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Study of Hyponatremia and its Outcome in Cirrhosis of Liver

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Hyponatremia; Chronic liver disease

1. Abstract

1.1. Background: Hyponatremia in cirrhosis is currently defined as a serum sodium level of less than 130 meq/L. Recent studies have reported that lower serum sodium levels are associated with increased complications and mortality leading to incorporation of sodium in the Model For End Stage Liver Disease. Therefore, we undertook this study in our tertiary hospital to study serum sodium levels in patients admitted with cirrhosis of liver and its outcome.

1.2. Materials and Methods: A hospital based survey was conducted on 100 patients of liver cirrhosis admitted to our tertiary care hospital during the study period of 18 months from January 2018 to September 2019. Informed consent was obtained from all patients enrolled for the study. The data of the patients was collected in a well-designed pro forma (consisting of the patient's particulars, detailed history, clinical examination and investigations). The status of the patients at the time of inclusion (inpatient or outpatient) as well as severity of cirrhosis was assessed using Child-Pugh score and Model for End Stage Liver Disease (MELD) Score.

1.3. Results: Based on the serum sodium levels, 34% of patients had serum sodium levels less than or equal to 130. Grade 1 hepatic encephalopathy prevalence was 72.7% in sodium<130., grade 2 hepatic encephalopathy prevalence 38.9%, and grade 3 hepatic encephalopathy 57.1%. Similarly, the prevalence of SBP in the hyponatremia group is 63.6% which is statistically significant. (p value =0.004). p value for hepatorenal syndrome was 0.030 which is again statistically significant. The prevalence of coagulopathy is 44.4% among hyponatremia group which is statistically significant. (p value =0.003). The mean CHILD PUGH SCORE in the sodium group less than or equal to 130 is 11.62, the mean CPS in 131-135 subgroup is 11.66 and the mean CPS in sodium subgroup more than 135 is 9.30. The difference in CPS among the 3 subgroups is statistically significant. Out of the 40 patients, belonging to MELD 20-29 47.1% had sodium levels less than 130,51.7% had sodium levels between 131-135.Of the 29 patients having MELD SCORE >30 ,50% had sodium levels below 130. All these differences are statistically significant (p value <=0.001)

1.4. Conclusion: Patients with decreased serum sodium levels should be considered a high risk population because of the increased frequency of complications and mortality.

2. Introduction

Sodium is an essential nutrient involved in the maintenance of normal cellular homeostasis and in the regulation of fluid and electrolyte balance and blood pressure. An imbalance in the regulation of total body water can lead to abnormal sodium levels. The normal range of serum sodium is 135-145 mEq/L. Hyponatremia is defined as concentration of sodium less than 135 mEq/L. Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. Chronic liver disease is said to be present when the disease process lasts for six months. Cirrhosis of liver is associated with disturbance in water homeostasis leading to dysnatremias [1-7] Hyponatremia in cirrhosis is currently defined as a serum sodium level of less than 130 meq/L Patients with cirrhosis may develop hyponatremia due to either hypovolemia (example: loss of extracellular fluid due to diuretics) or hypervolemia (expanded extracellular fluid volume due to the inability of the kidneys to excrete solute-free water proportionate to the amount of free water ingested). It is the most common electrolyte disorder in hospitalized patients and more so in cirrhosis patients [6,7,8-15]. 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. Recent studies have reported that lower serum sodium levels were associated with increased complications and mortality leading to incorporation of sodium in the MODEL FOR END STAGE LIVER DISEASE score [6,8,11,13-15] . Hyponatremia when present is also associated with increased mortality. Therefore, we undertook this study in our tertiary hospital to study serum sodium levels in patients admitted with cirrhosis of liver and study its outcome.

3. Materials and Methods

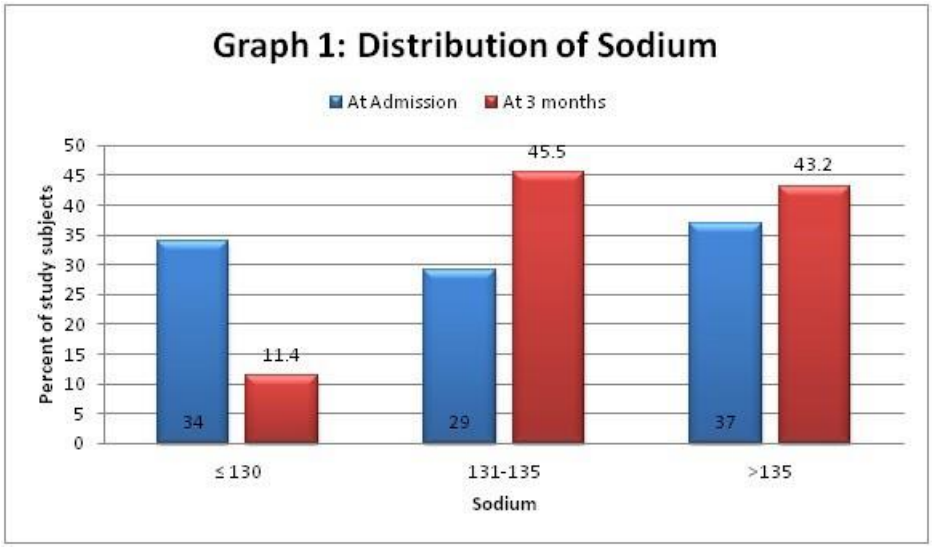
A hospital based survey was conducted on 100 patients of liver cirrhosis admitted to our tertiary care hospital during the study period of 18 months from January 2018 to September 2019. Informed consent was obtained from all patients enrolled for the study. The data of the patients was collected in a well-designed pro forma (consisting of the patient's particulars, detailed history, clinical examination and investigations). The status of the patients at the time of inclusion (inpatient or outpatient) as well as severity of cirrhosis was assessed using Child-Pugh score, Model for End Stage Liver Disease (MELD) Score. The selection of patients was based on the findings of clinical examinations, biochemical tests and ultrasound. The patients were followed over a period of 3 months with serum sodium levels measured at intervals of 3 months. A comparative analysis of the incidence of individual complications of cirrhosis as well as mortality was made with different values of serum sodium determined in these cirrhotic patients. Investigations such as Serum Sodium, Prothrombin Time (PT/INR), Total protein with Serum Albumin and Globulin along with A:G Ratio, Serum Bilirubin (both total as well as direct fraction), Serum Creatinine, Blood Urea Nitrogen, Ultrasound Whole Abdomen, Upper Gastrointestinal Endoscopy, HbSAg, anti HCV etc. noted down from indoor case paper. Outcome measured as, • Improvement• Development of complication or death. All patients age more than 18 years and diagnosed as cirrhosis of liver were included in the study Patients with Congestive cardiac failure, Nephrotic syndrome, Psychogenic polydipsia, Patients on SSRI and MAOA&B inhibitors, Patients/ relatives refusing to participate in study were excluded from the study. Data analysis was done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Association between Variables was analyzed by using Chi-Square test for categorical Variables. Comparison of mean of quantitative variables were analyzed using unpaired t test and ANOVA (Analysis of Variance). Level of significance was set at 0.05.

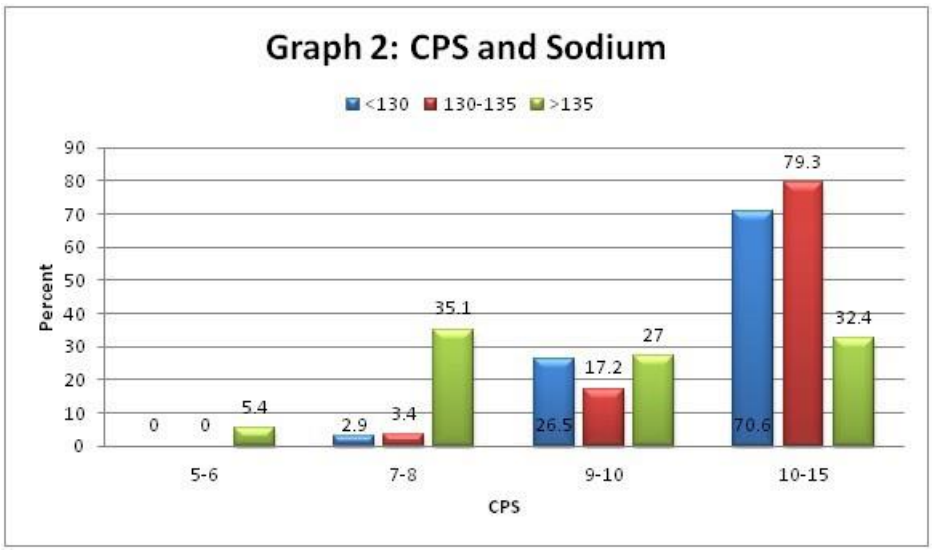
4. Results

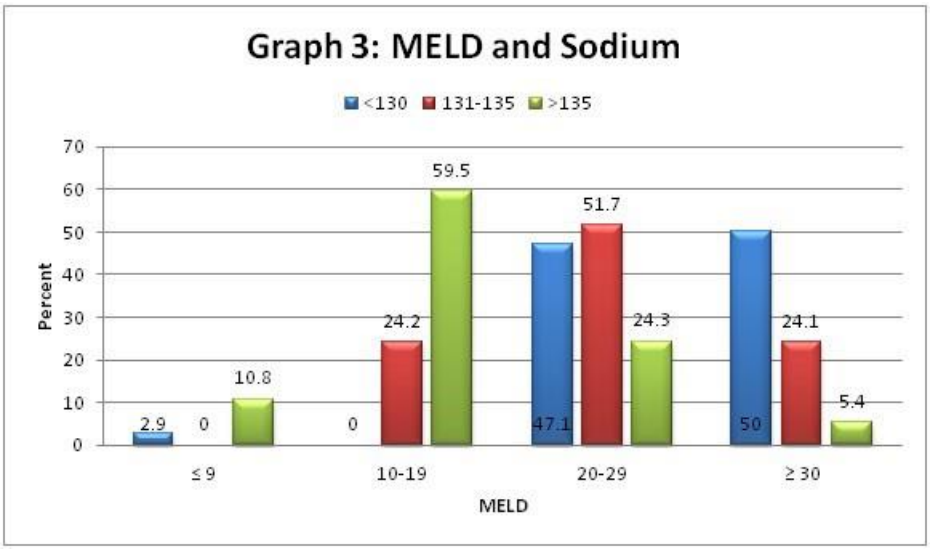
Alcoholic liver disease was the commonest cause of cirrhosis of liver accounting for 91% of the causes while chronic hepatitis B and C were the causative factor in 8% and 2% cases respectively. Autoimmune causes accounted for another 2% cases out of the total 100. At admission, the mean concentration of sodium of all patients was 133.33 with a range of 105-141. Based on the serum sodium levels, 34% of patients had serum sodium levels less than or equal to 130. 29% of patients had serum sodium levels between 131 and 135, while 37% of patients had serum sodium level>135. Patients were followed up over 3 months. During the period of 3 months' patients received treatment for liver cirrhosis and its complications. At 3 months follow up, the mean concentration of sodium was 134.81. Based on the serum sodium levels, 10 %of patients had serum sodium levels less than or equal to 130. 40% of patients had serum sodium levels between 131 and 135, while 38% of patients had serum sodium levels >135. Around 12% of patients expired. The difference between the sodium levels at admission and at 3 months was statistically significant (p value= <0.001) (Graph 1) Grade 1 hepatic encephalopathy prevalence was 72.7% in sodium<130, grade 2 hepatic encephalopathy prevalence 38.9%, and grade 3 hepatic encephalopathy 57.1%. The difference in the prevalence of hepatic encephalopathy in the various subgroups of sodium was statistically significant (p value=<0.001). Similarly in hyponatremia group, the prevalence of SBP (p value =0.004), hepatorenal syndrome (p-0.030) and coagulopathy (p value =0.003) are statistically significant.(Table 1)

The mean CHILD PUGH SCORE in the sodium group less than or equal to 130 is 11.62, in 131-135 subgroup is 11.66 and the in sodium subgroup more than 135 is 9.30. The difference in CPS among the 3 subgroups is statistically significant. (Graph2) Out of the 40 patients, belonging to MELD 20-29 47.1% had sodium levels less than 130,51.7% had sodium levels between 131-135. Of the 29 patients having MELD SCORE >30 ,50% had sodium levels below 130. All these differences are statistically significant (p value <=0.001) (Graph 3) Comparing various parameters with sodium, it is seen that blood urea nitrogen has a higher mean value (22.56) in the hyponatremia group than in sodium above 135(14.73). This difference is statistically significant (p value =0.012).Similarly creatinine also has a higher mean value in the hyponatremia group than in normal sodium levels and it is statistically significant(p value =0.003). Total bilirubin, (p value =0.002), albumin (p value=0.010), prothrombin time (p value=0.001), INR (p value =<0.001) all show statistically significant differences among the different sodium subgroups.

The mean serum osmolality in the hyponatremia group is 263.94 which is lower than in the normal sodium group and this difference is statistically significant (p value=<0.001). Likewise, urine sodium and urine osmolality have a lower mean value in the hyponatremia group than in the group with normal sodium levels and this difference is again statistically significant (p value=<0.001). Among 34 patients with serum sodium levels ≤130, 11 patients (32.4%) died. Among 29 patients with serum sodium levels between 131 and 135, 1 patient (3.4%) died. There were no deaths among patients with sodium levels ≥136. The difference in mortality among these three groups was statistically significant. (p value- <=0.001) (Graph 4)


Graph 1: Distribution of Sodium
At Admission
At 3 months
Percent of study subjects
50
45
40
35
30
25
20
15
10
5
0
34
11.4
29
45.5
37
43.2
≤ 130
131-135
>135
Sodium


Graph 2: CPS and Sodium
<130
130-135
>135
Percent
90
80
70
60
50
40
30
20
10
0
0
0
5.4
2.9
3.4
35.1
26.5
17.2
27
70.6
79.3
32.4
5-6
7-8
9-10
10-15
CPS


Graph 3: MELD and Sodium
<130
131-135
>135
Percent
70
60
50
40
30
20
10
0
2.9
0
10.8
0
24.2
59.5
47.1
51.7
24.3
50
24.1
5.4
≤ 9
10-19
20-29
≥ 30
MELD

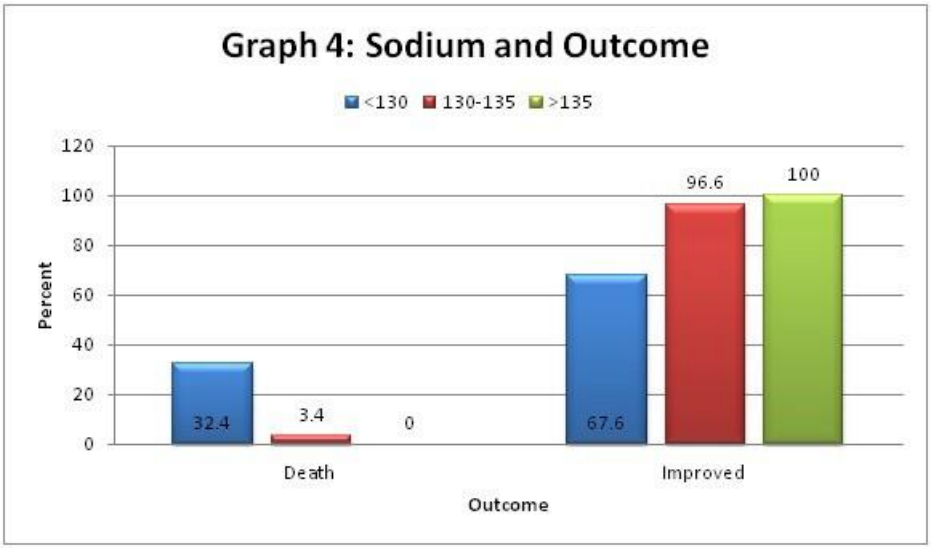


Table 1: Corelation of Complications with Sodium level

Complications	Sodium			P Value
	≤ 130 n (%)	131-135n (%)	>135 n (%)	
Portal Hypertension	34 (35.4)	28 (29.2)	34 (35.4)	0.216
	0	1 (25.0)	3 (75.0)	
Hepatic Encephalopathy				
Grade 1	8 (72.7)	3 (27.3)	0	<0.001*
Grade 2	7 (38.9)	9 (50.0)	2 (11.1)	
Grade 3	4 (57.1)	2 (28.6)	1 (14.3)	
Absent	15 (23.4)	15 (23.4)	34 (53.2)	
Spontaneous Bacterial Peritonitis	14 (63.6)	4 (18.2)	4 (18.2)	0.004*
	20 (25.6)	25 (32.1)	33 (42.3)	
Hepatorenal Syndrome	9 (64.3)	3 (21.4)	2 (14.3)	0.030*
	25 (29.1)	26 (30.2)	35 (40.7)	
GI Bleeding	15 (34.1)	16 (36.4)	13 (29.5)	0.266
	19 (33.9)	13 (23.2)	24 (42.9)	
Coagulopathy	20 (44.4)	18 (37.8)	8 (17.8)	0.003*
	14 (25.9)	11 (20.4)	29 (53.7)	
Chi-Square Test, P Value *Significant				

5. Discussion

A significant proportion of patients with liver cirrhosis have abnormal serum sodium concentration. Hyponatremia is the most common occurrence in our study**.** No patients presented with serum sodium levels greater than 141.Lowest serum sodium level was 105. At presentation, 63% of patients had serum sodium levels less than 135, while 34% patients had serum sodium levels than 130. At 3 months follow up, 50% patients had serum sodium levels less than 135 while 10% patients had serum sodium levels less than 130. There was a statistically significant association between hyponatremia and hepatitis B as cause of cirrhosis. Out of the 8 patients with hepatitis B about 75% had hyponatremia (sodium <130) and the p value was 0.038.

In the present study, patients with serum sodium levels ≤130 mEq/L had frequency of hepatic encephalopathy 55.8% compared to the other two groups (p value =<0.001).The increased frequency of hepatic encephalopathy in patients having hyponatremia could correlate with the fact that both hepatic encephalopathy and hyponatremia will lead to altered sensorium. Similar findings were seen in Jong Hoon Kim et al study [16] 43.1% of patients with serum sodium levels less than or equal to 130 mEq/L developed hepatic encephalopathy compared to 35.8% with serum sodium levels between 131 and 135 mEq/L. In our study ,64.3% of patients having serum sodium <=130mEq developed hepatorenal syndrome

compared to 14.3% having serum sodium levels greater than 135 mEq/L. Angeli P et a l [17] found that 17% of patients with serum sodium levels ≤130 mEq/L had hepatorenal syndrome compared to 10% and 6% in patients with serum sodium levels 131-135 mEq/L and more than 135 mEq/L respectively.

We found that 63.6% patients with serum sodium levels <=130mEq/L had SBP compared to 18.2% and 18.2% with patients having serum sodium 131-135 mEq/L and >=135mEq/L. In the present study, the average CPS score in patients having <=135 mEq/L was 11.62 compared to 9.30 in patients with sodium levels more than 135mEq/L. The average MELD score in serum sodium levels less than 130 mEq/L was 29.6 compared to 16.76 in patients having sodium levels greater than 135 mEq/L.

Jong Hoon Kim et al [s] found that lower sodium levels were associated with increased MELD score and Child Pugh score. This indicates that lower serum sodium levels were associated with severe disease. Also, comparing various parameters with sodium, it is seen that blood urea nitrogen has a higher mean value (22.56) in the hyponatremia group than in sodium above 135(14.73).This difference is statistically significant (p value =0.012).Similarly creatinine also has a higher mean value in the hyponatremia group than in normal sodium levels and it is statistically significant(p value =0.003).Similarly total bilirubin,(p value =0.002),albumin(p value=0.010),prothrombin time(p value=0.001),INR(p value =<0.001) all show statistically significant differences among the different sodium subgroups. Similarly, the mean serum osmolarity in the hyponatremia group is 263.94 which is lower than in the normal sodium group and this difference is statistically significant (p value=<0.001). Likewise, urine sodium and urine osmolarity have a lower mean value in the hyponatremia group than in the group with normal sodium levels and this difference is again statistically significant (p value=<0.001). The present study also showed mortality of 32.4% among patients with sodium levels. <=135mEq/L as compared to 0% mortality in patients having serum sodium levels greater than 135 mEq/L. (P value =0.001). This could again be explained by the fact that hyponatremia was associated with increased frequency of complications and hence increased mortality. Comparing various parameters with outcome, the mean value of blood urea nitrogen, creatinine, total bilirubin was higher in the patients who died than patients who improved and this difference is statistically significant (p value=<0.001). Similarly, the mean INR was higher among patients who expired than among patients who improved (p value=0.009). Similarly, mean sodium, serum osmolarity, urine sodium and urine osmolarity was at a lower level than in the patients who improved and this difference was statistically significant. (p value=<0.001)

6. Conclusion

Liver cirrhosis is associated with abnormal serum sodium concentration. Hyponatremia is themost common abnormality in this study. Serum sodium levels less than 135mEq/L is associated with increased frequency of complications such as Hepatic Encephalopathy, Hepatorenal Syndrome, Spontaneous Bacterial Peritonitis and Coagulopathy when compared to patients with serum sodium levels >135 mEq/L. Patients with serum sodium concentration less than 130 mEq/L are the most affected. Lower serum sodium levels are associated with increased MELD score, increased CPS score and increased mortality indicating the inverse relationship between serum sodium levels and the severity of disease. Thus patients with decreased serum sodium levels should be considered a high risk population because of the increased frequency of complications and mortality and prompt treatment should be given to them to reduce morbidity and mortality.

7. Limitations

1. Some of the patients included in the study were already on diuretics, so the low sodium levels could be due to diuretic use.

2. The sample size was small. A larger sample size would be needed to extrapolate the results to a larger population.

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