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Can Hyponatremia Play a Role in Morbidity and Mortality in Chronic Hepatic Patients in ICU at Aswan University?

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ABSTRACT

Backgound: Hyponatremia is a frequent complication of advanced chronic liver diseases related to an impairment in the renal capacity to eliminate solute-free water that causes a retention of water that is disproportionate to the retention of sodium, thus causing a reduction in serum sodium concentration and hypoosmolality.

Objective: The aim of this study is to evaluate the role of hyponatremia on morbidity and mortality in chronic liver diseased patient in ICU unit at Aswan University Hospital. **Matients and methods:** This study included 90 patients who were suffering of hyponatremia with chronic liver disease and selected from patients in Aswan University Hospital. The patients were 61 males (67.78%) and 29 females (32.22%). **Results:** About (40%) of patients were discharged and (60%) of patients died. ***First group***: patients with mild hyponatremia about (67.71%) were discharged and about (35.29%) died. ***Second group:*** patients with moderate hyponatremia about (65.7%) were discharged and about (34.21%) died. ***Third group:*** all patients with severe hyponatremia (100 %) died.

Conclusion: hyponatremia play important role in mortality rate of patients with chronic liver disease.

Keywords: Hyponatremia, Morbidity and Mortality, Chronic Hepatic diseases, ICU.

INTRODUCTION

Chronic liver diseases (CLD) and its complications are the major health problem, due to big burden of hepatitis C virus and hepatitis B virus in the community. It is very common reason of admission to hospitals [(1)]. In the decompensation condition, cases having CLD are generally presented with ascites, jaundice, portal hypertension, gastrointestinal hemorrhage, spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy [(2)]. About 30% of patients with CLD usually die due to portosystemic encephalopathy [(3)].

The clinical course of patients with CLD is frequently complicated due to increase in the renal function abnormalities and imbalance of electrolytes [(4)]. The body disturbance of the water is the main sign of advance cirrhosis [(5)], this phenomenon of disturbance of water is linked to the existence of ascites and is characterized by the development of dilutional hyponatremia, which is a frequent complication and sequel of chronic liver disease [(4)]. One study indicated that hyponatremia is a key prognostic factor in patients with CLD [(6)]. The prevalence of hyponatremia [serum Na < 130 mEq/L] in patients with cirrhosis with ascites is approximately 30% [(7)].

The relationship between hyponatremia and severity of cirrhosis is associated with the development of complications. Hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis (SBP) are more presented in cases having serum concentration < 130 mEq [(6)].

Furthermore in cases having ascites, those having hyponatremia have a lower diuretics response, higher frequency of refractory ascites, and frequent requirement of the therapeutic paracentesis [(8)]. A study from Pakistan demonstrated that 51.6% of CLD cases had serum sodium concentration below the normal level [(4)]. **Bernardi *et al.*** [(8)] reported that hyponatremia was in 30% of CLD cases and hyponatremia can induce or aggravate hepatic encephalopathy, leading to disease progression like seizures, coma and even brain death.

AIM OF THE WORK

The aim of this study is to evaluate the role of hyponatremia on morbidity and mortality in chronic liver diseased patient in ICU unit at Aswan University Hospital.

PATIENTS AND METHODS

This study included 90 patients who were suffering of hyponatremia with chronic liver disease and selected from patients in Aswan University Hospital.

Inclusion criteria:

1. Both genders were included.
2. Chronic liver disease of any etiology presented by hepatic encephalopathy, hematemesis, melena, refractory ascites and SBP.

Exclusion criteria:

1. Patients with hepatocellular carcinoma.
2. Heart failure.
3. Chronic kidney disease (CKD).

Procedure:

The patients were 61 male (67.78%) and 29 female (32.22%).

The study is a cohort study and was conducted at Aswan University Hospital (ICU unit). The study was hospital-based clinical study on chronic liver

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disease patients diagnosed by clinical assessment and investigations (laboratory and imaging). Patients were presented by hepatic encephalopathy, hematemesis, melena, refractory ascites and SBP associated with hyponatremia and were admitted to ICU at Aswan University Hospital.

Methods:

All patients were subjected to the following:

1. Full history.
2. Full examination.
3. Routine investigations (laboratory and imaging) for diagnosis of chronic liver disease (abdominal ultrasound, viral markers, liver function test, prothrombin time and concentration,…etc.)
4. Serum sodium.

   The severity of decreased sodium concentration was assessed as normal serum sodium [Na+] level is 135-145 mEq/L and the value < 135 was labeled as low or hyponatremia. The severity of hyponatremia was categorized as: 130–135 mEq/L (mild), 125–130 mEq/L (moderate) and < 125 mEq/L (severe).
5. All patients presented by hyponatremia and chronic liver disease were divided to three groups according to the degree of hyponatremia.

- ***First group***: patients with mild hyponatremia about (32.6%).
- ***Second group:*** patients with moderate hyponatremia about (29.2%).
- ***Third group:*** patients with severe hyponatremia about (38.2%).

All the patients in ICU received medical treatment and were followed up for serum sodium up to discharge.

Ethical considerations:

An approval of the study was obtained from Aswan University academic and ethical committee.

Every patient signed an informed written consent for acceptance of the operation.

Confidentiality:

The confidentiality of all participants admitted to this study was protected to the fullest extent possible. The study participants were not identified by name in any report or publication resulting from data collected in this study.

Research statement:

Before participants were admitted in this study, the purpose and nature of the study as well as the risks were explained to them. The participants agreed that they understand the investigational nature of the study, its inherent risks and benefits, their rights to terminate participation in this study without affecting their rights in having proper health care in the study site, whom to contact with questions regarding the study and that they were freely given an informed consent to participate in this study.

Statistical Analysis

The collected data were revised, coded, tabulated and introduced to a PC using statistical package for social science **(SPSS, 25).** Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

i. Descriptive statistics:

1. Mean and Standard deviation (± SD) for parametric numerical data, while median and interquartile range (IQR) for non-parametric numerical data.

2. Frequency and percentage of non-numerical data.

ii. Analytical statistics:

1. ***ANOVA test*** was used to assess the statistical significance of the difference between more than two study groups' means.
2. ***The Kruskal-Wallis*** test is was used to assess the statistical significance of the difference between more than two study groups' ordinal variables.
3. ***Post-hoc test*** is used for comparisons of all possible pairs of group means
4. ***Chi-Square test*** was used to examine the relationship between two qualitative variables
5. ***Fisher's exact test*** was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.

P- value: level of significance

- P>0.05: Non significant (NS).
- P< 0.05: Significant (S).
- P<0.01: Highly significant (HS).

RESULTS

Table (1): Personal data for whole group.

		Mean / N	SD / %	Median (IQR)
Gender	Male	61	67.78%	
	Female	29	32.22%	
	Age	63.06	9.67	63 (56 – 70)
Age (Years)	30-60	36	40.0%	
	>60	54	60.0%	

- This table shows the age and gender of the patients.

Table (2): Outcome of hyponatremia at admission and discharge.

	Outcome		P-Value
	Discharged N=36	Died N=54	
	Mean ± SD	Mean ± SD	
Na^+ at admission	128.53 ± 1.93	122.28 ±5.27	<0.001
Na^+ at discharge	130.43 ± 2.05	121.8 ± 5.54	<0.001
Hemoglobin	9.6 ± 1.93	9.25 ± 1.96	0.406
Platelet count	117.08 ± 54.36	96.41 ± 35.85	0.032
Prothrombin concentration %	61.06 ± 8.89	50.17 ± 9.65	<0.001

This table shows that: Sodium at admission also at discharge play significant role on mortality rate.

Table (3): Personal data between groups of severity of hyponatremia.

		Hyponatremia grade at admission			P-Value
		Mild N=17	Moderate N= 38	Severe N=35	
		N (%)	N (%)	N (%)	
Gender	Male	15 (88.24%)	31 (81.58%)	15 (42.86%)	<0.001
	Female	2 (11.76%)	7 (18.42%)	20 (57.14%)	
Age	30-60	5 (29.41%)	21 (55.26%)	10 (28.57%)	0.041
	>60	12 (70.59%)	17 (44.74%)	25 (71.43%)	

This table shows that: Age and gender play significant role with grade of hyponatremia.

Table (4): Comparing of past history and chronic diseases among the groups of severity of hyponatremia.

		Hyponatremia grade at admission			P-Value
		Mild N=17	Moderate N= 38	Severe N=35	
		N (%)	N (%)	N (%)	
DM		9 (52.94%)	17 (44.74%)	20 (57.14%)	0.563
HTN		6 (35.29%)	12 (31.58%)	17 (48.57%)	0.312
IHD		0 (0%)	0 (0%)	2 (5.71%)	0.331
COPD		5 (29.41%)	6 (15.79%)	1 (2.86%)	0.019
Renal dis.		0 (0%)	2 (5.26%)	0 (0%)	0.668
Asthma		0 (0%)	3 (7.89%)	5 (14.29%)	0.266
CLD		17 (100%)	38 (100%)	35 (100%)	
Viral hepatitis	No	2 (11.76%)	2 (5.26%)	10 (28.57%)	0.001
	HBV	0 (0%)	8 (21.05%)	11 (31.43%)	
	HCV	15 (88.24%)	28 (73.68%)	14 (40%)	
Peptic ulcer		1 (5.88%)	3 (7.89%)	6 (17.14%)	0.452
Bilharziasis		0 (0%)	1 (2.63%)	1 (2.86%)	1.00
Drugs		0 (0%)	0 (0%)	0 (0%)	
Upper endoscopy		10 (58.82%)	19 (50%)	18 (51.43%)	0.827

This table shows that: Viral hepatitis played a significant role on severity of hyponatremia and also the patients who had COPD.

Table (5): Comparison of vital signs among groups according to the severity of hyponatremia

		Hyponatremia grade at admission			P-Value
		Mild N=17	Moderate N= 38	Severe N=35	
		Mean ± SD N (%)	Mean ± SD N (%)	Mean ± SD N (%)	
Systolic blood pressure		105.29 ± 15.05	100.79 ± 0.05	93.43 ±19.39	0.079
Diastolic blood pressure		67.06 ± 10.47	60.53 ± 11.84	57.14 ±11.78	0.018 **(A1)**
Hemodynamically	Unstable	0 (0%)	12 (31.58%)	11 (31.43%)	0.027
	Stable	17 (100%)	26 (68.42%)	24 (68.57%)	
Temperature		37.6 ± 0.61	37.65 ± 0.72	37.28 ± 0.54	0.039 **(A2)**
Pulse		71.47 ± 12.72	81.32 ± 16.59	84.29 ± 9.29	0.043 **(A1)**
Respiratory rate		20.94 ± 3.68	21.87 ± 2.64	20.57 ± 2.69	0.152

(A1) Significant difference: Mild group **Vs** Severe group.
(A2) Significant difference: Moderate group **Vs** Severe group.
This table shows that: Good vital signs and hemodynamically stability played significant role.

Table (6): Comparison of Lab investigations among groups according to the severity of hyponatremia

		Hyponatremia grade at admission			P-Value
		Mild N=17	Moderate N= 38	Severe N=35	
		N (%) Mean ± SD Median (IQR)	N (%) Mean ± SD Median (IQR)	N (%) Mean ± SD Median (IQR)	
Hb grade	<5	0 (0%)	1 (2.63%)	1 (2.86%)	1.00
	5 - 8	4 (23.53%)	9 (23.68%)	9 (25.71%)	
	>8	13 (76.47%)	28 (73.68%)	25 (71.43%)	
MCV		85.24 ± 14.06	79.46 ± 6.55	82.9 ± 7.61	0.06
HCT		30.41 ± 5.3	28.45 ± 5.62	28.52 ± 4.25	0.371
WBCs		10 (5 - 13.1)	11 (7.5 - 13)	12 (10 - 14.5)	0.037**(K1)**
PLT grades	<50	2 (11.76%)	4 (10.53%)	0 (0%)	0.029
	50 - 100	7 (41.18%)	12 (31.58%)	22 (62.86%)	
	>100	8 (47.06%)	22 (57.89%)	13 (37.14%)	
PT		15.05 ± 3.4	16.16 ± 3.17	17.4 ± 3.02	0.037**(A1)**
PC % grade	<40%	0 (0%)	2 (5.26%)	2 (5.71%)	0.734
	40% - 70%	17 (100%)	33 (86.84%)	32 (91.43%)	
	>70%	0 (0%)	3 (7.89%)	1 (2.86%)	
INR		1.76 ± 0.22	1.82 ± 0.76	2.09 ± 0.79	0.168
AST		36 (35 - 64)	55 (38 - 83)	55 (39 - 75)	0.301
ALT		40 (26 - 52)	34 (26 - 40)	33 (25 - 40)	0.523
Total Bilirubin		3 (1.5 - 12)	2 (1.2 - 4.6)	1.5 (1.2 - 5)	0.566
Indirect bilirubin		1.5 (0.4 - 5)	1 (0.5 - 2)	0.5 (0.3 - 1.7)	0.038**(K1)**
Alb.		2.35 ± 0.5	2.43 ± 0.66	2.32 ± 0.57	0.73
Alb. Grade	<2.5	6 (35.29%)	16 (43.24%)	20 (60.61%)	0.166
	2.5 - 3	11 (64.71%)	17 (45.95%)	10 (30.3%)	
	>3	0 (0%)	4 (10.81%)	3 (9.09%)	
Na. at admission		130.53 ± 1.01	127.26 ± 1.35	119.29 ± 3.88	<0.001**(A2)**
Na. at discharge		128.94 ± 6.14	128.32 ± 3.51	120.09 ± 4.93	<0.001**(A3)**
Hyponatremia grade at discharge	Mild	12 (75%)	16 (42.11%)	1 (2.86%)	<0.001
	Moderate	2 (12.5%)	19 (50%)	5 (14.29%)	
	Severe	2 (12.5%)	3 (7.89%)	29 (82.86%)	

(K1) By using Kruskal-Wallis test; the difference is significant: Mild group **Vs.** Severe group.
(A1) Significant difference: Mild group **Vs.** Severe group. **(A2)** Significant difference among all groups.
(A3) Significant difference: Severe group Vs. (Mild and moderate groups)

Table (6) shows that:

- Investigations as (WBCs, PLT, indirect bilirubin, sodium level at admission or discharge and grade of hyponatremia at discharge) had significant role on outcome of studied sample.

Table (7): Outcome between groups of severity of hyponatremia.

		Hyponatremia grade at admission			P-Value
		Mild N=17	Moderate N= 38	Severe N=35	
		N (%)	N (%)	N (%)	
Outcome	Discharge	11 (64.71%)	25 (65.79%)	0 (0%)	<0.001
	Died	6 (35.29%)	13 (34.21%)	35 (100%)	

This table shows that: All patients with severe hyponatremia at admission have died (100%). The majority of patients with moderate or mild hyponatremia were discharged.

DISCUSSION

This study was done to assess the association of the severity of hepatic tissue damage and the serum electrolytes profiles. Study total number of cases was 90. Mean age was 63 ± 9 years. 61 (67.8%) patients were males while 29 (32.2%) patients were females.

Similarly **Qureshi *et al.*** [4] reported that out of 202 patients, 90 (44.6%) were males and 112 (55.4%) were females. Eighty-one (40.1%) patients were of the age greater than 60 years.

The most common complication of chronic liver disease was hepatic encephalopathy in 23 cases (25.6 %) then upper GIT bleeding 18 cases (20 %) while hepatic encephalopathy (HE) with upper GIT bleeding was in 10 cases (11.1 %) and hepatic encephalopathy with jaundice was in 13 cases (14.4 %). Similarly, HE was more frequent in hyponatremic patients and the more severe the hyponatremia the greater was the grade of HE as reported in the study by **Shaikh *et al.*** [6]**.** Moreover, the other complications of liver cirrhosis (e.g. ascites) were also found with increased frequency as the severity of hyponatremia increased.

These results showed that severe hyponatremia is associated with increased severity of HE, which is in agreement with previous studies [9, 10]**.**

In our study we considered chronic hyponatremia in those who had serum sodium level >130 mEq/L and taking this level as cut-off point we found about (17.7%) patient with cirrhosis had hyponatremia. The number of cases presented by hyponatremia less than 125 was 35 case about (38.8%) of all cases of this study.

The percentage of hyponatremia sought in this study more or less conforms to study done by **Gines *et al.*** [5]**.** The percent of people with cirrhosis affected by chronic hyponatremia increases to 50 percent if a cutoff for serum sodium concentration of 135 mEq/L, the lower limit of normal, is used [5]**.** The frequency of such profound hyponatremia as seen at presentation in the patient greater than in this case (serum sodium concentration of 105 mEq/L) is unclear; a population survey reported that the prevalence of patients with cirrhosis and serum sodium concentrations less than or equal to 120 mEq/L is 1.2 percent [11]**.**

Association between HE and serum sodium levels may be described as; severe liver failure in cases with level of serum sodium< 130 meq/l, and these both events may be pathophysiologically associated [12]**.** Decreased sodium level in cases having CLD, is associated with remarkable reduction of organic osmolytes in the cerebral concentration that probably reflects compensatory osmoregulatory mechanisms against cell.

Swelling **Restuccia *et al.*** [13] **and Ha¨ussinger *et al.*** [14] the greater frequency of hyponatremia was seen in patients having hepatic encephalopathy.

The most common reason for chronic hyponatremia in cirrhosis is impairment in renal solute-free water secretion due to increased antidiuretic hormone secretion and decreased effective arterial volume [15]**.** The brain is able to compensate for the increased osmolar pressure (which leads to cerebral edema) in chronic hyponatremia by extruding intracellular osmolytes, such as potassium, glutamine and myoinositol, which can take 48 hours for full effect [16]. This adaptive mechanism explains why patients with chronic hyponatremia and serum sodium concentrations above 120 mEq/L are often asymptomatic. In patients with cirrhosis, it is important to recognize the symptoms of hyponatremia, identify and treat any exacerbating conditions early in their course, and correct the serum sodium concentration slowly with frequent monitoring. **Kim *et al.*** [15] sought that the serum sodium level was strongly associated with the severity of liver function impairment as assessed by Child-Pugh and MELD score (p<0.0001).

Similarly several studies all over the world found that the cirrhosis of the liver frequently leads to

a state of chronic hypervolemic hyponatremia. The cause of the hyponatremia is related to a decrease in systemic vascular resistance, which is more prominent in the splanchnic circulation, and compensatory neurohormonal mechanisms that are activated due to the hemodynamic changes. Hyponatremia in cirrhosis can be a severe problem and has been shown to be an independent predictor of mortality in patients waiting for liver transplantation.

In other studies, the severity of hyponatremia, particularly at sodium level ≤ 130 mmol/L, corresponded to increase the risks of ascites, hepatic encephalopathy and other complications of cirrhosis, as compared to those with the serum sodium level ≤ 136 mmol/L [7,10].

In this study all patients had hyponatremia with hepatic encephalopathy incidence (25.6 %) while in a study of Egyptian hospitalized patients with liver cirrhosis by **Khalil *et al.*** [17], the prevalence of hyponatremia of <130 mEq/L was 45.5%. In a local study from Islamabad, hyponatremia was found in 30.7% patients [18], whereas from Hyderabad Sind, its frequency was found to be 26.7% [6], and in an Italian study, prevalence of hyponatremia was 29.8% [19].

In this study the outcome of cirrhotic patients with hyponatremia had increased in-hospital deaths and poor survival with high mortality rate. Number of died cases was 54 (60%) with highly significant p-value (<0.001). Cases died with hepatic encephalopathy were 14 (25.93 %) similarly as in Taiwan cirrhotic patients with hyponatremia were found to have increased in-hospital deaths and poor survival at 6-months [20].

In this study the most chronic disease associated with chronic liver disease was diabetes mellitus in 46 case (51.1%), then hypertension in 35 case (38.9%).

Also most of cases had positive hepatitis C virus; 57 case (63.3%) of cases. On the other hand hepatitis B virus was positive in 19 cases (21.1%). Cases with negative serology were 14 cases (15.6%). Cases presented by alcoholic cirrhosis in another study were hepatitis B virus (68%), and hepatitis C (19%) virus. The study done by **Levesque *et al*.** [16] showed the frequency of alcoholic cirrhosis was 68% while HBV and HCV were the cause of cirrhosis in 4% and 14% of patients [2]. This picture might reflect high consumption of alcohol in western life than in Egypt. Hyponatremia was present more in patient with positive serology than negative serology with highly significant p-value (0.001)

47 (52.2%) cases had previous upper endoscopy; most of them had moderate to severe hyponatremia with no significant difference.

In this study there is strong relation between ascites and hyponatremia with highly significant value p-value (0.006).

In this study cirrhotic patients with hyponatremia have mortality rate more than patient with normal sodium level and as hyponatremia increases the rate of death also increases, which mean that hyponatremia affect mortality rate in cirrhotic patient admitted in ICU at Aswan University Hospital. In cases with mild hyponatremia; 11 cases were discharged (64.71%) and 6 cases died (35.29%). In cases with moderate hyponatremia; 25 cases were discharged (65.79%) and 13 cases died (34.21%). All the 35 cases with severe hyponatremia died (100%).

CONCLUSION

Hyponatremia was a common feature in patients with cirrhosis and its severity increased with the severity of liver disease. The existence of serum sodium concentration < 135 mEq/L was associated with greater frequency of hepatic encephalopathy, infection, ascites and renal impairment. It was also noticed that the more severe the hyponatremia, the greater is the grade of hepatic encephalopathy or other complications. Close monitoring of serum sodium concentration should be performed in patients with cirrhosis in order to prevent the rapid development of cirrhosis-related complications.

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