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IMPACTS OF HYPONATRAEMIA ON THE COMPLICATIONS OF LIVER CIRRHOSIS

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ABSTRACT

Objectives: To observe the effects of hyponatraemia on the complications of liver cirrhosis

Study design: Descriptive case series study.

Setting: Department of Medicine, Isra University Hospital and Department of Medicine, Liaquat University Hospital Hyderabad / Jamshoro

Duration of Study: August 2010 to February 2011.

Subjects & Methods: This study comprised of 100 cases of cirrhosis of liver who were admitted in Department of Medicine, Isra University, and Department of Medicine, LUMHS, Jamshoro/Hyderabad. The presenting complaints were presence of distention of abdomen, stupor, irritability, altered sleep pattern, coma and hematemesis. After giving immediate treatment adequate historical information, physical examination and specific pertinent laboratory test results were recorded to the specifically designed proforma after obtaining the informed consent. The main variables studied were frequency of hyponatremia, assessment of degrees of hyponatremia and its effects on the complications of cirrhosis of liver.

Results: Out of 100 cases, 67(67%) were male and 33(33%) were female. Hyponatremia was present in 35% patients (n=35/100, total 100). Out of these 20% (n=20) were having mild hyponatremia (Na 135-130 mEq/L), 14% (n=14) moderate hyponatremia (Na 130-125 mEq/L) and only 1% (n=1) severe hyponatremia (Na <125 mEq/L). Twenty eight percent (28%) patients were suffering from hepatic encephalopathy, 23% from bleeding esophageal varices and 9% from spontaneous bacterial peritonitis respectively. Primary outcome was: 63 patients improved and were discharged, 27 patients didn't improved and were still being managed, and lastly 10% patients expired while on treatment.

Conclusions: Among hepatic encephalopathy and spontaneous bacterial peritonitis, moderate and severe hyponatremia is one of the major risk factor of mortality and morbidity while normal serum sodium and mild hyponatremia had no effect.

Key words: Cirrhosis, Hepatic-encephalopathy, Precipitating factor, Hyponatremia.

INTRODUCTION

There is definite dearth of data on the frequency, incidence and prevalence of hyponatremia in Pakistan. Although at present orthotropic liver transplantation (OLT) is not being carried out in our setup but it is a very promising procedure which would benefit the patients greatly in near future. The waiting list for OLT is graded according to Model of Endstage Liver Disease (MELD). Nowadays there is suggestion of addition of serum sodium to MELD so that it would improve the waiting list mortality of patients waiting for orthotopic liver transplantation.[1] Local experience regarding this mortality prediction is also limited and therefore this study can serve as a primer for incorporation of serum sodium in the MELD when appropriate time comes. [1,2]

In order to understand hyponatremia one should be familiar with the interplay between body water and sodium. The reason for this is that hyponatremia primarily means that there is little sodium 'compared' to water. Hyponatermia is not at all concerned with

the total quantity of sodium in the body, as some falsely try to explain. In fact total body sodium can be reduced; can be normal or even elevated in case of hyponatremia. Important idea is that these values are only important when 'speedy' development of hyponatremia is going on. Pathophysiology of development of hyponatremia: The most important concept in the idea of hyponatremia is that water imbalance not the sodium imbalance is responsible for the development of hyponatremia.[3] It should always be emphasized that hyponatremia cannot indicate anything about the total quantity of sodium in the body (as total quantity can be increased, normal or decreased in a patient with hyponatremia). Not much data is currently available regarding the hospital prevalence of hyponatremia in Pakistan.[4] However hyponatremia as an exacerbating factor of worsening hepatic encephalopathy in cirrhosis of liver has been actively studied. In hospitalized cirrhotics the frequency of hyponatremia is around 28-50%. Patients with renal failure and hyponatremia may have normal or high plasma osmolality because of the urea retention. However, as urea is not an effective osmole, the patient should be treated as per hypotonic hyponatremia. Hyponatremia in cirrhosis is dilutional and thus fluid restriction (500-1500 mL/day) forms the basis of therapy.[5]

The use of hypertonic saline is not recommended as the patients are already in a sodium retaining state and are at little risk for seizures. Also, rapid rises in serum sodium can lead to central pontine myelinolysis. The difficulty with fluid restriction is poor patient compliance as few patients are able to tolerate this approach for a prolonged period of time, especially in an outpatient setting. Thus, aquaretic drugs have been sought for a number of years. The first agent to be tried was demeclocycline, which inhibited the effects of AVP on the kidney. Although it was effective in treating the dilutional hyponatremia, it also caused renal failure in patients with cirrhosis and thus could not be used. The data on the use of more specific agents is more encouraging. A number of vasopressin receptor antagonists have been developed and used in the treatment of hyponatremia. [6]

However, the problem with this class of drugs is that several patients develop an increase in thirst and in the drug was withheld because of a too rapid rise in serum sodium or a serum sodium of >142 mmol/L. An alternative to vasopressin receptor blockade is to use K-opioid agonists. K-opioid agonists have been known to increase free water clearance for a number of years. K-opioid agonists appear to work both by blocking the release of AVP and by acting directly on the kidney as well.[6,7] They are potent aquaretics in normal humans and cirrhotic rats. Their role in the management of hyponatremia in cirrhotics remains to be determined. In conclusion, hyponatremia is an important complication in patients with decompensated cirrhosis and its development is associated with significant morbidity.[8]

New aquaretic agents offer hope for the treatment of this disorder. Numerous unresolved issues however, remain and need to be resolved before these agents can be widely used. The long-term effects of these agents are unknown. Also unknown is how aquaretic agents and diuretics such as furosemide interact. The combined use of these drugs is of great interest given the fact that the development of hyponatremia is a common complication of diuretic therapy, thus limiting their usefulness in cirrhotic patients.[9] If aquaretic agents could reduce the risk of diuretic induced hyponatremia then this combination of drugs would make the management of the decompensated cirrhotic much easier. However, there is concern that the potential for dehydration may be greater when these agents are used in combination. [8-10]

The rationale of the study is to find out the frequency of hyponatremia in our own community with that of other countries. Secondly the purpose was to specifically find out the importance of hyponatremia in cirrhosis of liver and its effects over complications.

MATERIAL & METHODS

SETTING: The patients selected were all admitted in the Department of Medicine, Isra University, Hyderabad and Department of Medicine, Liaquat University Hospital Hyderabad/Jamshoro. 100 Patients after obtaining informed consent were included in this study from August 2010 to February 2011 with cirrhosis of liver were identified using clinical and radiological data. Relevant demographic and clinical details including presentation, past medical history, drug history and examination findings were collected, along with the results of the biochemical and radiological investigations (and recorded proforma specifically designed for this study) requested by the physicians responsible for the patients' care.

STUDY DESIGN: Descriptive Case series study.

SAMPLE TECHNIQUE: Non probability purposive sampling

INCLUSION CRITERIA: Both male and females patients diagnosed with cirrhosis of liver from 12-60 years were included in the study.

EXCLUSION CRITERIA:

- Dehydrated patients.
- Patients who are suffering from hepatocellular carcinoma.
- Patients without ascites at the time of admission.
- Patients with fluid overload assessed by raised jugular venous pressure (JVP)

DATA COLLECTION PROCEDURE: At the very beginning an informed consent was obtained from each patient who met the inclusion criteria of this study. Specific proforma was used and important historical data such as the history of distention of abdomen, edema, hematemesis, melena and irritability, altered sleep pattern and stupor/coma was obtained and a thorough physical examination was performed in each case, which included general physical examination which evaluated the patient for the presence of jaundice, edema, palmar erythema, spider nevi and examination of gastrointestinal system for hepatosplenomegaly, presence of ascites and the stage of hepatic encephalopathy. Immediate medical care was provided to those patients who were suffering from severe complications of cirrhosis (e.g., hepatic encephalopathy, bleeding and infections). After controlling the basic hemodynamic status (maintaing pulse, B.P, temperature and respiration) of the patients, blood samples were obtained for routine investigation like serum levels of electrolytes, urea, creatinine, SGPT, SGOT, alkaline phosphatase, hemoglobin, total leukocyte count, platelet count, prothrombin time, albumin, HBsAg and Anti HCV levels. Abdominal ultrasonography was also performed. Ascitic fluid samples were also obtained for D/R and C/S and no special investigation was ordered. All the data including the socio-demographic information of the patients were recorded on the specifically designed proforma for this study.

DATA ANALYSIS: Statistical package for social sciences SPSS was used for statistical analysis of the study data. Descriptive statistics for quantitative variables such as Age, Albumin (mg/dL), Alkaline Phosphatase (U/L), Bilirubin (mg/dL), Child Score, Creatinine

(mg/dL), Hemoglobin (mg/dL), Hepatic Encephalopathy Grade, Platelet Count, Serum Potassium (K) [mEq/L], Prothrombin Time (sec), SGOT (U/L), SGPT (U/L), Serum Sodium (Na) [mEq/L], Total Leukocyte Count and Urea (mg/dL) was processed for mean and standard deviation (SD). Qualitative variables such as sex, presence of ascites, jaundice, edema, spontaneous bacterial peritonitis, hepatic encephalopathy, melena, hematemesis, palmar erythema, spider nevi, HBsAg, AntiHCV, hyponatremia, degrees of hyponatremia, Child class and patients outcome were presented as frequencies and percentage tables (having percentage and cumulative frequency), or bar charts or pie charts wherever applicable. In the end cross tabulation of hyponatremia with hepatic encephalopathy, bleeding esophageal varices and spontaneous bacterial peritonitis is presented. As this was a descriptive case series study no test of significance or p value calculation was considered necessary.

RESULTS

Over the study period, 100 in-patients were enrolled. They were diagnosed as cirrhotic and were suffering from complications such as ascites, hematemesis and hepatic encephalopathy. The mean age was 46.7 years (SD ± 11.7); 67 were male and 33 were females – Table I. At admission, serum sodium concentrations ranged from 123 to 159 mEq/L, whereas mean value was 137.2 with a standard deviation of 6.9. Normal serum sodium (135-150 mEq/L) was present in 65 patients and a total of 35 patients (35%) were having hyponatremia.. Out of these 35 patients 20 (20%, n=100) had mild hyponatremia (Na <135-130), 14 (14%) patients had moderate hyponatremia (<130-125 mEq/L) and only 1 (1%) had severe hyponatremia (<125 mEq/L). Table 2 labels the outcome of Hematemesis with Hyponatremia. Table 3 describes Outcome of Spontaneous bacterial Peritonitis with Hyponatremia. Outcome of Hepatic Encephalopathy with Hyponatremia are outlined in Table 4.

TABLE 1:
SEX DISTRIBUTION OF CASES (N=100).

SEX	n(%)
Male.	67(67)
Female.	33(33)

DISCUSSION

This study demonstrates high frequency of hyponatremia in cirrhotic in-patients. Moreover it also points out towards poor outcome associated with all degrees of hyponatraemia in cirrhotic in-patients. Hyponatraemia quite frequently has a complex and multifactorial etiology in the majority of our patients. Farooqui et al presented a detailed account of severe hyponatraemia in hospital setting.[11] Our in-patient mortality rate was very different to that described by Farooqui et al., (our mortality was 10% which was lower) although their study was different as they only studied hyponatremia indiscriminately and only concentrated on severe hyponatremia, whereas our study population consisted of cirrhotics and we studied all categories of hyponatremia. Our breakdown of patients' outcome by the level of hyponatremia supports previously published data suggesting that hyponatraemia is a common precipitating factor for hepatic encephalopathy in cirrhosis of liver. When compared with Farooqui et al severe hyponatraemic patients showed a similar pattern of mortality, however survival analysis was not computed though.

Alam et al [12] studied all the factors which worsen hepatic encephalopathy in Pakistani patients. According to them 28% of patients had one or another electrolyte imbalance. Our study was quite similar to them except that we only concentrated on hyponatraemia as a precipitating factor for hepatic encephalopathy. Our frequency of hyponatremia closely resembled the result of Alam et al. This further confirms that a huge proportion of patients is affected by hyponatraemia in our local setup, which may be due to diuretic use [13] A similar study was done by Maqsood et al [14] which mainly focused on patients suffering from hepatic encephalopathy. This study reported presence of hyponatraemia in 50% of patients, which is far greater figure when compared with our study, as we only reported a frequency of 35%. Studies done on hepatic encephalopathy [15] show similar results when compared with our study.

Angeli P et al[16] has described high frequency of hepatic encephalopathy, spontaneous bacterial peritonitis and no effect on occurrence of gastrointestinal bleeding in low serum sodium

TABLE 2:
OUTCOME OF HEMATEMESIS WITH HYPONATREMIA.

Outcome	Hematemesis	Hyponatremia				
		Normal	Mild < 135-130	Moderate 125-130	Severe <125	Total
Improved and discharged	Yes	06	02	02	0	10
	No	35	12	06	0	53
No Improvement	Yes	05	02	01	0	08
	No	14	02	03	0	19
Expired	Yes	02	02	0	01	05
	No	03	0	02	0	05
Total		65	20	14	01	100

TABLE 3:
OUTCOME OF SPONTANEOUS BACTERIAL PERITONITIS WITH HYPONATREMIA

Outcome	Spontaneous Bacterial Peritonitis	Hyponatremia		Moderate 125-130	Severe <125	Total
		Normal	Mild <135-130			
Improved and discharged	Yes	01	03	02	0	06
	No	40	11	06	0	57
No Improvement	Yes	0	0	0	0	0
	No	19	04	04	0	27
Expired	Yes	01	0	01	01	03
	No	04	02	01	0	07
Total		65	20	14	01	100

TABLE 4:
OUTCOME OF HEPATIC ENCEPHALOPATHY WITH HYPONATREMIA.

Outcome	Hepatic Encephalopathy	Hyponatremia		Moderate 125-130	Severe <125	Total
		Normal	Mild <135-130			
Improved and discharged	Yes	07	05	0	0	12
	No	34	09	08	0	51
No Improvement	Yes	06	01	02	0	09
	No	13	03	02	0	18
Expired	Yes	04	0	02	01	07
	No	01	02	0	0	03
Total		65	20	14	01	100

patients. Arce I et al [17] also showed significant relationship of hyponatremia and morbidity/mortality. According to them morbidity and mortality is increased two folds if hyponatremia is present in cirrhotic patients.

Another study conducted by Rafael Valdivia L, Ferrandiz Quiroz J. at Guillermo Almenara Irigoyen state hospital Peru[18] observed that hyponatremic patients had greater frequency of infection like spontaneous bacterial peritonitis and found that hyponatremia is an independent risk factor.

This study clearly matches the results of these above studies. We observed deleterious effects of moderate to severe hyponatremia on complications like SBP, hepatic encephalopathy HE but no effect on hematemesis. Further we observed that mild hyponatremia had no effect on complications. Among patients with moderate to severe hyponatremia and HE, 60% patients expired while in case of normal serum sodium level patients, only 23.5% patients expired, this shows more than two fold increase in mortality among moderate to severe hyponatremic patients, as observed by Arce I et al. Among patients with severe hyponatremia and SBP, 100% patients expired while in case of normal serum sodium level patients, only 50% patients expired, this shows more than two fold increase in mortality among severe hyponatremic patients, while in patients with mild and moderate hyponatremia and SBP, mortality rate is low. Among patients with hematemesis, there is no significant effect of hyponatremia and normal sodium level was observed. On the whole our study has shown that hyponatremia is very common among cirrhotic patients and had deleterious effects on the mortality, so when moderate to severe hyponatremia is encountered in patients with cirrhosis the physician should become alert and pay attention to reverse the condition.

CONCLUSION

In this study it was found that the frequency of hyponatremia was 35%, and hyponatremia had significant effect on hepatic encephalopathy and spontaneous bacterial peritonitis but no significant effect was observed on hematemesis.

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