

HYPONATRAEMIA IN CIRRHOSIS- PREVALENCE AND CORRELATION WITH THE COMPLICATIONS OF CIRRHOSIS

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ABSTRACT

BACKGROUND

Hyponatraemia is one of the complications in cirrhotic patients, occurring in more than one-third of the patients with chronic liver disease and is believed to be caused by defective water homeostasis. The objective of our study is to establish the prevalence of hyponatraemia in cirrhosis and to investigate if hyponatraemia predicts a rate of severity of complications in cirrhosis.

MATERIALS AND METHODS

A cross-sectional study was done in patients diagnosed with cirrhosis by a combination of clinical, biochemical and radiological findings. Demographic data and biochemical parameters including serum sodium levels were recorded at the time of admission or at the time of presentation in the outpatient department and patients were stratified into three groups: Group A- serum sodium < 130 mmol/L; Group B- serum sodium between 131 - 135 mmol/L; Group C- serum sodium > 136 mmol/L. A detailed case report proforma was used for data collection for each patient.

RESULTS

Hundred patients were included in the study. 44 patients had serum sodium level of < 130 mmol/L (Group A), 26 patients had serum sodium 131 - 135 mmol/L (Group B) and 30 patients noted to have serum sodium > 136 mmol/L (Group C). Majority of Group A patients belonged to 31 - 40 years of age (34%) and male gender (77%). Group A patients had rising serum bilirubin levels of 10.01 to 20 mg/dL (34%) compared to Group B and C (3.85% and 3.3% respectively). 84% of Group A patients had serum albumin < 3.5 g/dL. Blood urea levels > 40 mg/dL and serum creatinine > 1.3 mg/dL are associated with > 50% of Group A patients. 37 patients had worsening hepatic encephalopathy in Group A. 38% of Group A are associated with spontaneous bacterial peritonitis. 95% of Group A patients had portal hypertension compared to 65% of Group B and 11% of Group C. The incidence of class 3 Child-Turcotte Pugh score was significantly higher in Group A (70.28%). High MELD score (20 - 29) is associated with Group A patients (43.18%).

CONCLUSION

This study was undertaken to establish serum sodium as an independent variable in the prognosis of patients with decompensated liver disease, irrespective of the aetiology. MELD Na scores calculated using serum sodium values have been recently found to supersede MELD scores to determine prognosis. By comparing MELD vs. MELD Na scores, this study concludes that MELD Na scores have been found to be more significant as a prognostic marker in patients with cirrhosis and its complications.

KEYWORDS

Cirrhosis, Portal Hypertension, Hyponatraemia, Coagulopathy, Hepatorenal Syndrome, Spontaneous Bacterial Peritonitis.

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BACKGROUND

Cirrhosis can be defined as a dynamic process associated with fibrosis and alteration of normal liver structure into architecturally abnormal nodules.

Hyponatraemia is a common complication, occurring in more than one-third of patients with chronic liver disease and is believed to be caused by defective water homeostasis. Hyponatraemia may be of two types; hypovolaemic hyponatraemia or hypervolaemic hyponatraemia.¹

Hypervolaemic hyponatraemia is more common and is associated with low serum sodium levels and expansion of the extracellular fluid volume.² It may occur spontaneously or as a result of administering excessive fluids that are hypotonic in nature. It can also occur due to other complications of cirrhosis, such as bacterial infections. On the other hand, hypovolaemic hyponatraemia is less common and characterised by reduced sodium levels without the presence of ascites and oedema, often secondary to overzealous diuretic therapy.³

Dilutional hyponatraemia in cirrhotic patients is usually associated with a decreased ability to excrete appropriate water in urine due to various factors. The most important factor is increased synthesis of vasopressin⁴ due to hypovolaemia caused by decreased effective circulating volume secondary to splanchnic vasodilation.⁵

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Patients who have End Stage Liver Disease with Volume Overload Status have-

- Decreased urine sodium values.
- Decreased total serum sodium values.
- Increase in total body water content.

Sodium values of less than 130 mEq/L carry a poorer prognosis, whereas values less than 120 mEq/L indicates impending hepatorenal syndrome.^{6,7}

The neurological manifestations may not be seen in all patients of cirrhosis with hyponatraemia⁸; however, the presence of hyponatraemia has a huge negative impact on hepatic encephalopathy in these patients.^{9,10}

Hyponatraemia in cirrhosis is associated with an increased morbidity and mortality. Studies suggest that hyponatraemia is a very important prognostic indicator in cirrhosis when included in the model for end-stage liver disease (MELD) score in those cirrhotic patients awaiting liver transplantation.^{11,12,13}

Despite a large amount of medical literature suggesting the role of serum sodium as a prognostic factor in cirrhosis, the clinical significance of serum sodium levels and whether it is associated with a higher rate of specific complications in cirrhosis is not lucid. Only few studies have been undertaken to assess the correlation between serum sodium levels with prevalence and severity of complications of liver cirrhosis.^{14,15}

There is no study conducted in the Indian subcontinent so far on this topic, which makes this study pertinent.

Hyponatraemia is probably more common among our patients because:

Most Indian liquid diets are not sodium rich and the tropical climate aggravates the amount of sodium lost in sweat.

Aims and Objectives

The aim of this study is to establish the prevalence of hyponatraemia in cirrhosis and to investigate if hyponatraemia predicts an increased rate and severity of complications in cirrhosis.

MATERIALS AND METHODS

Place of Study

Department of General Medicine, Govt. Stanley Medical College and Hospital.

Study Design

A cross-sectional study.

Study Population

100.

Study Period

March 2016 to August 2016.

Inclusion Criteria

1. Age \geq 18 years.
2. Patients diagnosed by a combination of clinical/biochemical and radiological findings: Patients with clinical signs of liver cell failure; clinical features of portal hypertension, hypoalbuminaemia and reversal of A/G ratio; deranged prothrombin time and international

normalised ratio (INR); ultrasound abdomen showing surface nodularity, coarse/ altered echotexture, parenchymal inhomogeneity in the liver with/ without ascites alone or with the features of portal hypertension like portal vein diameter \geq 13 mm, presence of collaterals and splenomegaly OR

3. Patients diagnosed with histological diagnosis of cirrhosis.

Exclusion Criteria

The Patients with following comorbidities have been excluded-

1. Cardiac failure.
2. Cerebrovascular accident.
3. Acute CNS infections.
4. Hepatocellular carcinoma.

Data Collection

After obtaining informed consent, age, gender, risk factors and vital parameters were recorded in all patients.

History and clinical examination was done with special emphasis on the presence of jaundice and signs and symptoms of liver cell failure and complications of cirrhosis.

The patient was assessed and investigated for the presence and severity of the complications like Ascites, Hepatic encephalopathy, Spontaneous bacterial peritonitis (SBP), Hepatorenal syndrome and Upper GI bleed.

Investigations Included

- Serum Sodium.
- Liver Function Test.
- Renal Function Test.
- Prothrombin Time (PT), INR, activated partial thromboplastin time (aPTT).
- USG abdomen for hepatoportal system and to rule out mild ascites.
- Doppler for splenoportal axis.
- Upper gastrointestinal endoscopy.
- Ascitic fluid cytology.
- Ascitic fluid culture and sensitivity.
- Chest x-ray.
- Urine routine microscopy.

Patients were stratified into three groups: Group A (Serum sodium $<$ 130 mmol/L), Group B (Serum sodium 131 – 135 mmol/L) and Group C (Serum sodium $>$ 136 mmol/L).

Severity of the liver disease assessed according to Child-Turcotte Pugh score, MELD score and MELD Na score.

Data Analysis

The collected data were analysed with IBM. SPSS statistics software 23.0 version. To describe about the data descriptive statistics, mean and SD were used. For multiple group comparison analysis, one-way ANOVA with Tukey's Post-Hoc test was used. For analysis of categorical variables, Fisher's Exact Test is used. In the above statistical tools, the probability value of .05 is considered as significant level.

RESULTS

For purposes of better comparison and understanding the effects of hyponatraemia, our study population of 100 patients have been divided into 3 groups on the basis of

serum sodium levels as Group A < 130 mmol/L, Group B 131 - 135 mmol/L and Group C > 136 mmol/L levels. The prevalence of hyponatraemia in these groups are 44%, 26% and 30% respectively (Table 1). The association between the level of hyponatraemia in cirrhosis and various factors such as age, gender, biochemical values as well as other complications of cirrhosis has been compared using these groups (Table 2). Majority of the Group A patients belonged to 31 - 40 years age and male gender. The association between the study groups and age and gender status is considered not statistically significant. Serum albumin of <3.5 g/dL is found in 84% of Group A patients, 9% of Group B patients and 13% of Group C patients. Prolongation of INR < 2 is associated with 52% of Group A cases, 7% of Group B and 6% of Group C patients. Similarly, blood urea levels of >100 mg/dL is found in 13% of Group A patients. 38% of Group A patients had > 2 mg/dL of serum creatinine levels. Similarly, 84% of Group A patients were associated with > 20 MELD scoring system and 72% of Group A patients belonged to > 30 MELD Na score (Table 2). It is clearly evident that as hyponatraemia worsens, the liver function and renal function would decline which is evidenced by the significant association of hyponatraemia with parameters like Total bilirubin, Direct bilirubin, Serum albumin, INR, Urea,

Creatinine, MELD and MELD Na scores (Table 2). Majority of the Group A (n= 16, 36.36%) patients had hepatorenal syndrome. The incidence of Portal Hypertension was 95% in patients with severe hyponatraemia (Group A). It was noted that 81% of Group A patients were categorised into Class C Child-Turcotte Pugh score. Majority of the Group A (n= 37, 84.09%) patients had hepatorenal syndrome. It is seen that the incidence of complications like hepatic encephalopathy, hepatorenal-syndrome, spontaneous bacterial peritonitis and portal hypertension are more in severe hyponatraemia (Group A) (Table 3).

Groups	Description	Number	Percentage
Group A	Serum Sodium ≤130mmol/L	44	44
Group B	Serum Sodium Between 131-135mmol/L	26	26
Group C	Serum Sodium ≥136mmol/L	30	30
Total		100	100

Table 1. Prevalence of Hyponatraemia in Groups as per Serum Sodium Levels

Characteristics	Groups	Mean	Standard Deviation	F-value	P-value (One-Way ANOVA with Tukey's Post-Hoc Test)	Statistical Significance
Age	A	45	11	2.11	0.127	Not Significant
	B	48	9			
	C	50	11			
T.B	A	10.59	7	26.07	0.0005	Significant
	B	3.8	3.3			
	C	2.72	2.4			
D.B	A	7.02	4.8	26.01	0.0005	Significant
	B	2.16	2.9			
	C	1.45	1.5			
SGOT	A	100.98	79.6	2.14	0.123	Not Significant
	B	76.23	41.9			
	C	72.63	54.3			
SGPT	A	68.07	50.7	1.14	0.323	Not Significant
	B	54.58	53.7			
	C	48.77	65.8			
ALP	A	287.77	133.4	0.84	0.431	Not Significant
	B	344.27	291.9			
	C	281.27	184.6			
Albumin	A	2.93	0.6	5.78	0.004	Significant
	B	3.24	0.6			
	C	3.42	0.6			
INR	A	2.12	0.6	24.66	0.0005	Significant
	B	1.47	0.4			
	C	1.38	0.4			
Urea	A	53.91	34.5	6.48	0.002	Significant
	B	27.46	14			
	C	33.42	40.4			
Creatin	A	1.89	1.3	3.21	0.045	Significant
	B	1.1	0.5			
	C	1.38	1.8			
K	A	3.55	0.9	1.58	0.209	Not Significant
	B	3.89	0.8			
	C	5.01	6.3			
MELD	A	27.7	8	33.02	0.0005	Significant
	B	15.86	6.7			
	C	14.51	8			

MELD Na	A	33.32	5.9	70.96	0.0005	Significant
	B	19.88	5.9			
	C	15.62	8.1			
Note: Post-hoc test has been done and the statistical significance has been checked by Tukey's post-hoc test						

Table 2. Comparison of Groups with Various Characteristics

Sl. No.	Complications	Grade	Group A (n=44)	Group B (n=26)	Group C (n=30)	P-value (As Per Fisher's Exact Test)	Significance
1	Hepatic encephalopathy	NIL	7 (15.91%)	23 (88.46%)	29 (96.67%)	<0.0001	Significant
		1	7 (15.91%)	2 (7.69%)	0 (0%)		
		2	16 (36.36%)	0 (0%)	0 (0%)		
		3	7 (15.91%)	1 (3.85%)	1 (3.33%)		
		4	7 (15.91%)	0 (0%)	0 (0%)		
2	Hepatorenal syndrome	No	28 (63.64%)	25 (96.15%)	28 (93.33%)	0.0005	Significant
		Yes	16 (36.36%)	1 (3.85%)	2 (6.67%)		
3	Spontaneous bacterial peritonitis	No	27 (61.36%)	24 (92.31%)	25 (83.33%)	0.0078	Significant
		Yes	17 (38.64%)	2 (7.69%)	5 (16.67%)		
4	Portal hypertension	No	2 (4.55%)	9 (34.62%)	19 (63.33%)	<0.0001	Significant
		Yes	42 (95.45%)	17 (65.38%)	11 (36.67%)		
5	Child-Turcotte Pugh score	A	0 (0%)	7 (26.92%)	19 (63.33%)	<0.0001	Significant
		B	8 (18.18%)	16 (61.54%)	8 (26.67%)		
		C	36 (81.82%)	3 (11.54%)	3 (10.00%)		

Table 3. Occurrence of Complications in Cirrhosis with Varying Levels of Hyponatraemia

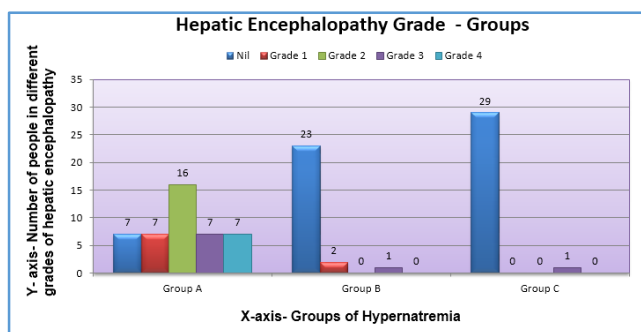


Figure 1. Hepatic Encephalopathy Grade - Groups

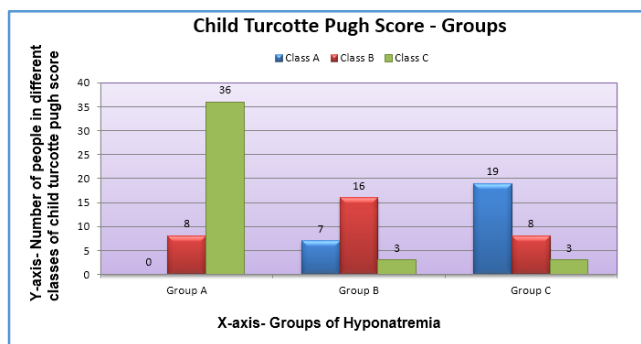


Figure 2. Child-Turcotte Pugh Score

DISCUSSION

In our study group of 100 patients, 44% had serum sodium <130 mmol (Group A), 26% had 131 - 135 mmol (Group B) and 30% had serum sodium > 136 mmol (Group C). Majority of the Group A patients belonged to the age group of 31 - 40 years and of the male gender. The association between these

variables and hyponatraemia is however not statistically significant.

Increasing Bilirubin levels > 10 mg/dL associated with severe hyponatraemia was noted in Group A. Similarly, significantly a high level of direct Bilirubin levels was also observed in Group A. Although, increased liver enzymes SGOT > 100 U/L and SGPT > 57 U/L was also associated with severe hyponatraemia in 44% of Group A patients, a statistical significance could not be established. Thus, serum Bilirubin but not SGPT/ SGOT has more significance with regard to the severity of hyponatraemia in cirrhosis.

Serum albumin of < 3.5 g/dL is found in 84% of Group A patients, 9% of Group B and 13% of Group C patients. This establishes a clear association between serum albumin levels and the severity of hyponatraemia. Similar findings were observed, and a significant association ascertained with INR. Prolongation of INR > 2% was found in 57% of Group A patients, but only amongst 7% and 6% of patients of Groups B and C respectively. Likewise, blood urea levels of >100 mg/dL is found in 13% of Group A patients and 38% of Group A patients had > 2 mg/dL of serum creatinine levels.

85% of Group A patients had hepatic encephalopathy of varying degrees between grades 1 - 4, while 38% were found to have spontaneous bacterial peritonitis. The incidence of hepatorenal syndrome was also significantly higher in Group A compared to Group B (9.45 times higher) or Group C.¹⁶ The incidence of Portal Hypertension was 95% in patients with severe hyponatraemia of Group A. It was noted that 81% of Group A patients were categorised into Class C Child-Turcotte Pugh score. Similarly, 84% of Group A patients were associated with > 20 MELD scoring system and 72% of Group A patients belonged to > 30 MELD Na score. Hence, a clear statistical significance has been established between the above-mentioned factors and the severity of hyponatraemia in cirrhosis.

CONCLUSION

Hyponatraemia in cirrhosis is associated with an increase in mortality and morbidity. Studies suggest that hyponatraemia is a very important prognostic indicator in cirrhosis when included in MELD score in those patients waiting for liver transplantation. Hyponatraemia also has high propensity to cause Osmotic demyelination syndrome with severe neurological dysfunction shortly after liver transplantation.

In our study group, the prevalence of hyponatraemia as per sodium < 130 mmol/L, 131 – 135 mmol/L and > 136 mmol/L levels are 44%, 26% and 30% respectively. The association between the study groups and age and sex distribution is not statistically significant. Our study also established that severe hyponatraemia was associated with worsening jaundice, portal hypertension, higher grades of encephalopathy, increasing incidence of hepatorenal syndrome and spontaneous bacterial peritonitis.

Patients with moderate and severe hyponatraemia had higher Child Pugh and MELD scores in comparison to those in the study group with either mild hyponatraemia or normal sodium values. MELD Na scores have shown a greater significance in establishing and association as well as assessing the severity of the hyponatraemia.

Our study established the increased prevalence of hyponatraemia in cirrhosis and also worsening sodium levels are associated with the complications of cirrhosis.

So early identification of hyponatraemia in cirrhosis can be helpful for prompt and appropriate treatment, thereby attenuating the morbidity and mortality associated with the disease.

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