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Study of Hyponatremia in Cirrhosis of Liver and It's Prognostic Value

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Abstract
Objective: *Study conducted to know the prevalence of hyponatremia in cirrhosis and to evaluate the association between hyponatremia and complications in cirrhosis and its prognostic value.*
Methods: *Patients were selected based on clinical examination, biochemical tests and ultrasound abdomen. All the patients were examined at the time of admission in the hospital and their serum sodium levels were checked and the patients were followed during their stay in the hospital. The severity of cirrhosis was assessed according to Child-Pugh score. MELD score and MELD-Na score were also calculated at the time of admission.*
Results: *Study done on 100 cirrhotic patients, most common etiology for cirrhosis in this study was alcohol. 53% had hyponatremia(<136meq/l). Complications of cirrhosis were more in hyponatremia patients. Among the complications portal hypertension (57%), hepatic encephalopathy(89.28%), hepatorenal syndrome (42.8%) among hyponatremia cirrhotic patients are statistically significant(p<0.05). child pughturcot score, MELD, MELD-Na score are also high in hyponatremia. Mortality also seen more in severe hyponatremia.*
Conclusion: *Dilutional hyponatremia is frequent in cirrhotic patients and associated with severe complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome. Hyponatremia is also associated with high morbidity and mortality in cirrhotic patients.*
Keywords: *Cirrhosis, Hyponatremia ,Child Pugh Turcot score, MELD,MELD-Na,*

Introduction

Hyponatremia is common in cirrhosis. It mostly occurs in an advanced stage of the disease and is associated with complications and increased mortality. Either hypovolemic or, more commonly, hypervolemic hyponatremia can be seen in cirrhosis. Impaired renal sodium handling due to renal hypoperfusion and increased arginine-vasopressin secretion secondary to reduced effective volemia due to peripheral arterial vasodilation represent the main mechanisms leading to dilutional hyponatremia in this setting[1]. Patients with cirrhosis usually develop slowly progressing hyponatremia. In different clinical contexts, it is associated with neurological manifestations due to increased brain water content, where the intensity is often magnified by concomitant hyperammonemia leading to hepatic encephalopathy. Severe hyponatremia requiring hypertonic saline infusion is rare in cirrhosis. The management of asymptomatic or mildly symptomatic hyponatremia mainly rely on the

identification and treatment of precipitating factors. However, sustained resolution of hyponatremia is often difficult to achieve. V2 receptor blockade by Vaptans is certainly effective, but their long-term safety, especially when associated to diuretics given to control ascites, has not been established as yet. As in other conditions, a rapid correction of long-standing hyponatremia can lead to irreversible brain damage. The liver transplant setting represents a condition at high risk for the occurrence of such complications[1]

Methods

Patients were selected based on clinical examination, biochemical tests and ultrasound abdomen. Informed consent was obtained from all patients enrolled for the study. The data of the patients like relevant clinical history, examination findings, laboratory investigations were recorded in a proforma sheet. All the patients enrolled in the study were examined at the time of admission in the hospital and their serum sodium levels were checked and the patients were followed during their stay in the hospital. The severity of cirrhosis was assessed according to Child-Pugh score. MELD score and MELD-Na score were also calculated at the time of admission.

Inclusion Criteria

All the patients with cirrhosis of liver.

Exclusion Criteria

Patients with cardiac failure

Patients with chronic kidney disease

Patients on diuretic therapy

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 Numbers (%). Significance is assessed at 5% level of significance. The following assumptions on data is made,

Assumptions: 1. Dependent variables must be normally distributed, 2. Samples drawn from population should be random, cases of the samples should be independent.

Chi-Square/Fishers Exact Test has been used to find the significance of study parameters on categorical scale between two or more groups.

Sample Size Estimation

Proportions Known populations

$n = [(z^2 * p * q) + ME^2] / [ME^2 + z^2 * p * q / N]$

Proportion Unknown populations

$n = [(z^2 * p * q) + ME^2] / (ME^2)$

ME is the margin of error, measure of precision.

And z is 1.96 as critical value at 95% CI.

N is the population size.

n : Sample Size

σ : Standard Deviation

z: Critical value based on Normal distribution at 95% Confidence Interval

Standard Deviation: SD= $\sqrt{\frac{\sum(x-\bar{x})^2}{n-1}}$

Fishers Exact Test

The Fishers exact test looks at contingency table which displays how different treatments have produced different outcomes. Its null hypothesis is that treatment do not affect outcomes – that the two are independent. Reject the null hypothesis (i.e, conclude treatments affect outcome) if p is "small".

The usual approach to contingency table is to apply the χ^2 statistic to each of the cell of the table. One should probably use the χ^2 approach, unless you have a special reason. The most common reason toavoid χ^2 is because you have small expectation values.

Fishers exact test (rxc tables) Let there exist two such variables X and Y with m and n observed states, respectively.

Now form an mXn matrix in which the entries a_{ij} represent the number of observations in which x=i and y=j. Calculate the row and column sums R_i and C_j, respectively and the total sum, of the matrix.

$$N = \sum_i R_i = \sum_j C_j$$

Chi-square goodness of fit test: The test statistics are mainly used to find out the association between different categorical variables of outcomes in patients with sodium ≤130,131-135,≥136 from inception of treatment.

The formula for Chi-square test was $\chi^2 = \frac{O_{ij} - E_{ij}}{E_{ij}}$

O_{ij} = Observed value for the ith row and j th column.

E_{ij} = Expected value for the ith row and j th column.

$\chi 2$ = Chi Sqaure

Expected Value = $\frac{Row\ x\ Column}{N}$

Positive predictive Value (PPV) = $\frac{a}{a+b}\ x\ 100$

Negative Predictive Value(NPV) = $\frac{d}{c+d}$

Specificity(%) = $\frac{d}{b+d} x\ 100$

Sensitivity(%) = $\frac{a}{a+c} x100$

Standard Deviation(SD) : $\sqrt{\frac{\sum_{i=1}^{100} (x-\overline{x})^2}{N}}$

x= Observed value for the patients age.

$\overline{x}$ = Mean age of the patients.

N = total no. of observations.(100)

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

*Moderately Significant(P value :0.01<P≤0.05)

**Strongly significant (P value: P ≤0.01)

Statistical Software: The statistical softwares namely SocSci statistics.com, SPSS 15.0, Med Calc 9.0.1, were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

This study is conducted in 100 cirrhotic patients out of which 90 (90%) are males and 10(10%) are females. The mean age of the patients was 46.10 ± 10.55 years. Causative factors for liver cirrhosis included alcoholism in 90% of patients, hepatitis B in 9% of patients and hepatitis C in 6% of the patients. Alcohol was the most common etiology in present study, seen in 90% patients. Patients were classified according to serum sodium level, 25(25%) belong to serum sodium level ≤130meq/L, 28(28%) belong to serum sodium level 131-135meq/L and 47(47%) belong to serum sodium levels ≥136 meq/L.

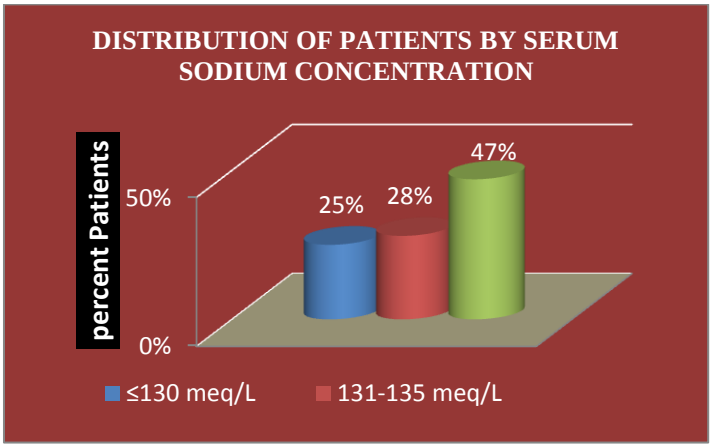

Figure:1

The mean MELD score of patients with serum sodium concentration ≤ 130 meq/L was 21.4±8.35.It was 16.32±6.68 in group with serum sodium levels between 131-135 meq/L.It was 13.28±5.84 in the group with serum sodium concentration ≤ 130 meq/L. There was significant difference with respect to MELD score in these three groups (p value = <0.0001).

Table: 1 Comparison of the mean meld score of the three groups

SR. NO.	COMPLICATIONS	≤130 meq/L n=25	131-135meq/L n=28	≥136meq/L n=47	Pvalue
1	**MELD Score** (Mean±SD)	21.4±8.35	16.32±6.68	13.28±5.84	<0.0001

Using ANOVA test p <0.05 statistically significant

The mean Child-Pugh score in the group with serum sodium levels ≤ 130 meq/L was 11.6±2.The mean score in the group with serum sodium levels between 131-135 meq/l was 10.3±1.85.The mean score in patients with serum sodium levels ≥ 136 meq/L was 9.4±1.53. There was significant difference in these three groups with respect to Child-Pugh score (p value = < 0.0001)

Low serum sodium had significantly high child-pugh class compared to normal serum sodium. Among 25 patients with serum sodium ≤ 130 meq/L, 20 patients were in Child-Pugh class C and 5 patients were in Child-Pugh class B. Among 28 patients with serum sodium levels between 131-135 meq/L, 18 patients were in class C and 10 patients were in class B.

There is significant statistical difference in these three groups with respect to Child-Pugh class (p value = 0.005)

Table: 2 Comparison of mean Child-Pugh score and Child-Pugh class

SR. NO	COMPLICATIONS	≤130 meq/L n=25	131 - 135meq/L n=28	≥136meq/L n=47	Pvalue
1	**Child-Pugh score**	11.6±2	10.3±1.85	9.4±1.53	<0.0001

SR.NO.	Child-Pugh class	≤130 meq/L n=25	131 - 135meq/L n=28	≥136meq/L n=47	Pvalue
1	**ClassA** **Class B** **Class C**	0 5 20	0 10 18	1 27 19	0.0058

Out of 100 patients of cirrhosis, 100 patients (100%) had ascites, 89 patients (89%) had portal hypertension, 30 patients (30%) had hepatic encephalopathy, 18 patients(18%) had gastrointestinal bleeding, 3 patients (3%) had coagulopathy, 14 patients(14%) had Hepatorenal syndrome. In the present study, ascites is present in all 25 patients with serum sodium levels <130 meq/L, in all 28 patients with serum sodium levels between 131-135 meq/L and it is present in all 47 patients with serum sodium levels>136 meq/L. There is no statistical significant difference in these three groups with respect to ascites.

Portal hypertension is present in all 25 patients with serum sodium level< 130 meq/L (100%). 26 out of 28 patients (93%) with serum sodium levels between 131-135 had portal hypertension. 38 out of 47 patients (81%) with serum sodium levels >136meq/L had portal hypertension. There was significant statistical difference in these three groups with respect to portal hypertension (p value 0.0412)

Hepatic encephalopathy was present in 15 patients out of 25 (60%) with serum sodium levels <130 meq/L, 11 out of 28 patients (39%) in patients with serum sodium level between 131-135 meq/L and in 4 out of 47 (9%) patients with serum sodium levels >136 meq/L. There is significant statistical difference in these groups with respect to hepatic encephalopathy (p value 0.00001).

Gastrointestinal bleeding is present in 8 out of 25 patients with serum sodium levels <130 meq/L, in 2 out of 28 patients with serum sodium levels between 131-135 meq/L and in 8 patients out of 47 patients with serum sodium levels >136 meq/L. There is no significant statistical significance in these three groups with respect to gastrointestinal bleeding (p value = 0.057)

Coagulopathy is present in 2 out of 25 patients with serum sodium levels <130 meq/L, in 1 out of 47 patients with serum sodium levels >136 meq/L. There is no significant significance in these three groups with respect to coagulopathy (p value = 0.6301)

Hepatorenal syndrome is present in 7 out of 25 patients in patients with serumsodium <130 meq/L, 4 out of 28 patients with serum sodium levels between 131-135 meq/L and in 3 out of 47 patients with serum sodium levels>136 meq/L. There is statistical significance in these three groups with respect to hepatorenal syndrome (p value = 0.038)

Table: 3 Frequency of complications by serum sodium concentration

Sr. No.	COMPLICATIONS	≤130meq/L n=25	131 - 135meq/L n=28	≥136meq/L n=47	Pvalue@
1	Ascites	25(100%)	28(100%)	47(100%)	0.93
2	Portal Hypertension	25(100%)	26(93%)	38(81%)	0.0412
3	**Hepatic encephalopahy**	15(60%)	11(39%)	4(9%)	**0.00001**
4	**GI Bleeding**	8(32%)	2(7%)	8(17%)	**0.05755**
5	Coagulopathy	2(8%)	0(0%)	1(2%)	0.63011
6	**HRS**	7(28%)	4(14%)	3(6%)	**0.038**

In the group of serum sodium levels ≤ 130 meq/L, 5 (20%) patients died, while 3(11%) patients died in group of serum sodium levels 131-135 meq/L. No patient died in group of serum sodium levels ≥ 136 meq/L. Hence statistically significant difference was found in mortality among these three groups .

Table: 4 Mortality according to serum sodium concentration

	≤130 meq/L n=25	131-135 meq/L n=28	≥136meq/L n=47	Pvalue @
Mortality	5(20%)	3(11%)	0	0.03

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

Discussion

Hyponatremia is frequent in cirrhosis of liver. This is thought to be due to a higher rate of renal retention of water in relation to sodium due to a reduction in solute free water clearance.

In the present study, which is conducted among 100 patients with cirrhosis of liver, hyponatremia is present in more than half (53%) of patients with cirrhosis i.e serum sodium less than 135meq/L. 28% patients have serum sodium levels less than 130meq/L. Angeli P et al[2] conducted a trial on 997 patients with liver cirrhosis. prevalence of hyponatremia at serum sodium <135meq/L was 49.4% and, ≤130meq/L it is 21.6% respectively in their study. Borroni G et al[3] conducted a study on 156 patients with cirrhosis of liver. In that study, the prevalence of hyponatremia, was 29.8% if serum sodium concentration is < 130 meq/L.

According to other studies like Kim JH et al[4], BorroniS et al[3], Shaikh S et al[5], similar results seen, that there is no association between etiology of cirrhosis and serum sodium levels was proved. In the present study, there was significant difference in these groups with respect to child-pugh (p value = 0.0001). In patients with hyponatremia, the mean child-pugh score was higher as compared to the mean child-pugh score in group with normal serum sodium levels, among 25 patients with serum sodium levels ≤ 130 meq/L, 20 patients were in child-pugh class C and 5 patients were in class B, among 28 patients with serum sodium levels between 131-135 meq/L, 18 patients were in class C and 10 patients were in class B. According to Angeli P et al[2], 55% of patients with low serum sodium levels belong to child pugh class C.

In Shaikh S et al[5], low serum sodium levels were more frequent in patients with severe liver failure (child-pugh class C). This indicate that as hyponatremia became more severe, severity of liver disease is also more.

In present study, in patients with hyponatremia there is no difference among the three groups with respect to ascites. But in patients with serum sodium ≤130 meq/L, there is increased incidence of gross ascites requiring paracentesis. In Angeli P et al[2] study also, low serum sodium level was associated with higher prevalence of refractory ascites, greater fluid accumulation, greater likelihood of undergoing paracentesis .According to Shaikh et al, the patients with serum sodium level <130 meq/L have a higher frequency of refractory ascites

According to Angeli P et al, hepatic encephalopathy was present in 38% of the patients with serum <130meq/L and is present in 24% of patients with serum sodium between 131 and 135 meq/L and 15% of patients with serum sodium >135meq/LIn the present study, 60% of patients with serum sodium levels <130 meq/L had hepatic encephalopathy compared to 39.2% of patients with serum sodium concentration between 131 to 135meq/L had hepatic encephalopathy. In patients with serum sodium levels >136 meq/L, 8.5% of patients had hepatic encephalopathy. Hence there is significant association between hepatic encephalopathy and hyponatremia (p value = 0.00001), the results of this study were similar to the above mentioned other studies.

In the present study, Hepatorenal syndrome is present in 28% (i.e 7/25) of patients with serum sodium levels <130meq/L compared to 14.28%(i.e 4/28) in patients with serum sodium 131 to 135meq/L. Hepatorenal syndrome is present in 6.38% (i.e 3/47)of patients with serum sodium levels >135meq/L. There is significant statistical difference in frequency of hepatorenal syndrome in the three groups. There is significant association between hepatorenal syndrome and hyponatremia (p value =0.038). According to Kim JH et al[4], Hepatorenal syndrome is present in 17% of patients serum sodium <130meq/L compared with 10% in patients with serum sodium 130-135meq/L. According to Angeli P et al[2], hepatorenal syndrome is present in 17.6% of patients with serum sodium

<130 meq/L compared to 10% in patients with serum sodium 130-135meq/L. hyponatremia is a major risk factor for the development of hepatorenal syndrome in patients with ascites. The increased risk of hepatorenal syndrome may be related to a more severe circulatory dysfunction of patients with hyponatremia.

In the present study, mortality is more in patients with low serum sodium (≤ 135 meq/L) compared to those with normal sodium concentration. 8 patients died in group with low serum sodium concentration and no death in patients with normal serum sodium. All these deaths occurred in patients with higher MELD scores. Mean MELD score in the present study in expired group was 23 ± 7.76. The mean MELD-Na score in the expired group was 27.37 ± 6.02 .The mean MELD and MELD-Na scores in the survived group patients were 15.56 ± 7.18 and 18.75 ± 7.313 respectively. Sodium is incorporated in MELD.MELD-Na score is proposed by severeral studies to be superior to MELD score in predicting mortality in patients awaiting liver transplantation. According to Moini M et al[6], serum sodium <130 meq/L and an increased MELD score are significant predictors of early mortality in patients listed for liver transplantation.

Low serum sodium is a negative prognostic indicator in patients with cirrhosis of liver. Borroni G et al[3], in an inpatient study showed that hyponatremia is a negative prognostic indicator for short term in hospital mortality. In Heuman DM et al[7] study suggests MELD score, persistent ascites, low serum sodium (<135 meq/L) were independent predictors of early mortality.

Conclusion

Dilutional hyponatremia is frequent in cirrhotic patients and low serum sodium levels are associated with severe complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome.

Hyponatremia is also associated with high morbidity and mortality in cirrhotic patients. Hence hyponatremia is a valuable marker that can be used to assess the prognosis in patients with cirrhosis of liver. Incorporation of sodium levels in MELD score is much more useful than MELD score alone to assess the prognosis and to refer the patient for liver transplantation.

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