PREVELANC OF HYPONATREMIA AND ITS ASSOCIATION WITH DEVELOPMENT AND SEVERITY OF COMPLICATIONS IN CIRRHOTIC PATIENTS

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ABSTRACT

Hyponatremia is common in advanced liver cirrhosis. Recently it has attracted an interest as a possible prognostic factor for liver cirrhosis complications. This study was conducted to assess the prevalence of hyponatremia in complicated cirrhotic patients admitted to medical ICU and to identify its relationship to development and severity of these complications. 200 patients with liver cirrhosis were included in this study. According to serum sodium, they were classified into three groups: group 1 with serum sodium ≤130 meq/L (severe hyponatremia), group 2 with serum sodium from 131 to 135 meq/L (mild hyponatremia) and group 3 with serum sodium ≥136 meq/L (normo-natremia). Demographic, clinical, and laboratory variables were prospectively recorded for analysis.

In our study The prevalence of total hyponatremia was 131/200 patients (65.5%) and those with severe hyponatremia were 91/200 (45.5%) .There was a statistically significant increase in frequency of occurance ($p<0.01$) and relative risk each of ascites (1.3fold),intractable ascites (9.5fold), spontaneous bacterial peritonitis (2.6fold), hepatic hydrothorax (1.5fold) and hepatic encephalopathy (2.8fold), in hyponatremic groups compared to normonatremic one while there was no significant difference regarding hepatorenal syndrome, esophageal varices and variceal bleeding between different groups. Also there was a statistically significant negative correlation betwee serum sodium level and the two scoring systems: Child-Pugh score ($r =-0.690$, $p<0.001$) and Model for End – stage Liver Disease (MELD) score($r =-0.586$, $p<0.001$).

We can conclude that In critically ill patients with liver cirrhosis, the prevalence of total hyponatremia(Na ≤ 135 meq/L) was 65.5% while those with severe hyponatremia (Na ≤130) was 45.5%. Low serum sodium level was associated with high complications of liver cirrhosis. The relative risk of occurance, frequencies and severity of ascitis, intractable ascitis, hepatic hydrothorax, hepatic encephalopathy and spontineous bacterial peritonitis were increased in cirrhotic patients especially those with serum sodium levels ≤ 130 meq/L.So the Management of hyponatremia may decrease the incidence and severity of the liver cirrhosis complications with better quality of their life. Thus more interest should be tried towards the use of vasopressin receptor antagonists as a line of treatment of complicated cirrhotic patients with hyponatremia without salt overload

INTRODUCTION

Hyponatremia is defined as a decrease in the serum sodium concentration (Na^+) to < 136 (normal range136–148) meq/L. This disorder is commonly observed, occurring in up to 6% of hospitalized patients[1] **.**

Hyponatremia a frequent complication of advanced cirrhosis, is 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 hypo-osmolality**[2] .**Several mechanisms participate in the impairment of solute-free water excretion in cirrhosis and subsequent development of hyponatremia, including reduced filterate delivery to distal nephron, impaired renal prostaglandin synthesis and hypersecretion of arginine vasopressin. Of these, reduced effective circulating volume owing to arterial splanchnic vasodilatation is considered the most important afferent factor in baroreceptor-mediated nonosmotic stimulation of vasopressin release from the neurohypophysis in cirrhosis **[2].**

A large proportion of patients with cirrhosis has abnormal values of serum sodium concentration. Some studies were done to incorporate serum sodium level in the scoring systems which evaluate the prognosis and risk of mortality of cirrhotic patients, for example, MELD (The Model for End-Stage Liver Disease) which was initially created to predict survival following elective placement of TIPS (transjugular intrahepatic portosystemic shunt) **[3],** then widely applied in recent years and shown to predict mortality across a broad spectrum of liver diseases in most studies, ***Londono*** has been subjected to the incorporation of serum sodium level giving rise to new three models which have enhanced the prognostic accuracy of MELD score**[4].** These new models are MELD-Na (the MELD with the incorporation of serum sodium), iMELD (the integrated MELD), and MESO index (the MELD to sodium index) **[5].** So, low serum sodium concentration is an independent predictor of mortality in patients with cirrhosis, but its prevalence and clinical significance is unclear **[6].**

To date, no studies have been conducted to assess the prevalence of hyponatremia in Egyptian hospitalized patients with liver cirrhosis. In fact, few studies have evaluated the association between serum sodium levels and the occurrence and severity of complications due to liver cirrhosis. Therefore, this study was conducted to assess the prevalence of hyponatremia in complicated cirrhotic patients admitted to medical ICU and to determine the relationship between

hyponatremia and the development and severity of major complications of cirrhosis.

SUBJECTS AND METHODS

This study has been carried out in the medical ICU at Zagazig university hospital in the period from October 2010 to January 2011.

Two hundreds patients with complicated liver cirrhosis were enrolled in this study. The local ethics committee approved the study protocol. Formal concent were obtained from the patients or their relatives. These complications included ascites, hepatic encephalopathy, hepatic hydrothorax, hepatorenal syndrome, spontanous bacterial peritonitis and variceal bleeding.

The patients of this study were classified into three groups according to their serum sodium levels. ***[7]***.

1) Group 1: (severe hyponatremic group)

Patients with serum sodium level lower than or equal 130 meq/L . This group included 91 patients (71male and 20 female) their ages ranged from 40 years to 82 years with mean values ± SD 57.47± 9.82 years. Their serum sodium level ranged from 101 meq/L to 130 meq/L with mean values ± SD of (123.26 ± 5.57 meq/L). From them, 87 patients were ascitic, 57 patients had hepatic encephalopathy, 23 patients had spontaneous bacterial peritonitis, 31 patients had hepatic hydrothorax, 9 patients had hepatorenal syndrome and 41 patients had variceal bleeding.

2) Group 2: (mild hyponatremic group)

Patients with serum sodium level from 131 meq/L to 135 meq/L and. This group included 40 patients (30male and 10 female) their ages ranged from 23 years to 83 years with mean values ± SD 55.45± 11.36 years. Their serum sodium level ranged from 131 meq/L to 135 meq/L with mean values ± SD of (132.74 ± 1.47 meq/L). From them, 37 patients were ascitic, 25 patients had hepatic encephalopathy, 7 patients had spontaneous bacterial peritonitis, 11 patients had hepatic hydrothorax, 3 patients had hepatorenal syndrome and 15 patients had variceal bleeding.

3)Group 3: (normal serum sodium group)

Patients with serum sodium higher than or equal 136 meq/L and. This group included 69 patients (50male and 19 female) their ages ranged from 34 years to 86 years with mean values ± SD 58.06± 9.68 years. Their serum sodium level ranged from 136 meq/L to 148 meq/L with mean values ± SD of (139.99 ± 3.26 meq/L). From them, 50 patients were ascitic, 29 patients had hepatic encephalopathy, 6 patients had spontaneous bacterial peritonitis, 8 patients had hepatic hydrothorax, 2 patients had hepatorenal syndrome and 35patients had variceal bleeding.

Exclusion criteria:

All subjects of this study were selected to be free from Hepatocellular carcinoma, Chronic kidney Disease, Recent surgical abdominal procedure and Patients with past history of cerebrovascular accident.

*** Methods:**

All subjects of the study were subjected to the following:

A) Full history **and thorough clinical examination.**

B) **Routine investigation:** including

1- Complete blood picture.
2- Liver function tests.
3- Renal function test.
4- Bleeding profile.
5- Ascetic fluid sample analysis.
6- 24-hour urinary protein.
7- Hepatitis Viral markers.
8- Real-time Abdominal Ultrasound.
9- Upper GIT endoscopy.

C) Specific Assessment: including

1- Serum Sodium Level:

Serum Na^+ level was estimated by cobas b 121 system for arterial blood gases and electrolytes analysis**[8]** .

2- Severity assessment:

by using the most commonly used scoring systems in chronic liver disease MELD score and Child Pugh score.

a) MELD Score: (Model for End-stage Liver Disease) is calculated from the following equation

MELD Score *= 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dL)] + 6.4*

-In our study we used Microsoft Office Excel 2007 to calculate this formula .

b) Child Pugh Score.

RESULTS

Table (1) shows the prevalence of hyponatremia among the 200 patients enrolled in this study. From them, 91 patients (45.5%) had serum $Na^+ \leq$ 130 meq/L and they were considered as severe hyponatremics, 40 patients (20%) had serum Na^+ between 131 and 135 meq/L and they were classified as mild hyponatremics, while the rest 69 patients (34.5%) had serum $Na^+ \geq$ 136 meq/L which is the normal sodium level. So, 131 patients from total 200 patients (65.5%) were hyponatremics with serum $Na^+ \leq$ 135 meq/L.

Table (1):*The prevalence of hyponatremia in complicated cirrhotic patients*.

	Number of patients	Percentage
Group1: Severe hyponatremic patients (serum $Na^+ \leq$ 130 meq/L)	**91/200**	**45.5%**
Group2: Mild hyponatremic patients (serum Na^+ between 131 and 135 meq/L)	**40/200**	**20%**
Group3: Normo-natremic patients (serum $Na^+ \geq$ 136 meq/L)	**69/200**	**34.5%**

Table (2): *Demographic and Laboratory data of studied groups using ANOVA test.*

Demographic and Lab data	Group 1 (n=91)	Group 2 (n=40)	Group 3 (n=69)	F	*p* value
Sex					
- M	71	30	50	0.327	NS
- F	20	10	19		
Age (Years)	57.5±9.8	55.5±11.4	58.06±9.7	0.878	NS
Etiology					
-HCV	77	37	61	1.007	NS
-HBV	6	1	6		
-Non	8	2	2		
Serum Albumin(gm/dl)	2.01±0.48	2.02±0.42	2.4±0.58 **a-b**	13.306	<0.001
Serum Bilirubin(mg/dl)	3.3± 2.02	3.58± 2.86	2.6± 2	2.861	NS
Serum Creatinine(mg/dl)	1.73± 1.46	1.77± 2.1	1.17± 0.86 **a-b**	3.602	0.029
INR	1.74±.45	1.52±0.29 **a**	1.5±0.32 **a**	9.371	<0.001

a : sig. as. compared to group 1
b ; sig. as. compared to group 2

Table (2) There was a statistically significant increase in the mean values ±SD of INR (P=0.003) in group 1 (1.74±.45) as compared to group 2 (1.52±0.29) and statistically highly significant increase of INR (1.74±45) in group 1 (P<0.001) as compared to group 3 (1.5±0.32), and there was no statistically significant difference in this respect between group 2 (1.52±0.29) compared to group 3 (1.5±0.32).
Also this table shows a statistically highly significant decrease in the mean values ±SD of serum albumin (P<0.001) in group1 (2.01±0.48) and group 2 (2.02±0.42) as compared to group 3 (2.4±0.58)), Also there was a statistically significant increase in the mean values ±SD of serum creatinine (P=0.016) and (P=0.036) in group 1 (1.73±1.46) and group 2 (1.77± 2.1) respectively as compared to group 3 (1.17± 0.86), while there was no statistically significant difference in this respect between group1 and group 2 respectively.

Table(3): ***Comparison of Child Score, and MELD Score by ANOVA test and of Child Class by Chi-Square Test among studied groups:***

	Group 1 (n=91)	Group 2 (n=40)	Group 3 (n=69)	F	*P* value
Child score	11.15±1.96	10.55±2.22	9.26±1.96 **a-b**	9.914	<0.0001
Child class A B C	 0 (0%) 20 (22%) 71 (78%)	 0 (0%) 14 (35%) 26 (65%)	 5 (7.25%) 35 (50.7%) 29 (42%) **a-b**		<0.0001
MELD score	19.07±8.48	17.18±7.34	13.64±6.62 **a-b**	17.513	<0.0001

Table (3) shows that There was a statistically highly significant increase in the mean values ±SD of MELD score (P<0.001) in group 1 (19.07±8.48) as compared to group 3 (13.64±6.62) and statistically significant increase (P=0.003) in group 2 (17.18±7.34) as compared to group 3 (13.64±6.62). There was also a statistically highly significant increase in the mean values ±SD of Child score (P<0.001) in group 1 (11.15±1.96) and group 2 (10.55±2.22) respectively as compared to group 3 (9.26±1.96), while there was no statistically significant difference in this respect between group 1 and group 2 in both scores.

Table (4): ***Correlation coefficient (r) value of serum Na^+(meq/L) versus MELD and Child Pugh scores in all patients.***

	Serum Na^+(meq/L)	
	R	P
MELD Score	-0.586	<0.001 (HS)
Child Pugh Score	-0.690	<0.001 (HS)

Table (4), shows a statistically significant negative correlation between serum sodium levels and each of MELD score (r = -0.286 , p<0.001) and Child Pugh score (r = -0.390 , p<0.001).

Table(5):*Comparison of Frequences of complications of liver cirrhosis among studied groups by Chi-Square Test.*

Complication	Group 1 (n=91)	Group 2 (n=40)	Group 3 (n=69)	*P* value
Ascites	87 (95.6%)	37 (92.5%)	50 (72.5%) **a-b**	<0.001
Intractable Ascites	14 (15.4%)	4 (10%)	1 (1.4%) **a-b**	0.012
Hepatic Hydrothorax	31 (34.1%)	11 (27.5%)	8 (11.5%) **a-b**	0.004
Spontaneous Bacterial Peritonitis	23 (25.3%)	7 (17.5%)	6 (8.7%) **a**	0.026
Hepatorenal Syndrome	9 (9.9%)	3 (7.5%)	2 (2.9%)	NS
Hepatic Encephalopathy	57 (62.6%)	25 (62.5%)	29 (42%) **a-b**	0.021
Variceal Bleeding	41 (45.1%)	15 (37.5%)	35 (50.7%)	NS
Esophageal Varices	76 (83.5%)	33 (82.5%)	60 (87%)	NS
Gastric Varices	23 (25.3%)	11 (27.5%)	10 (14.5%)	NS

Table (5) shows that there were statistically significant increase in frequencies of some liver cirrhosis complications including ascites (P<0.001), intractable ascites (P=0.012), hepatic hydrothorax (P=0.004), spontaneous bacterial peritonitis (P=0.026) and hepatic encephalopathy (P=0.021), in hyponatremic patients compared to those without hyponatremia while no significant differences was found in frequencies of hepatorenal syndrome, esophageal varices, gastric varices and variceal bleeding**.**

Table(6): ***Relative risk of occurence of some liver cirrohsis complication in total hyponatremic patients more than normonatremic patients.***

	Hyponatremia	Normonatremia	RR
Ascites	124/131	50/69	1.3
Intractable ascites	18/131	1/69	9.5
Hepatic encephalopathy	82/131	26/69	2.8
Hepatic hydrothorax	42/131	8/69	1.5
Spontaneous bacterial peritonitis	30/131	6/69	2.6

Table (6) show increased relative risk of development of ascites 1.3 fold, intractable ascites 9.5 fold, hepatic encephalopathy 1.5 fold, hepatic hydrothorax 2.8 folds and spontaneous bacterial peritonitis 2.6 fold in hyponatremic patients (with serum $Na^+ \leq 135$ meq/L) than in normonatremic patients.

Table(7): ***Relative risk of occurence of some liver cirrohsis complication in severe hyponatremic patients more than normonatremic patients.***

	Severe Hyponatremia	Normonatremia	RR
Ascites	87/91	50/69	1.32
Intractable ascites	14/91	1/69	10.6
Hepatic encephalopathy	57/91	29/69	1.5
Hepatic hydrothorax	31/91	8/69	2.9
Spontaneous bacterial peritonitis	23/69	6/69	2.9

Table(7) show increased relative risk of development of ascites 1.32 fold, intractable ascites 10.6 fold, hepatic encephalopathy 1.5 fold, hepatic hydrothorax 2.9 fold and spontaneous bacterial peritonitis 2.9 fold in severe hyponatremic patients (with serum $Na^+ \leq 130$ meq/L) than in normonatremic patients.

DISCUSSION

In recent years, hyponatremia has attracted interest as a possible prognostic factor for liver cirrhosis. To date, no studies have been conducted to assess the prevalence of hyponatremia in Egyptian hospitalized patients with liver cirrhosis. In fact, few studies have evaluated the association between serum sodium levels and the occurrence and severity of complications due to liver cirrhosis. A notable finding of this study is that the prevalence of hyponatremia in patients with liver cirrhosis (serum sodium ≤135 meq/L) was 131/200 (65.5%) while that with severe hyponatremia (serum sodium ≤ 130 meq/L) was 91/200 (45.5%). In a previous study, **Angeli et al** found lower prevalence of hyponatremia**[6].** [Their study involved the prospective collection of data on patients from 28 hospital hepatology departments in Europe, North and South America, and Asia, for a period of 28 days at each center, they found that 486/983 patients (49.4%) had values below the normal range and 211/983 patients (21.6%) had values <130 meq/L, which is the cutoff value widely used to define hyponatremia as reported by **Shaikh et al [9].** In another study conducted in patients hospitalized with complications due to liver cirrhosis, **Kim et al** found that the prevalence of hyponatremia at a serum sodium concentration ≤135 meq/L was 47.9%, and that of severe hyponatremia was 27.1% **[10]. Upadhyay et al** found that hyponatremia occurs even more commonly in cirrhosis, in upwards of 30% to 35% of patients, particularly those with advanced chronic disease**[11].** This relatively high prevalence found in our study may be due to the overuse of diuretics taken without follow up before admission, and also a large proportion of patients are of Child- Pugh class C, which had the highest prevalence of hyponatremia 97/131 (74%).

In this work, the association of serum sodium levels with the severity of the chronic liver disease in cirrhotic patients was evidenced by the statistically significant negative correlation between serum sodium level and the two scoring systems: Child-Pugh score ($r = -0.690$, $p < 0.001$) and Model for End-stage Liver Disease (MELD) score ($r = -0.586$, $p < 0.001$) which are widely used in assessing severity of chronic liver disease. Also, there was a statistically highl significant difference in Child-Pugh score and MELD score among the three studied groups, this was in agreement with **Kim et al** who obtained the same results regarding this correlation between serum sodium level and the main two scoring systems of severity of chronic liver disease**[10].** These results may indicate that hyponatremia is associated with the severity of chronic liver disease, so some recent studies were conducted as a trial to incorporate serum sodium level in the severity and prognosis assessment. **Jiang et al** tried to assess new models in which serum sodium was incorporated, these models were MELD-Na (the MELD with the incorporation of serum sodium), iMELD (the integrated MELD) and MESO index (the MELD to sodium index)**[5].**

The serum levels of creatinine, bilirubin and INR are the three variables included in the equation of MELD score, so these parameters were studied regarding the serum sodium level. Also serum

albumin level was incorporated as a variable factor in the study, as the serum albumin level is a good indicator for the synthetic function of liver . The present study showed statistically significant decrease in serum albumin level ($p< 0.001$) and serum creatinine level ($p= 0.029$) and statistically significant increase in INR ($p< 0.001$) among the three studied groups, but regarding serum bilirubin there was no significant differences between the three groups, nearly the same results were reported by **Borroni et al [12]** except the statistically significant decrease in serum bilirubin between hyponatremic patients and patients with normal sodium level. These results support and explain the strong correlation between serum sodium level and MELD score.

In the current study, some complications due to liver cirrhosis had statistically significant different frequencies among our three groups, including ascites ($p<0.001$), intractable ascites ($p=0.012$), spontaneous bacterial peritonitis ($p=0.026$), hepatic hydrothorax ($p=0.004$), and hepatic encephalopathy ($p=0.021$), whereas the frequencies of other complications such as hepatorenal syndrome, esophageal varices, gastric varices and varceal bleeding did not differ significantly among the three groups. This is in agreement with the study done by **Kim et al [10]** with only one exception which was the insignificant different frequencies of intractable ascites among the three groups. **Arroyo et al [13]** reported that the presence of severe hyponatremia was associated with lower glomerular filtration rate and solute-free water clearance and a poorer response to diuretics compared with patients with serum sodium>130 meq/L supporting our finding. **Chang et al** reported that hyponatremia increases the risk of major complications of hepatorenal syndrome, infection complications and neurological disorders in cirrhotic patients compared with normonatremia while there was no significant association between gastrointestinal bleeding and serum sodium**[14].**

In the present study, we tried to determine the significance of different frequencies of complications between every two groups of patients separately. We found that there was no statistically significant increase in frequencies of all liver cirrhosis complications in severe hyponatremic patients (Na<130 meq/L) when compared with mild hyponatremic patients (Na between 131 and 135meq/L), but there was a statistically significant increase in frequencies of ascites, intractable ascites, hepatic hydrothorax and hepatic encephalopathy in both mild and severe hyponatremic groups when compared with normonatremic group. This is in agreement with the study done by **Kim et al [10].** So, although, the severe hyponatremia is associated with slight higher incidence of liver cirrhosis complications than mild hyponatremia, mild hyponatremia still associated with the occurrence of liver cirrhosis complications.

Also we found that severe hyponatremic patients had a significantly increased frequency of hepatic encephalopathy as compared with those with normal serum sodium, this is in agreement with **Angeli et al** who reported that encephalopathy was present in 38% of the severe hyponatremic patients compared with 24% of patients with mild hyponatremia and 15% of patients had normal serum sodium concentration**[6].**

Angeli et al found a clear inverse relationship between serum sodium levels and frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome**[6].** In agreement with this, **Shaikh et al** found that hepatorenal syndrome was also strongly associated with low serum sodium concentration as 8/13 patients with refractory ascites with severe hyponatremia developed hepatorenal syndrome during follow up as compared to one patient with mild hyponatremia and none with normal serum sodium concentration**[9].** This inverse relationship between serum sodium levels and hepatorenal syndrome was found to be statistically insignificant by **Kim et al [10]**, in agreement with our study where we did not find significant differences in the frequency of hepatorenal syndrome among our three groups.

As regard the role of hyponatremia in relation to development of liver cirrhosis complications, we found that hyponatremia in general (mild and severe) increase the relative risk (RR) of ascites, intractable ascites, hepatic hydrothorax, hepatic encephalopathy and spontaneous bacterial peritonitis by 1.3, 9.5, 2.8, 1.5 and 2.6 fold respectively than in normonatremic patients. When we compared severe hyponatremic with normonatremic patients, we found that severe hyponatremia increase the relative risk (RR) of ascites, intractable ascites, hepatic hydrothorax, hepatic encephalopathy and spontaneous bacterial peritonitis by 1.32, 10.6, 2.9, 1.5 and 2.9 folds respectively than in normontremic patients. We can notice clearly that there was slight increase in relative risk (RR) in severe hyponatremics than in total hyponatremic patients. This is in agreement with findings reported by **Angeli et al [6]**. They found that even patients with a mild reduction in serum sodium concentration should be considered a high risk population because of their more severe ascites and greater frequency of major complications of cirrhosis compared with patients

with normal serum sodium concentration. This means that hyponatremia in advanced liver cirrhosis may indicate the development of liver cirrhosis complications.

In general, we can conclude that hyponatremia is a common problem in complicated cirrhotic patients. Hyponatremia was found to be associated with increased frequencies and severity of some liver cirrhosis complications including ascites, intractable ascites, hepatic hydrothorax, hepatic encephalopathy and spontaneous bacterial peritonitis. Also hyponatremia was associated with a higher severity of illness scores (Child-Pugh and MELD scores). . Management of hyponatremia may decrease the incidence and severity of the liver cirrhosis complications with better quality of their life. So more interest should be tried towards the use of vasopressin receptor antagonists as a line of treatment of complicated cirrhotic patients with hyponatremia without salt overload

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