



“TO STUDY THE ASSOCIATION OF HYPONATREMIA WITH THE SEVERITY OF CHRONIC LIVER DISEASE IN PATIENTS OF CIRRHOSIS.”

General Medicine

Ashutosh Kori* Assistant Professor Dept. Of General Medicine, CIMS Bilaspur. *Corresponding Author

Aniketh Prabhakar Associate Professor Dept. Of General Medicine, Pt. JNM medical college, Raipur.

Chandras Dhruw Assistant Professor Dept. Of Radiotherapy, CIMS Bilaspur.

Jaipal Chandravanshi Associate Professor Dept. Of General Medicine, CIMS Bilaspur.

ABSTRACT

Background: Cirrhosis is among the leading causes of death and results in serious complications of cirrhosis like ascites, hepatic encephalopathy and variceal hemorrhage. The clinical course of patients with chronic liver disease (CLD) is frequently complicated by the development of abnormalities in renal function and electrolyte levels and hyponatremia is the most common disorder seen in these patients. Recent studies indicate that hyponatremia was a key prognostic factor in patients with CLD and patients with hyponatremia had a poor survival compared with that of patients without hyponatremia. Impairment in body water homeostasis is a common feature of advanced cirrhosis. 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. In recent years, great advances have been made in the knowledge of the pathogenesis of reduced solute-free water clearance in patients with advanced cirrhosis. The inability to excrete an adequate amount of solute-free water in the urine is related to several factors, the most important of which is increased vasopressin release. A reduction of effective circulating volume due to arterial splanchnic vasodilation is considered the afferent factor leading to a baroreceptor mediated non-osmotic stimulation of vasopressin release in cirrhosis. Additional factors in the pathogenesis of hyponatremia in cirrhosis are thought to be reduced production of solute-free water due to a reduced sodium delivery to the distal tubule as a consequence of reduction of glomerular filtration rate and/or increase of sodium reabsorption in the proximal tubule. Several studies in large cohorts of patients with cirrhosis have shown that the renal ability to excrete free water, as assessed either by measuring solute-free water clearance or serum sodium concentration shows an excellent correlation with survival. **Objective:** To study the association of hyponatremia with the severity of chronic liver disease in patients of cirrhosis.

Method: This prospective clinical study comprises of 100 patients of cirrhosis of liver diagnosed and treated in the Department of Medicine, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur from October 2014 to Sept 2015. Informed written consent, detail history and complete Physical examination were performed in every patient. Cirrhosis is confirmed by clinical, biochemical and ultra-sonographic findings. Frequency tables were used to describe impact of treatment on different stages using chi-square test. **Result:** This prospective study included 100 cirrhotic patients out of which 84 (84%) males and 16 (16%) females and the mean age of the patients were 44.89 ± 10.27 years (range, 22-70 years). Causative factors for liver cirrhosis included alcoholic liver disease (96 cases, 96%), chronic hepatitis B (4 cases 4%). All patients (100%) presented to hospital with abdominal distension and jaundice. 99(99%) patients had lower limb swelling at the time of presentation to the hospital. Altered sensorium and gastrointestinal bleeding were present in 50(50%) and 24(24%) of patients respectively. Mean serum sodium for the study was $130.84 \text{ meq/L} \pm 9.87$. Patients were classified according to level of serum sodium, 46(46%) belong to the group of serum sodium concentrations $\geq 136 \text{ meq/L}$. While, 34(34%) and 20(20%) patients were belong to serum sodium concentration group of $\leq 130 \text{ meq/L}$ and 131- 135 meq/L respectively. The following were the characteristics of the three groups based on age sex and cause of cirrhosis. Mean age in these three groups, $\leq 130 \text{ meq/L}$, 131-135 meq/L and $\geq 136 \text{ meq/L}$ was 45.47 ± 10.28 , 45.75 ± 11.93 and 44.09 ± 9.640 respectively. **Conclusion:** The present study proves that serum sodium level is of utmost importance in patients with liver disease. The numbers in this study only highlight the much discussed and described correlation between disease prognosis in patients of chronic liver disease and their level of serum sodium. Hyponatremia being dilutional in most or diuretic induced in treated patients and mixed picture in almost all patients just needs water restriction and judicious diuretic use for correction. Newer agents like vaptans have still not been proven safe and efficacious in liver disease.

KEYWORDS

Cirrhosis, Hyponatremia, chronic liver disease, Reabsorption

INTRODUCTION

Cirrhosis is among the leading causes of death and results in serious complications of cirrhosis like ascites, hepatic encephalopathy and variceal hemorrhage.^[1] The clinical course of patients with chronic liver disease (CLD) is frequently complicated by the development of abnormalities in renal function and electrolyte levels and hyponatremia is the most common disorder seen in these patients.^[2] Recent studies indicate that hyponatremia was a key prognostic factor in patients with CLD and patients with hyponatremia had a poor survival compared with that of patients without hyponatremia.^{[3][4]} Impairment in body water homeostasis is a common feature of advanced cirrhosis.^{[5][6]} 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. In recent years, great advances have been made in the knowledge of the pathogenesis of reduced solute-free water clearance in patients with advanced cirrhosis. The inability to excrete an adequate amount of solute-free water in the urine is related to several factors, the most important of which is increased vasopressin release. A reduction of effective circulating volume due to arterial splanchnic vasodilation is considered the afferent factor leading to a baroreceptor mediated non-osmotic stimulation of vasopressin release in cirrhosis.

^[7] Additional factors in the pathogenesis of hyponatremia in cirrhosis are thought to be reduced production of solute-free water due to a reduced sodium delivery to the distal tubule as a consequence of reduction of glomerular filtration rate and/or increase of sodium reabsorption in the proximal tubule.^[8-12] Several studies in large cohorts of patients with cirrhosis have shown that the renal ability to excrete free water, as assessed either by measuring solute-free water clearance or serum sodium concentration shows an excellent correlation with survival. Patients with hyponatremia have a poor survival compared with that of patients without hyponatremia.^[13-15] Moreover, recent studies have shown that serum sodium concentration correlates with survival in patients with cirrhosis awaiting liver transplantation, and the suggestion has been made that serum sodium could be added to the calculation of model for end-stage liver disease score to improve the accuracy of this scoring system in organ allocation for liver transplantation.^[16-18] In contrast with the large amount of information that has been accumulated on the value of serum sodium in the prediction of prognosis, little is known regarding the clinical significance of the presence of hyponatremia, particularly the relationship between serum sodium levels and severity of liver disease. With this in mind we undertook an observational study in our institution to correlate the prognosis and severity of liver disease in patients of cirrhosis with hyponatremia.

OBJECTIVE:

To study the association of hyponatremia with the severity of chronic liver disease in patients of cirrhosis.

MATERIAL AND METHOD:

This prospective clinical study study comprises of 100 patients of cirrhosis of liver diagnosed and treated in the Department of Medicine, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur from October 2014 to Sept 2015. Informed written consent, detail history and complete Physical examination were performed in every patient. Cirrhosis is confirmed by clinical, biochemical and ultra-sonographic findings.

Major Variables

- 1) Age
- 2) Sex
- 3) Etiology
- 4) Clinical Presentation
- 5) Serum Sodium

Outcome Variables

- 1) Hyponatremia
- 2) Severity of chronic liver diseases

Methodology

- This study was performed in the Department of Medicine, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur from October 2014 to Sept 2015.
- Informed written consent was taken from every patient.
- Detail history was recorded from each patient pertaining to the onset and duration of present complaint.
- Physical examination was done on all patients including general, local and systemic examination.
- All the routine investigations including complete blood count, Blood glucose, Serum sodium Serum bilirubin, Serum albumin, Serum creatinine, Prothrombin time
- Grades of ascites and hepatic encephalopathy were determined using the standard references.
- CHILDS Score and MELD Score was calculated for each patient.
- After collecting data the patients were divided into three groups

1. Normal Sodium level ≥ 136
2. Mild hyponatremia 130-135
3. Severe hyponatremia ≤ 129

- After dividing into three groups the patients the mean MELD score in each group was calculated
- Mean child Pugh score was calculated in each group and later was also divided on basis of their Child Class- A,B,C

Calculation of result:

The data comprised both categorical and continuous variables are obtained during the analysis. The continuous variables are analyzed using the correlation tools in Microsoft excel. The categorical variables will be analyzed using the chi square test 3 x 3 tables with chi square calculator available on turner.faculty.swau.edu. P value of less than 0.05 will be considered significant.

RESULTS

This prospective clinical study study comprises of 100 patients of cirrhosis of liver diagnosed and treated in the Department of Medicine, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur from October 2014 to Sept 2015. Informed written consent, detail history and complete Physical examination were performed in every patient. Cirrhosis is confirmed by clinical, biochemical and ultra-sonographic findings. The results were as follows

Age and Sex

This prospective study included 100 cirrhotic patients out of which 84 (84%) males and 16 (16%) females and the mean age of the patients were 44.89 ± 10.27 years (range, 22-70 years). Causative factors for liver cirrhosis included alcoholic liver disease (96 cases, 96%), chronic hepatitis B (4 cases 4%).

Table 1 Age, sex and etiology wise distribution of patients

SN	Characteristic	N
1	Age(years) (Mean $\pm$ SD)	44.89 10.27
2	Sex: (Number) (%)	
	Males	84%
	Females	16%

3	Cause of cirrhosis: (Number) (%)	100
	Alcohol	96(96%)
	HBV	04(4%)
	HCV	0
	Others	0

Clinical presentation

All patients (100%) presented to hospital with abdominal distension and jaundice. 99(99%) patients had lower limb swelling at the time of presentation to the hospital. Altered sensorium and gastrointestinal bleeding were present in 50(50%) and 24(24%) of patients respectively. Only one patient with liver cirrhosis was having concurrent seizures at the time of hospital admission.

Table 2 Clinical Presentation wise Distribution

SN	PRESENTATION	%
1	Abdominal Distention	100
2	Lower Limb Swelling	99
3	Jaundice	100
4	Altered Sensorium	50
5	Gastrointestinal Bleeding	24
6	Seizures	1

Serum sodium

Mean serum sodium for the study was $130.84 \text{ meq/L} \pm 9.87$. Patients were classified according to level of serum sodium, 46(46%) belong to the group of serum sodium concentrations $\geq 136 \text{ meq/L}$. While, 34(34%) and 20(20%) patients were belong to serum sodium concentration group of $\leq 130 \text{ meq/L}$ and 131- 135 meq/L respectively. The following were the characteristics of the three groups based on age sex and cause of cirrhosis. Mean age in these three groups, $\leq 130 \text{ meq/L}$, 131-135 meq/L and $\geq 136 \text{ meq/L}$ was 45.47 ± 10.28 , 45.75 ± 11.93 and 44.09 ± 9.640 respectively. In the present study around 85% were males and 15% were females in all three groups

Table 3 Serum Sodium v/s other characteristics

SN	Characteristic	$\leq 130 \text{ meq/L}$ n = 34	131-135 meq/L n = 20	≥ 136 meq/L n = 4
1	Age(years) (Mean $\pm$ SD)	45.47 ± 10.28	45.75 ± 11.93	44.09 ± 9.640
2	Sex (Number) %			
	M	29(85%)	17(85%)	38(83%)
	F	5(15%)	3(15%)	8(17%)
3	Cause of cirrhosis (Number)(%)			
	Alcohol	32(94%)	20(100%)	44(96%)
	HBV	2(6%)	0(0)	2(4%)
	HCV	0(0)	0(0)	0(0)
	Others	0(0)	0(0)	0(0)

Meld Score

The mean MELD score was 22.77 ± 8.262 (range, 9-46); and when classified according to the groups the observations were as follows

Table 4 Meld Score

SN	Characteristic	$\leq 130 \text{ meq/L}$ n = 34	131-135 meq/L n = 20	≥ 136 meq/L n = 4
1	Meld Score (Mean)	26.4	27.15	18.17

Child Pugh Score and Class

The mean Child Pugh score was 8.9 ± 2.32 and when classified according to the groups the observations were as follows

Table 5 Child Pugh Score and Class

SN	Characteristic	$\leq 130 \text{ meq/L}$ n = 34	131-135 meq/L n = 20	≥ 136 meq/L n = 4
1	Child Pugh Score (Mean)	10.2	8.4	8.1
2	Child Pugh Class			
	A	1	4	13
	B	12	10	21
	C	21	6	12

The P Value

The p value for correlation between serum sodium levels and corresponding child pugh score was 0.000126 proving the correlation to be significant. After division into three groups p value was calculated for different child class the p value was found to be 0.0054

which was significant.

DISCUSSION

In our study the mean age group was 45 years which ranged from 22-70 years. There was predominance of male patients with 84(84%) male and 16(16%) female subjects in the study. In the study conducted by **Angeli P et al** on 997 patients mean age was 59 years and there were 650(68.2%) male and 347 (31.8) female patients. **Boronni et al** studied 191 patients in which 156 were cirrhotics, the mean age was 56 years and out of them 134 (70%) were males and 57 (30%) were females. **Serste et al** studied 174 patients with mean age 60 years and 139 (79.8%) were male and 34 (20.2%) were female patients. It's important to determine the cause of cirrhosis because treating that underlying cause can help prevent further liver damage. A wide range of diseases and conditions can damage the liver and lead to cirrhosis many of which are discussed above. Sometimes if the etiology of cirrhosis cannot be determined then it can be termed as cryptogenic or idiopathic. In the present study 96(96%) of patients with chronic liver disease had significant alcohol consumption history and in them alcohol can be attributed as the cause of cirrhosis. There were a small number of patients 4 (4%). In the study conducted on 156 cirrhotics by **Boronni et al** in Rome, Italy reflected that only 29(18.4%) had alcohol as their etiology of cirrhosis, a large no. of patients 113(72%) were having viral etiology of their cirrhosis. In the rest 14(8.9%) had other causes of cirrhosis. In the multicenter study by **Angeli et al** on 997 patients in Europe, north and south America and Asia found that alcohol was the etiology in 501(50.2%) , 421(42%) had viral etiology for their cirrhosis. In 75(7.6%) had other etiologies for cirrhosis. 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. Studies have 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 observational study to examine the prevalence of hyponatremia and association between hyponatremia and the severity of liver disease. **Jong Huon Kim et al (2009)** showed prevalence of hyponatremia was 27.1%, 20.8 % and 52.1% in patients with serum sodium <130 meq/L, 131-135 meq/L and >135meq/L respectively. **Shaikh S et al (2010)** 104 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, more than one half (54%) of patients with cirrhosis had values of serum sodium concentration below the normal range (<135 meq/L) and one third (34%) had values <130 meq/L. Low serum sodium levels were not associated with age, sex, or etiology of cirrhosis Child score takes into account the serum bilirubin serum albumin coagulopathy, grade of hepatic encephalopathy and ascites to create a score and divide the patients into CLASS A , B, C and which indicates prognosis, the higher the class the worse in the prognosis. **Qureshi et al** studied 202 liver disease patients in 2012 and similarly found that in group of normal serum sodium n(85) 13 belong to class A, 47 belonged to class B and 25 belonged to class C, in the group with mild hyponatremia (Na+ 131-135) n(55) 3 patients were in class A, 21 in class b, 31 in class c. in the group with significant hyponatremia n(62) maximum patients 45 were in class c , 17 in class B and none in class A. **In Shaik et al's** 217 patients studied in 2007, out of 58 patients belonging to significant hyponatremia group 48 were in class c and 10 in class b. 52 patients in mild hyponatremia 35 were in class c and 17 class B and also 41 patients were found to be in class c out of 105 patients with normal sodium levels rest of the 64 patients were in class B. this was also statistically significant. MELD Score is calculated as MELD score = 9.6 loge (creatinine mg/dl) + 3.8 loge (bilirubin mg/dl) + 11.2 loge INR + 6.4 (cause of cirrhosis; 0 = cholestatic/alcohol, 1 = other) In a study done on 174 patients by **Serste et al** the patients were divided into two groups only serum sodium <130, and ≥131. It was observed that the mean value of MELD in the group with hyponatremia was 17.9 and in the group with serum Na+ ≥ 135 was having a mean MELD of 19.1, the statistical analysis proved this correlation to be non significant.

The group of **Andres e ruf** studied similar 194 patients but found that the group with low serum sodium levels to be having a higher mean

MELD Score of 21.1 and lower mean MELD score of 15.4 this data was statistically significant with p value of <0.001

In our present study we have taken 100 patients and found that the mean MELD Score was higher in patients in the groups of significant and mild hyponatremia and also lower mean MELD Value in patients with normal serum sodium.(p<0.001).

CONCLUSION

The present study proves that serum sodium level is of utmost importance in patients with liver disease. The numbers in this study only highlight the much discussed and described correlation between disease prognosis in patients of chronic liver disease and their level of serum sodium. Hyponatremia being dilutional in most or diuretic induced in treated patients and mixed picture in almost all patients just needs water restriction and judicious diuretic use for correction. Newer agents like vaptans have still not been proven safe and efficacious in liver disease. In the present study, statistically significant p values were obtained from the collected data indicating the correlation between serum sodium and the indices of severity of liver disease like CHILD-PUGH and MELD score. This also establishes the fact that serum sodium can be used as in additive/ alternative tool for categorization of patients needing better care, counselling of relatives and also options for liver transplant in such patients with normal to low normal serum sodium levels as a part of their treatment plan for the next 5 years in a step forward to reduced mortality and morbidity in cirrhosis.

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