ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

FREQUENCY OF HYPONATRAEMIA AND ITS INFLUENCE ON LIVER CIRRHOSIS- RELATED COMPLICATIONS.

JivteshPreet Singh, Ashok Khurana , Devinder Singh.

Manuscript Info

Manuscript History:

Received: 18 December 2015
Final Accepted: 22 January 2016
Published Online: February 2016

Key words:

****Corresponding Author***

JivteshPreet Singh.

Abstract

Cirrhosis represents the final common pathway for a wide variety of chronic liver diseases. 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 solute-free water clearance. This leads to dilutional hyponatraemia. In the present study, 60 patients coming to OPD and indoor of SGRDIMSAR, Amritsar were recruited and divided into three groups. Patients were grouped on the basis of serum sodium concentration into three groups: (1) serum sodium <130 meq/l (Group1), (2) serum sodium between 131 - 135 meq/l (Group 2) and (3) serum sodium >135 meq/l (Group3). The patients with hyponatraemia Group1 (<130 meq/l) and group 2 (131-135meq/l) were compared with group 3 (>135 meq/l) for the serum bilirubin, serum albumin, prothrombin time, degree of ascites and hepatic encephalopathy. Impact of hyponatraemia on cirrhosis related complications was evaluated.

Introduction:-

Cirrhosis represents the final common pathway for a wide variety of chronic liver diseases. The term cirrhosis was first introduced by Laennec in 1826. It is derived from the Greek word "kirrhos," referring to the tawny yellow nodules associated with this entity. It is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules, leading to loss of liver function.[1]

Hyponatremia in cirrhosis was first described in the 1950′s, but its importance was overlooked for many years. 30 years later its importance as a predictor for the survival in cirrhosis was investigated.[2] Interest in hyponatremia was fostered by studies in the late 1970s and 1980s indicating that hyponatremia is an important prognostic indicator in cirrhosis.[3]

Hyponatremia in cirrhosis is defined as having a serum sodium level below 130 mmol/l.[4] According to this definition, the prevalence of hyponatremia in cirrhotic patients is of 21.6%. If the cut-off limit for serum sodium is considered to be of 135 mmol/l (that represents the lower limit of serum sodium in healthy subjects), then the prevalence is of 49.4%. Cirrhotic hyponatremia is associated with jaundice, hepatic encephalopathy, refractory ascites and hepatorenal syndrome.[5]

Serum sodium in cirrhosis that is below130 mmol/l is associated with a median transplant-free survival of less than 6 months.[6] Two types of hyponatremia have been described in cirrhotic patients:[7]

1. Hypovolemic hyponatremia - This condition is due to important losses of extra cellular fluid (excess use of diuretics or losses through GIT). It is characterised by low serum sodium and low plasma volume .These patients do not have ascites or edema and may show signs of dehydration and pre-renal azotemia .
2. Hypervolemic hyponatremia - It is also called as dilutional hyponatremia .This condition is associated with large ascites and edema .This is caused by renal impairment in excretion of solute free water causing dispropotionate water retention compared to sodium. This is due to reduced sodium delivery to the distal tubule as a consequence of reduction of glomerular filtration rate and /or increase of sodium reabsorption in

proximal tubule. Therefore, in this case, the plasma volume is expanded in absolute value but it is low as compared to marked arterial dilatation characteristic of advanced cirrhosis .

Hepatic encephalopathy is the most important clinical complication of hyponatremia. Besides this, hyponatremia is associated with other complications of cirrhosis. It is important to know that cirrhotic patients with hyponatremia are at very high risk of developing the hepatorenal syndrome.[8] In this situation, probably, hyponatremia is due to increased levels of arginine vasopressine (hepatorenal syndrome is characterized by intense stimulation of the renin angiotensin aldosterone system due to an extreme systemic vasodilatation) and to reduced glomerular filtration rate and increased proximal tubular sodium reabsorption.[9]

Aims and objectives:-

This study was conducted to evaluate the association between hyponatremia and complications of cirrhosis as assessed by Child-Pugh Score.

Review of literature:-

Shaikh S, Mal G et al[10] conducted a study to evaluate the frequency, clinical associations and prognostic impact of hyponatraemia on cirrhosis related complications in patients with cirrhosis of liver. In this case control study, 217 cirrhotic patients consecutively admitted to department from September 2006 to November 2007 were studied. Serum sodium levels were determined in all patients admitted. The cutoff level of 130 meq/l was chosen because it is widely accepted to define hyponatraemia in patients with cirrhosis while the level of 135 meq/L is the lower normal value. Patients were grouped on the basis of serum sodium concentration into: (1) serum sodium <130 meq/l (Group 1), (2) serum sodium between 131 - 135 meq/l (Group 2) and (3) serum sodium >135 meq/l (Group 3). The p value of less than 0.05 was considered as significant. The patients of Group 1 (<130 meq/l) and group 2 (131-135 meq/l) were compared with group 3 (>135 meq/l) for the severity of liver disease, degree of ascites and other cirrhosis related complications such as hepatorenal syndrome, spontaneous bacterial peritonitis and hepatic encephalopathy.

Hyponatraemia (sodium <130 meq/l) was found in 58/217 (26.7%) patients and 54/217 (24.9%) had serum sodium from 131-135 meq/l whereas 105/217 (48.4%) patients had serum sodium >135. In Group 1,out of 58 patients with hyponatraemia, 48 were in Child-Pugh C class (p=0.001). Patients with serum sodium <130 meq/l had more severe ascites (p = 0.001) requiring frequent paracentesis and higher dosages of diuretics. Hepatic encephalopathy was more frequent in patients with serum sodium <130 meq/l (p= 0.001). The cirrhosis related complications were also significantly increased in patients with mild hyponatraemia (131-135 meq/l) than in patients with normal serum sodium (>135 meq/l). They concluded that hyponatraemia was frequent in cirrhotic patients. It was seldom spontaneous and had a negative influence on cirrhosis related complications.

Borroni G, Maggi A et al[11] conducted a study to evaluate prevalence, clinical associations and prognostic impact of hyponatraemia in cirrhotic inpatients. A series of 156 cirrhotic patients were consecutively studied. Serum sodium levels were determined at admission and repeated at least weekly in all patients. The clinical status and the survival of patients with hyponatraemia (< or = 130 mmol/l) were compared to those of patients with normal sodium levels.

Hyponatraemia was found in 57 out of 191 admissions (29.8%). Bacterial infections and ascites were more frequent in patients with hyponatraemia than in those with normal sodium levels. In 3 cases, none of these conditions were present and hyponatraemia was defined as "spontaneous". Hospital death rate was increased in patients with hyponatraemia (26.3% versus 8. 9%, chi^2=8. 55, p=0.003). By multivariate analysis, the only parameters independently associated with survival were high serum bilirubin (p=0.006) and high serum urea levels (p=0.019). 25 patients developed severe hyponatraemia (<125 mmol/l) during hospital stay. They concluded that hyponatraemia is frequent in cirrhotic inpatients. It is seldom a spontaneous event but rather occurs in association with ascites, chronic use of diuretics or bacterial infections. It is a negative prognostic factor associated with increased short-term mortality.

Kim JH, Lee JS, Lee SH et al[12] studied the association between the serum sodium level and the severity of complications in liver cirrhosis. Data of inpatients with cirrhotic complications were collected retrospectively. The serum sodium levels and severity of complications of 188 inpatients were analyzed. They found that the prevalence

of dilutional hyponatremia, classified as serum sodium concentrations of <or=135 mmol/l, < or =130 mmol/l and < or =125 mmol/l, were 20.8%, 14.9%, and 12.2%, respectively. The serum sodium level was strongly associated with the severity of liver function impairment as assessed by Child-Pugh score (p<0.0001). Even a mild hyponatremia with a serum sodium concentration of 131-135 mmol/l was associated with severe complications. Sodium levels less than 130 mmol/l indicated the existence of massive ascites (OR, 2.685; CI, 1.316-5.477; p=0.007), grade III or higher hepatic encephalopathy (OR, 5.891; CI, 1.490-23.300; p=0.011), spontaneous bacterial peritonitis (OR, 2.562; CI, 1.162-5.653; p=0.020), and hepatic hydrothorax (OR, 5.723; CI, 1.889-17.336; p=0.002). Hence, they concluded that hyponatremia, especially serum levels <or=130 mmol/L, may indicate the existence of severe complications associated with liver cirrhosis.

A Bengus and RD Babiuc[9] concluded that hyponatremia is a frequent complication of the advanced liver disease. Hyponatremia is determined by the impaired capacity of the kidney to excrete free water, which leads to water retention disproportionate to sodium retention, thus causing low plasma osmolarity. Hyponatremia in cirrhosis is associated with a high morbidity and mortality, its presence suggesting a very advanced liver disease. Current evidence suggests that hyponatremia affects the brain function and predisposes to hepatic encephalopathy. In addition, hyponatremia is a risk factor for liver transplantation, being associated with a high frequency of complication and affecting short and long-term post-transplant survival.

Angeli P, Wong F et al[5] concluded that low serum sodium concentration is an independent predictor of mortality in patients with cirrhosis, but its prevalence and clinical significance is unclear. To evaluate prospectively the prevalence of low serum sodium concentration and the association between serum sodium levels and severity of ascites and complications of cirrhosis, prospective data were collected on 997 consecutive patients from 28 centers in Europe, North and South America, and Asia for a period of 28 days. The prevalence of low serum sodium concentration as defined by a serum sodium concentration < or = 135 mmol/l, < or = 130 mmol/l, < or = 125 mmol/l and < or = 120 mmol/l was 49.4%, 21.6%, 5.7%, and 1.2%, respectively. The prevalence of low serum sodium levels (<135 mmol/l) was high in both inpatients and outpatients (57% and 40%, respectively). The existence of serum sodium <135 mmol/l was associated with severe ascites, as indicated by high prevalence of refractory ascites, large fluid accumulation rate, frequent use of large-volume paracentesis, and impaired renal function, compared with normal serum sodium levels. Moreover, low serum sodium levels were also associated with greater frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome, but not gastrointestinal bleeding. Patients with serum sodium <130 mmol/l had the greatest frequency of these complications, but the frequency was also increased in patients with mild reduction in serum sodium levels (131-135 mmol/l). In conclusion, low serum sodium levels in cirrhosis are associated with severe ascites and high frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome.

Martin-Llahi M, Guevara M, Gines P[13] concluded that the presence of dilutional hyponatremia has a poor prognosis for survival in patients with cirrhosis and ascites. Effective and safe treatments are needed to improve prognosis in patients with cirrhosis and dilutional hyponatremia. The initial approach to management includes fluid restriction, low sodium diet and minimizing the use of diuretics. In addition, the use of hypertonic saline should be avoided in patients with cirrhosis and dilutional hyponatremia. Furthermore, patients should be placed on the top of the list for liver transplantati.

Material and methods:-

The study was conducted on 60 patients with cirrhosis of liver attending OPD and indoor of SGRDIMSAR, Amritsar. The recording of consecutive patients was designed to avoid any bias due to selection of patients. The study was carried out after the approval from hospital ethical committee and obtaining informed consent from the patients or their relatives.

The cirrhotic patients were confirmed by clinical, biochemical and ultrasonographic findings and presence of ascites determined via paracentesis or ultrasonography. All these patients underwent general physical examination, detailed systemic examination and necessary investigations .Serum sodium in these cirrhotic patients was compared to severity of cirrhosis as assessed by Child Pugh Score. A total score of 5-6, 7-9 and 10-15 was classified as class A, B and C respectively. Child Pugh Score was calculated as per the

following table :

Factor	Units	1	2	3
Serum Bilirubin	mg/dl	<2.0	2.0-3.0	>3.0
Serum Albumin	g/dl	>3.5	3.0-3.5	<3.0
Prothrombin Time	Seconds Prolonged	0-4	4-6	>6
Ascites		None	Easily controlled	Poorly controlled
Hepatic Encephalopathy		None	Minimal	Advanced

Serum sodium level was determined in all patients of liver cirrhosis. The cut-off level of 130 meq/l was chosen because it is widely accepted to define hyponatraemia in patients with cirrhosis while the level of 135 meq/l is the lower normal value. Patients were grouped on the basis of serum sodium concentration into three groups: (1) serum sodium <130 meq/L (Group1) (2) serum sodium between 131 - 135 meq /l (Group 2) and (3) serum sodium >135 meq /l (Group3). P values of less than 0.05 was considered as significant. The patients with hyponatraemia Group1 (<130 meq/l) and group 2 (131-135meq/l) were compared with group 3 (>135 meq/l) for the serum bilirubin, serum albumin, prothrombin time, degree of ascites and hepatic encephalopathy (child pugh score) .

Inclusion criteria:-The patients included in the study were those in which diagnosis of cirrhosis was confirmed by clinical, biochemical and USG findings and in patients in which presence or absence of ascites was determined via paracentesis or USG.

Exclusion criteria:-The patients with cardiac failure ,chronic kidney disease, hepatocellular carcinoma and exudative ascites, on drugs like SSRI, TCA, MAOI, cytotoxic drugs, anti-tubercular drugs, steroids were excluded from the study.

Laboratory investigations:-All the patients underwent the following investigations :Hb /TLC/ DLC/Platelet Count, urine c/e, FBS, urea, creatinine, serum bilirubin (total, direct), SGOT, SGPT, ALP, serum protein (albumin/globulin), PTI and INR, ascitic fluid analysis, HBsAg / HCV, ECG, chest X-ray, USG abdomen, serum sodium .

Discussion:-

Hyponatremia is an electrolyte imbalance that commonly occurs in hospitalized patients. Hyponatraemia is defined as a serum sodium level ≤ 136 mEq/L[18] while, in cirrhosis, it has classically been considered relevant only at a serum sodium level <130 mEq/L . Most cases are dilutional hyponatremia caused by the impairment of solute-free water clearance.[19].

Hyponatremia in cirrhosis was first described in the 1950′s, but its importance was overlooked for many years. 30 years later its importance as a predictor for the survival in cirrhosis was investigated.[2] Interest in hyponatremia was fostered by studies in the late 1970s and 1980s indicating that hyponatremia is an important prognostic indicator in cirrhosis.[3]

Studies has shown that severity of hyponatremia is associated with high complications of cirrhosis. In recent years, hyponatremia has attracted interest as apossible prognostic factor for liver cirrhosis. We conducted this prospective study toexamine the frequency of hyponatremia and association between hyponatremia and the occurrence of complications in patients with liver cirrhosis.

Patients were grouped on the basis of serum sodium concentration into three groups: (1) serum sodium <130 meq/l (Group1), (2) serum sodium between 131 - 135 meq/l (Group 2) and (3) serum sodium >135 meq/l (Group3). The patients with hyponatraemia Group1 (<130 meq/l) and group 2 (131-135meq/l) were compared with group 3 (>135 meq/l) for the serum bilirubin, serum albumin, prothrombin time, degree of ascites and hepatic encephalopathy (child pugh score) .

TABLE : Comparison of studies for prevalence of hyponatremia:-

Studies	<130 meq/L	131-135 meq/L	>135meq/L
Present study (n=60)	36.7%(22/60)	30%(18/60)	33.3%(20/60)
Angeli P et al (n=997)	21.6% (211/997)	27.8% (275/997)	50.6%(497/997)
Jong Hoon Kim et al (n=188)	27.1% (51/188)	20.8% (39/188)	52.1% (98/188)
Shaikh S (n=217)	26.7% (58/217)	24.9% (54/217)	48.4%(105/217)

Angeli P et al conducted multi-center study in overseas countries, 997 patients with liver cirrhosis and concurrent ascites, were assigned to three groups based on serum sodium concentration, in a manner similar to that of the current study. The prevalence of hyponatremia at a serum sodium ≤135 meq/L, >135meq/L was 49.4%, 50.6% respectively.
Jong Hoon 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) 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 (66.6%) of patients with cirrhosis had values of serum sodium concentration below the normal range (<135 meq/L) and almost one third (36.7%) had values <130 meq/L. Low serum sodium levels were not associated with age, sex, or etiology of cirrhosis.

Although it is generally believed that the existence of a serum sodium concentration <130meq/L is associated with difficult to treat ascites, few studies have been reported that specifically analyze the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy. Arroyo et al reported that the presence of serum sodium <130 meq/L was associated with lower glomerular filtration rate and solute-free clearance and a poorer response to diuretics compared with patients with serum sodium >130meq/L. Subsequent studies by Bernardi et al and Angeli et al showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics.

TABLE :Comparison of studies on association between hepatic encephalopathy and serum sodium concentration:-

Studies	<130meq/L	131-135meq/L	>135meq/L
Present study(n=60)	21(35%)	3(5%)	1(1.66%)
Angeli P et al (n=997)	38%	24%	15%
Kim JH et al (n=188)	23%	14%	24%

According to Angeli P et al, hepatic encephalopathy was present in 38% of the patients with serum sodium <130 meq/l compared with 24% of patients with serum sodium between 131 and 135 meq/l and 15% of patients had serum sodium levels >135 meq/l. Kim JH et al (2009) showed hepatic encephalopathy was present in 23% of the patients with serum sodium <130 meq/l compared with14% of patients with serum sodium between 131 and 135 meq/l and 24% of patients had serum sodium levels >135 meq/l. Shaikh S et al (2010) showed hepatic encephalopathy was present in 26/217 (11.9%) patients, of which15/58(25.8%) patients were with serum sodium <130meq/l. In present study the frequency of hepatic encephalopathy was associated with serum sodium levels in such a way that 20/34 (59%) patients with serum sodium <130 meq/l had hepatic encephalopathy compared to patients with normal serum sodium concentration 4/46 (8.7%). Patients with serum sodium between 131 and 135 meq/l had lower frequency of encephalopathy 3/18(16.6%) compared to patients with serum sodium <130 meq/l.

TABLE: Comparison of child pugh score with different serum sodium levels:-

Sr No.	Parameter	<130meq/l n=22	131-135 meq/l n=18	>135meq/l n=20	P value
1.	Child pugh score	13.18 ± 1.006	8.28 ± 1.487	6.55 ± 1.050	<0.001
2.	Child pugh class Class A Class B Class C	 0 0 22	 0 16 2	 12 8 0	 <0.001

In the present study ,group 1 and group 2 was compared with group 3 for child pugh score and it was found out that the child pugh score was significantly different for all the three groups .

Thus we conclude that hyponatremia in cirrhosis has been clearly described as an independent risk factor for mortality and is common in patients with end stage liver disease [2,15]. Low serum sodium has been shown to have a

negative impact on the quality of life in patients with cirrhosis and ascites[16]. Hepatic encephalopathy has been shown in several studies to be worsened by the presence of hyponatraemia.

Hyponatraemia with serum sodium _130 mEq/L is one of several predictive factors, along with a history of encephalopathy, serum creatinine and bilirubin, for the development of overt hepatic encephalopathy[17]

Bibliography:-

1. Jay V. The legacy of Laennec. Arch Pathol Lab Med. 2000;124(10):1420–1.
2. Arroyo V, Rodes J, Gutierrez Lizarraga MA, Revert L. Prognostic value of spontaneous Hyponatremia in cirrhosis with ascites. Am J Dig Dis. 1976;21(3):249-56.
3. Llach J, Gines P, Arroyo V, Rimola A, Tito L, Badalamenti S. Prognostic value of arterial pressure, endogenous vasoactive systems and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology. 1988;94(2):482-7.
4. Gines P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, Liard JF, Martin PY, Schrier RW. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology. 1998;28(3):851–64.
5. Angeli P, Wong F, Watson H, Gines P. Hyponatremia in cirrhosis: results of a patient population survey. Hepatology. 2006;44(6):1535–42.
6. Heuman DM, Abou–Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004;40(4):802–10.
7. Gines P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance and management. Hepatology. 2008;48(3):1002–10.
8. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, Navasa M, Claria J, Rimola A, Arroyo V. Incidence, predictive factors and prognosis of hepatorenal syndrome in cirrhosis. Gastroenterology. 1993 Jul;105(1):229–36.
9. Bengus A, Babiuc RD. Hyponatremia – predictor of adverse prognosis in cirrhosis. J Med Life. 2012 June 12;5(2):176–8.
10. Shaikh S, Mal G, Khalid S, Baloch GH, Akbar Y. Frequency of hyponatraemia and its influence on liver cirrhosis-related complications. J Pak Med Assoc. 2010 Feb;60(2):116-20.
11. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis. 2000 Oct;32(7):605-10.
12. Kim JH, Lee JS, Lee SH, Bae WK, Kim NH, Kim KA, Moon YS. The association between the serum sodium level and the severity of complications in liver cirrhosis. Korean J Intern Med. 2009 Jun;24(2):106-12.
13. Martin-Llahi M, Guevara M, Gines P. Hyponatremia in cirrhosis: clinical features and management. Gastroenterol Clin Biol. 2006 Oct;30(10):1144-51
14. Ahluwalia V, Wade JB, Thacker L et al. Differential impact of hyponatremia and hepatic encephalopathy on health-related quality of life and brain metabolite abnormalities in cirrhosis. J Hepatol 2013;59:467–73.
15. Biggins SW, Rodriguez HJ, Bacchetti P et al. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32–39.
16. Sola` E, Watson H, Graupera I et al. Factors related to quality of life in patients with cirrhosis and ascites: relevance of serum sodium concentration and leg edema. J Hepatol 2012;57:1199–206.
17. Guevara M, Baccaro ME, Torre A et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol 2009;104:1382–89.
18. Adrogue´ HJ and Madias NE. Hyponatremia. N Engl J Med 2000;342:1581–89.
19. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis.J Hepatol 2010;53:397–417.