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HYPOKALEMIA IN CIRRHOTIC PATIENTS

(Association of Hypokalemia with Hepatic Encephalopathy in Patients of Cirrhosis of Liver at Tertiary Care Hospital)

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Abstract:

Introduction: *Hypokalemia is a commonly founded electrolyte derangement, associated with hepatic encephalopathy, increased morbidity and mortality, prolonged hospital stay, high economical burden, and major cause of hospitalization in cirrhotic patients.*

Objectives: *To determine the association of hypokalemia with hepatic encephalopathy in patients of liver cirrhosis.*

Material and Methods: *This was a cross sectional research conducted at Department of Medicine Peoples Medical College Hospital Nawabshsah from 1st September 2016 to 31st August 2017 for duration of 01 year. Sample size was 300 subjects. Non-probability convenience sampling technique was applied.*

Liver Cirrhosis was diagnosed on history, clinical examination and confirmed with ultrasound or liver biopsy. Severity of hepatic encephalopathy was assessed with help of its grades on the day of admission and blood samples were sent on the same day to determine the serum potassium levels.

Ethical review committee of Peoples Medical College Hospital Nawabshsah approved the current study. Data was entered and analyzed on SPSS 20 version.

Results: *Hypokalemia was observed in 72% of cirrhotic patients admitted with or without hepatic encephalopathy. Association of hypokalemia with hepatic encephalopathy was significant ($p < 0.05$).*

Conclusion: *Hypokalemia is common and is associated with high rates of hepatic encephalopathy, morbidity and mortality in the cirrhotic patients.*

Key words: *Hypokalemia, Cirrhosis of liver, hepatic encephalopathy.*

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INTRODUCTION:

Cirrhosis is the seventh most common cause of death in both the developed and developing countries. According to the USA data, 26,050 people died during 1987 due to chronic liver diseases, cirrhosis or its complications. Since last two decades, there is rapid increase in the incidence of hepatitis in the world so also the cirrhosis. Economical burden due to disease or its complications has increased manifold [1].

Liver failure results in altered level of consciousness and is called as hepatic encephalopathy (HE) [2]. HE may be sudden or gradual in onset. Movement difficulties, mood or personality changes may be seen with hepatic encephalopathy [3]. HE could be seen in either acute or chronic liver disease. Coma is seen in the advanced stages. Complete blood picture, LFTs, serum electrolytes, urea, urine detailed report and x-ray chest are usually investigations done in these subjects [4]. Gastro intestinal bleeding, constipation, infections, electrolyte imbalance and some medications are the triggering factors for HE [5].

Prevalence of hypokalemia in cirrhotic patients is up to 80% as per international data. Many studies had proved that hypokalemia in cirrhotic patients is associated with increased rate of hepatic encephalopathy, its economical burden, high rates of morbidity, mortality and prolonged hospital stay [6].

Current recommendations for the management of hypokalemia associated with hepatic encephalopathy had proved worthwhile for the reduction in hospital stay, improved health, decreased morbidity and mortality [7].

Excitability of nerve and muscle cells are decreased in hypokalemia; that precipitate lethargy, easy fatigability, lassitude, generalized weakness, fits, coma and death. Correction of hypokalemia has resulted in improvement of overall health of the individuals, decreased economical burden, shortened hospital stay, dynamic health and decrease in the mortality and morbidity [8].

The present research was conducted to establish the association of hypokalemia with hepatic encephalopathy in cirrhotic patients. In current study, hypokalemia was observed in 72% of subjects. It was also observed that there were increased rates of hepatic encephalopathy, prolonged hospital stay, higher rates of morbidity and mortality in cirrhotic subjects with hypokalemia, hence correction of hypokalemia improves the health of patients, decreases hospital stay, mortality and morbidity in these subjects.

MATERIAL AND METHODS:

Sample size: 300 patients with chronic liver disease.

Study Design: This was a Cross Sectional study.

Setting: Current research was conducted in all three units of Medicine at Peoples Medical College Hospital (PMCH) Nawabshah; each medical unit consists of 60 beds. PMCH is 875-beded hospital, located in the centre of the Sindh province of Pakistan with tertiary care facilities.

Duration: One-year duration from 1st September 2016 to 31st August 2017.

Inclusion criteria: Subjects with diagnoses of chronic liver disease, with cirrhosis and its complications above the age of 20 years were included.

Exclusion criteria: Subjects with renal failure, recent blood transfusions, major trauma and diabetic ketoacidosis were excluded from study.

Operational Definitions:

Grades of Hepatic Encephalopathy [9]
Grade 0: Normal mental state.

Grade I: Mild confusion, anxiety or depression, slowing of ability to perform mental tasks (addition/subtraction).

Grade II: Drowsiness, lethargy, gross deficit in ability performs mental tasks. Personality changes and inappropriate behavior. Intermittent disorientation and Lack of sphincter control.

Grade III: Confused, arousable, somnolent, Persistent disorientation and inability to perform mental, tasks from time and place.

Grade IV: Coma with (iv a) or without (iv b) response to painful Stimuli.

Hypokalemia can be divided into three types:

Mild: When the serum potassium ranges from the 3.5 – 3 mEq/l.

Moderate: When the serum potassium ranges from 3-2.5mEq/l.

Severe: When the serum potassium level falls below 2.5mEq/l.

Subjects of chronic liver disease that admitted in the ward with ascites, generalized muscle weakness, fatigability, lassitude, confusion, delirium, psychosis, hallucination depression, persistent constipation, excessive somnolence, inability to perform the mental tasks of the daily life, altered mental behavior and failure to improve from hepatic encephalopathy should be suspected for hypokalemia.

Data Collection:
Ethical review committee of Peoples Medical College Hospital Nawabshsah approved the current study. Cirrhosis was diagnosed on history, clinical examination and confirmed with ultrasound of liver. Simultaneously severity of hepatic encephalopathy was assessed with help of its grades at the time of admission and blood samples were sent to determine the serum potassium levels.

Rao software for sample size calculation with 90% confidence level and 4.75% margin of error was used at the population of 1600000 with 50% distribution response rate.
All patients were investigated as mentioned in the protocol. Stages of hepatic encephalopathy were done. Treatment started after getting the results of serum electrolytes.

After confirming the diagnosis of hypokalemia, route of treatment depended upon the stage of hepatic encephalopathy. Potassium salt was given for three to five days depending up on the response of the patient. Response was assessed in context of the improvement of stage of hepatic encephalopathy, lethargy, lassitude, generalized muscle weakness etc. The cirrhosis is a continuously progressive disease and complications do not halt. Patient needs continuous treatment so therefore recurrence of hypokalemia was quite common.

DATA ANALYSIS:
SPSS software version 20.0 was used for analysis of collected data. Categorical variables like gender, presenting complains, frequency of hypokalemia, anemic status and outcome were computed for frequency and percentage. Mean ± SD, 95% CI (confidence interval), and median with interquartile range were computed for quantitative variables like age, pulse, SBP, DBP, serum potassium, serum sodium, bilirubin (total), SGPT, alkaline phosphate and gama GT.

Chi-square test with significant $P<0.05$ were performed to observe the association of hypokalemia and hepatic encephalopathy.

RESULTS:
Current study was consisted on total 300 diagnosed cirrhotic subjects with and without hepatic encephalopathy, with average age of 46.8±15.13 years. Minimum and maximum age ranged between 20 and 70 years. (Table 1) Mean with standard deviation, 95% confidence level and median with IQR of different variables of study such as; pulse, SBP, DBP, serum potassium, serum sodium, bilirubin (total), SGPT, alkaline phosphate and gamma GT are presented in **Table 1.**

In present study descriptive statistics of cirrhotic with hypocalemia were shown in table 2. It was consisted of total 216 / 300 diagnosed cirrhotic subjects with hepatic encephalopathy, with average age of 46.8±15.8 years. Minimum and maximum age ranged between 20 and 70 years. Mean with standard deviation, 95% confidence level and median with IQR of different variables of study such as; pulse, SBP, DBP, serum potassium, serum sodium, bilirubin (total), SGPT, alkaline phosphate and gamma GT are presented in **Table 2.**

In current study 51% (153) male and 49% (147) subjects were female with male to female ratio of 1.04:1. Regarding the serum potassium levels it was normal (3.5-5.5 mEq/l) in 27%, hypokalemia (<3.5 mEq/l) in 72% and hyperkalemia (>5.5 mEq/l) was noted in only 01.0% of subjects respectively. In subjects with hypokalemia females were dominant with 53% as compared with male males. **(Figure 1)**

Table 3 shows the frequency of clinical features in cirrhotic patients with and without hypokalemia. Symptom analysis of study subjects show that abdominal distension was the most common presenting feature and observed in 123 (41%), followed by HE with different grades in 75 (25%) subjects. Fever was noted in 36 (12%), vomiting in 21 (7%), melena in 18 (6%), shortness of breath in 15 (%%), edema in 9 (3%) and hepatosplenomegaly in 3 (1%) of subjects respectively. Abdominal pain was observed in 90 (41.7%), HE in 66 (30.6%). Melena was observed in 15 (6.9%), fever, breathlessness and vomiting in 12 (5.6%) subjects each while edema in 6 (2.8%) and hepatomegaly in 3 (1.4%) respectively**.(Table 3)**

Prevalence of hepatic encephalopathy was noted in 207 (69%) and 93 (31%) subjects were without hepatic encephalopathy. Most of the subjects in hepatic encephalopathy had hypokalemia as; 81/90 (90%), 69/84 (23%), 21/30 (7%) and 0/3 (0%) in grade 1 through grade 4. Cirrhotic patients with normal serum potassium levels also had hepatic

encephalopathy (all grades) with a frequency of 9/90 (10%), 15/84 (17.9%), 9/30 (30%) and 3/3(100%) respectively where as none of the subjects with hyperkalemia had hepatic encephalopathy. **(Table 4)**

Outcome of cirrhotic patients in current study observed that a large no of subjects 207/300 (69%) improved, out of them 144/207 (69.6%) had hypokalemia, 60/207 (28.9%) had normal potassium levels and 3/207 (1.5%) had hyperkalemia, 57/300 (19%) subjects expired, from which 36/57 (63.2%) had hypokalemia and 21/57(36.8%) were with normal serum potassium levels. 36/300 (12%) subjects leave without medical advice and all of them were hypokalemic. **(Table 4).**

Table 1: Descriptive Statistics of Study Variables. n= 300

Variables	Mean ± SD	95%CI	Median(IQR)
Age (Years)	46.81±15.13	43.81 to 49.8	45(20)
Pulse (per min)	97.46±13.47	94.78 to 100.2	100(16)
SBP (mm Hg)	106.71±52.24	96.34 to 117.1	100(20)
DBP (mm Hg)	65.10±12.35	62.65 to 67.6	60(10)
Serum Potassium	3.11±0.70	2.98 to 3.25	3(0.8)
Serum Sodium	130.8± 7.32	129.38 to 132.3	130(14)
Bilirubin Total	5.81±3.28	5.16 to 6.47	5.1(4.1)
SGPT	271.9±231.9	225.97 to 318.0	219(238)
Alkaline Phosphate	454.04±308.7	392.46 to 515.6	366(321)
Gama GT	103.02±57.53	91.60 to 114.4	88(44)

SBP= Systolic blood pressure, DBP= Diastolic blood pressure.

Table 2: Descriptive Statistics of Cirrhotic Patients with Hypokalemia n= 216/300

Variables	Mean ± SD	95%CI	Median(IQR)
Age (Years)	46.61 ± 15.8	42.87 to 50.34	45(25)
Pulse (per min)	96.38 ± 12.5	93.43 to 99.3	98(10)
SBP (mm Hg)	108.61 ± 61.6	94.02 to 123.2	100(20)
DBP (mm Hg)	64.23 ± 12.9	61.16 to 67.3	60(10)
Serum Potassium	2.783 ± 0.3	2.70 to 2.86	3(0.6)
Serum Sodium	130.0 ± 7.3	128.33 to 131.7	130(12)
Bilirubin Total	5.78 ± 3.3	5.0 to 6.56	5(4.8)
SGPT	266.1 ± 249	207.15 to 325	218(225)
Alkaline Phosphate	432.7 ± 321.8	356.6 to 508.9	327(286)
Gama GT	100.8 ± 58.6	87.0 to 114.75	87(39)

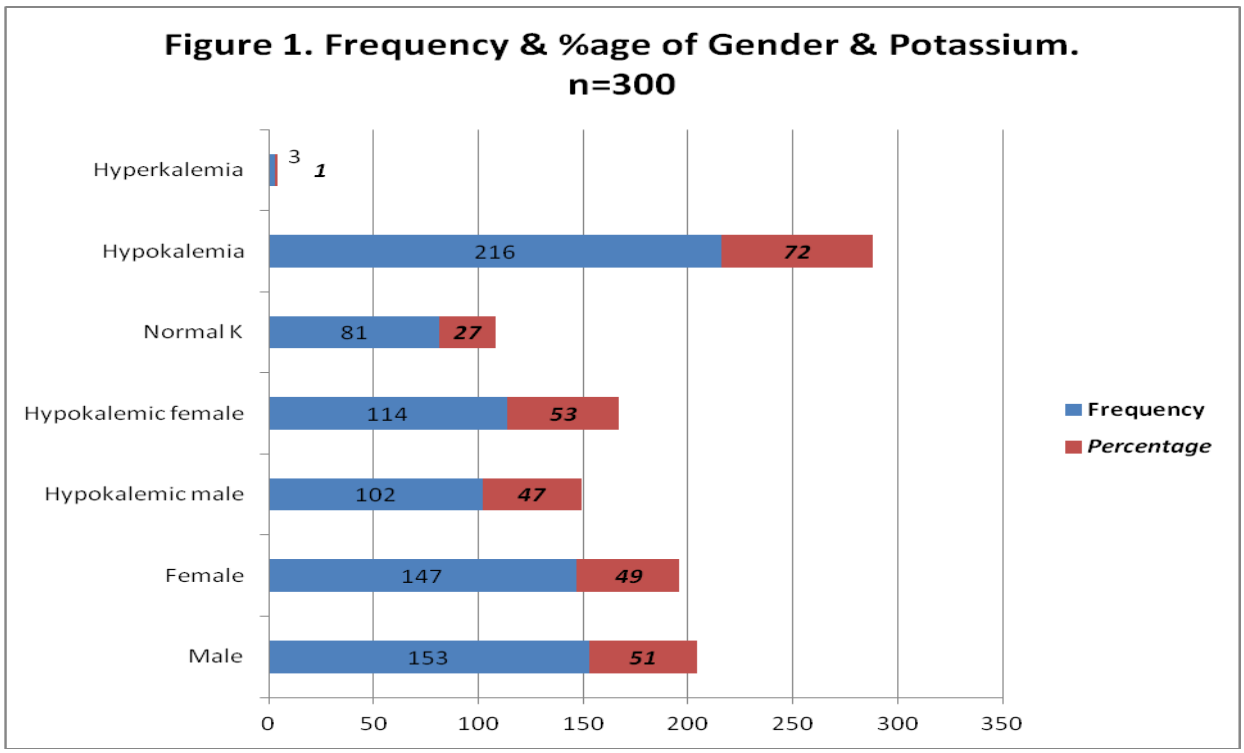

Table 3: Presenting Complaints in Cirrhotic Patients.

PRESENTING COMPLAINTS OF CIRRHOTIC PATIENTS. n=3OO		
Presenting Complain	Frequency of patients	Percentage
Abdominal Distention	123	41%
Hepatic Encephalopathy	75	25%
Fever	36	12%
Vomiting	21	7%
Melena	18	6%
Breathlessness	15	5%
Edema	9	3%
Hepatomegaly	3	1%
PRESENTING COMPLAIN OF CIRRHOTIC PATIENTS WITH HYPOKALEMIA n=216/300		
Abdominal Distention	90	41.7%
Hepatic Encephalopathy	66	30.6%
Fever	12	5.6%
Vomiting	12	5.6%
Melena	15	6.9%
Breathlessness	12	5.6%
Edema	06	2.8%
Hepatomegaly	03	1%

Table 4: Association of Hypokalemia with Hepatic Encephalopathy & Outcome in Cirrhotic Patients

ASSOCIATION OF HYPOKALEMIA WITH HEPATIC ENCEPHALOPATHY. n=300				
Grade of Hepatic Encephalopathy	**Hypokalemia**	**Eukalemic**	**Hyperkalemic**	**Total**
Grade 0	45(48.4%)	45(48.4%)	3(3.2%)	**93**
Grade 1	81(90%)	9(10%)	0(0%)	**90**
Grade 2	69(82.1%)	15(17.9%)	0(0%)	**84**
Grade 3	21(70%)	9(30%)	0(0%)	**30**
Grade 4	0(00%)	3(100%)	0(0%)	**3**
OUTCOME OF CIRRHOTIC PATIENTS. n=300				
Improved	144(69.6%)	60(28.9%)	3(1.5%)	**207**
Expired	36(63.2%)	21(36.8%)	0(0%)	**57**
Lama	36(17%)	0(0%)	0(0%)	**36**

Pearson Chi-Square = 18.44 df=8 p=0.018, Likelihood Ratio = 18.79 df= 8 p=0.016, 8 cells (53.3%) have expected count less than 5. The minimum expected count is .01. Recoded to avoid small cell numbers. Due to above condition of 8 cell, merge Grade 3 and 4 and Eukalemic and Hyperkalemic so Pearson Chi-Square = 13.27 df=3 p=0.004, Likelihood Ratio = 13.51. df= 3 p= 0.004

DISCUSSION:

Hypokalemia is a serious complication of cirrhosis, its treatment or due to its complications. According to international data, 50-80% of patients with treatment for cirrhosis and its complications develop hypokalemia. In current study, hpokalemia was observed in 72% of cirrhotic subjects that is similar to international data. Diverse studies has been done on the cirrhosis, its complications, spontaneous bacterial peritonitis or other aspects of the disease, while at the country level henceforth there is no available data on the potassium level in the context of adult medicine especially for the cirrhotic patients.

Hypokalemia results due to the movement of potassium from intracellular to extracellular stores. Extracellular hydrogen moves into the cells to maintain Electroneutrality, thus ammonia production increases due to intra cellular acidosis in renal tubular cell. The conversion of ammonium ($NH4^+$) is promoted by concomitant contribution of metabolic alkalosis; NH4+ is a charged element that cannot cross the blood brain barrier, while ammonia can enter the brain.

Use of diuretics can result in hypokalemia in subjects with chronic liver disease and ascites. It is needed that larger multi center studies be conducted to observe the involvement of these factors in producing the hypokalemia. Along with diuretics, other factors like; constipation, electrolyte abnormalities, bleeding from gastrointestinal tract come across as common triggers observed in large no of cirrhotic subjects. In majority of patients, usually a specific clinical or biochemical abuse is noted, but in less than 10% of subjects, more than one causative agent may be observed. Excess protein use with constipation, benzodiazepines in GI bleeding and large volume paracentesis also contribute for hypokalemia. [10]

Gaduputi V, investigated the prognosticate outcomes of hypokalemia in hepatic encephalopathy. Potential prognostic variables such as serum pH, systemic vascular resistance (SVR) and serum ammonia levels were also observed in subjects with low and normal potassium levels. Stay in the hospital (P Value= 0.0001) and ICU (P Value= 0.0003) were significantly longer among the subjects with hypokalemia (< 4mEq/L). Statistically significant correlation among serum potassium level and duration of hospital and ICU stay was observed.[11]

In subjects with ascites secondary to chronic liver disease on diuretic therapy; hypokalemia and

hyponatremia both were observed, in addition alkalosis , hypoxia, dehydration were also contributing factors. [12,13]

Ahmed et al[14] and Mehboob F. [15] had established association of hypokalaemia with Gastro Intestinal bleeding. In 34% subjects hypokalemia was noted and most patients had mild category of hypokalemia. Different other studies conducted from different areas had demonstrated hypokalemia in cirrhotic subjects ranging from 33% to 68%. [16-18]. Mumtaz K et al found Hypokalamia in 6.4% in patients suffering from liver diasese. [19]

Hypokalamia was found in 18% Alam I et al, 14% Ahmed I et al,11% Souheil Abu-Assi et al,18% Fallon WW et al and 9% in a study conducted by Conn HO et al. Many other studies conducted worldwide had shown variable frequency of hypokalemia in subjects suffering from chronic liver disease with complications or with treatment. [19] [20-24]

As the cirrhotic patients present with constellation of symptoms due to disease or its' complications which include hypokalemia, appropriate symptoms of hypokalemia cannot be separated but in suspected cases be confirmed by assessing low potassium levels with help of serum analysis for electrolytes.

In recent study 72% subjects of chronic liver disease were found hypokalemic, among them 25% had the symptoms of hepatic encephalopathy that validates the strong association of hypokalemia with hepatic encephalopathy. From 300 study subjects 69% patients were discharged after improvement, 19% patients expired whom 63% were hypokalemic and 36 subjects that all were hypokalemic left without medical advice.

Clinical features of subjects like; generalized weakness, lassitude, lethargy, and easy fatigability they improved with correction of the hypokalemia. The cirrhosis remains uncured and is progressive disease, and needs continuously diuretics, laxatives and other drugs for the treatment that make the person prone to develop hypokalemia. The need of diuretics should be assessed periodically, potassium rich diet should be advised, and potassium-sparing diuretics, angiotensin enzyme inhibitors or angiotensin receptor blockers are considered as the substitute if required. At least, periodic adequate potassium supplement should be ensured.

LIMITATIONS

No study was done at the country level that evolved uncertainty regarding hypokalemic status in the region; on the contrary, disease prevalence is more common. Abundance of studies have been done internationally which help and encourage for hypokalemic prevalence and its' complications in patients of cirrhosis.

CONCLUSIONS:

1. Prevalence of hypokalemia is quite high in hospitalized cirrhotic patients. Index of suspicious should be high to make an early diagnosis.
2. Serum potassium (electrolytes) analysis should be advised to all indoor patients of cirrhosis, encephalopathy due to cirrhosis or other suspected symptoms of hypokalemia.
3. Early diagnosis and prompt correction of hypokalemia decreases the expenses of the drugs, quickens the health improvement hence reduces morbidity and mortality.

RECOMMENDATIONS:

The results of this study were much encouraging which not only conformed to the international data but also proved helpful in managing our seriously morbid patients.

As the incidence and prevalence of cirrhosis is increasing in our society, so the economical burden and complications are also increasing. Hence, all the cirrhotic patients need complete thorough investigations for their proper management.

Electrolyte assessment should be considered in all the patients of cirrhosis admitted in the hospital so that patients can be helped from developing hypokalemia and related complications.

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