135 meq/L n = 13	≥136 meq/L n = 66	P value[@]
Mortality	5 (23.8%)	2 (15.38%)	0 (0%)	0.0037

5 (23.8%) patients died in group of serum sodium levels ≤130 meq/L, while 2 (15.38%)patients died in group of serum sodium levels 131-135 meq/L. No patient died in group of serum sodium levels ≥136 meq/L. Statistically significant difference wasfound in mortality in three groups (p value=0.0037).

Discussion

Hyponatremia is an electrolyte imbalance that commonly occurs in hospitalized patients. Most cases are dilutional hyponatremia caused by the impairment of solute-free water clearance. Hyponatremia resulting from the impairment of solute-free water excretion is commonly accompanied by portal hypertension. Multiple studies has shown that severity of hyponatremia associated with high complications of cirrhosis. In recent years, hyponatremia has attracted interest as a possible prognostic factor for liver cirrhosis. We conducted this prospective study to examine the prevalence of hyponatremia and association between hyponatremia and the occurrence major complications in patients with liver cirrhosis.

Table 6: Comparison of studies for prevalence of Hyponatremia

Studies	Prevalence of hyponatremia (%)		
	<130 meq/L	131-135 meq/L	>135meq/L
Present study (n=100)	21% (21/100)	13% (13/100)	66% (66/100)
Angeli P et al (n=997)	21.6% (211/997)	27.8% (275/997)	50.6% (497/997)
Jong Hoon Kim et al (n=188)	27.1% (51/188)	20.8% (39/188)	52.1% (98/188)
Shaikh S (n=217)	26.7% (58/217)	24.9% (54/217)	48.4% (105/217)
Borroni G et al (n=156)	29.8% (57/156)		

Angeli P et al conducted multi-center study in overseas countries, 997 patients with liver cirrhosis and concurrent ascites, were assigned to three groups based on serum sodium concentration, in a manner similar to that of the current study. The prevalence of hyponatremia at serum sodium 131-135 meq/L, <130meq/L was 27.8%, 21.6% respectively.

Borroni G et al conducted a study on 156 patients hospitalized with liver cirrhosis, the prevalence of hyponatremia, based on a serum sodium concentration≤130 meq/L, was 29.8%, and hyponatremia was significantly correlated with infection and ascites.Jong Hoon Kim et al (2009) showed prevalence of hyponatremia was 27.1%, and 52.1% in patients with serum sodium <130 meq/L, 131-135 meq/L and >135meq/L respectively. Shaikh S et al (2010)[15] conducted a case control study constituted 217 consecutive cirrhotic patients. Hyponatraemia (sodium <130meq/l) was present in 58/217(26.7%) patients and 54/ 217 (24.9%) patients had serum sodium from 131-135 meq/l while 105/ 217 (48.4%) patients had serum sodium >135 meq/l. In the present study the results indicate that a large proportion of patients with cirrhosis have abnormal values of serum sodium concentration. In fact, one third (34%) of patients with cirrhosis had values of serum sodium concentration belowthe normal range (<135 meq/L) and 21% had values <130 meq/L. Low serum sodium levels were not associated with age, sex, or etiology of cirrhosis. Although it is generally believed that the existence of a serum sodium concentration <130meq/L is associated with difficult to treat ascites, few studies have been

reported that specifically analyze the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy. Arroyo et al.[16] reported that the presence of serum sodium <130 meq/L was associated with lower glomerular filtration rate and solute-free clearance and a poorer response to diuretics compared with patients with serum sodium <130meq/L. Subsequent studies by Bernardi et al.[17]and Angeli et al. showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics.

Table 7: Association of severity serum sodium with the mortality.

Serum sodium	Mortality
<130 meq/L	5
131-135 meq/L	2
>136 meq/L	0

Finally our study also indicates that mortality is more in patient with low serum sodium compared to normal serum sodium concentration. 7 patients died in group had serum sodium <135 meq/L and no death in patients with normal serum sodium.

Conclusion

Dilutional hyponatremia is frequent in cirrhotic patients and low serum sodium levels in cirrhosis are associated with severe complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome and high morbidity and mortality. Treatment of hyponatremia is important to prevent possible complications of liver cirrhosis.

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