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RISK FACTORS FOR HYPERKALEMIA IN CIRRHOTIC PATIENTS RECEIVING SPIRONOLACTONE.

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ABSTRACT… Objectives: To determine the factors those may predict hyperkalemia in cirrhotic patients receiving spironolactone. **Study Design:** Cross sectional descriptive study. **Setting:** Medicine Department Shalamar Hospital, Lahore. **Period:** 15 days from 1st September to 15th September 2017. **Materials & Methods:** 150 patients with documented liver cirrhosis, receiving spironolactone and fulfilling the inclusion criteria were made part of the study. Five mL blood was drawn in two different vials; 2 mL in EDTA vial to check the prothrombin time (PT) and 3 mL in clotted vial to measure serum potassium, sodium, creatinine, urea, albumin, and bilirubin in serum after centrifugation. Potassium level was measured at baseline (Day-0) and two weeks later after receiving spironolactone. **Results:** Patients with raised serum creatinine (>1.3 mg/dL) and hyperbilirubinemia (>2.8 mg/dL) were found to have serum potassium more than 5 mmol/L. Increased potassium levels were found in patients receiving high dosage of spironolactone (>100mg/day). These patients had decompensated liver cirrhosis as evident from their child-class C and significant hypoalbuminemia. **Conclusion:** Decompensated cirrhotic patients with raised serum creatinine, hyperbilirubinemia, hypoalbuminemia and receiving high dosage of spironolactone remain at higher risk of developing hyperkalemia.

Key words: Cirrhosis, Hyperkalemia, Spironolactone.

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INTRODUCTION

Liver cirrhosis is characterized by fibrosis and regenerative nodules leading to vascular distortion. Statistical data from United States shows that it is the 10th leading cause of overall deaths including 400,000 hospitalizations and 27,000 deaths annually. It has a mortality rate above 50% without liver transplantation.[1-3]

The etiology of liver cirrhosis is multi-factorial. It can be due to viral hepatitis, excessive alcohol intake, metabolic illnesses (e.g. alpha-1 antitrypsin deficiency), primary biliary cirrhosis and congestive cardiac failure.[4] Chronic liver disease affects various types of liver functions including storage of fat soluble vitamins (A, D, E, K), hypoalbuminemia (causing peripheral edema and ascites), coagulopathy (due to deficiency of vitamin K dependant clotting factors) and loss of detoxification ability of the nitrogenous waste products.[5-8]

Hyperkalemia is defined as "serum potassium level>5mm ol/L".[9] It is more prevalent in patients with end stage renal disease (5-10%) carrying 2-5% mortality rate.[10-13] Etiology of hyperkalemia is multifactorial; it may be due to kidney dysfunction, metabolic acidosis, complicated diabetes mellitus, inter-compartmental shift (e.g. insulin deficiency), high dietary intake of potassium and use of drugs reducing urinary potassium excretion.[14-16] Raised serum potassium and urea/creatinine are the major markers of renal dysfunction in cirrhotic patients.[17]

With the falling of glomerular filtration rate (GFR), urinary potassium excretion is also markedly decreases and as a result plasma potassium level rises.[18] Renal perfusion is markedly reduced in cirrhotic patients that cause increase in re-absorption of sodium and water (27). This leads to increase in aldosterone secretion and as a result potassium is retained and sodium is excreted.[19]

Acute hyperkalemia is more fatal as it can cause cardiac arrhythmias.[20]

No much data is available regarding the risk factors for hyperkalemia in cirrhotic patients but studies in congestive cardiac failure and chronic kidney disease suggest that old age, deranged renal profile, excessive dietary potassium, cardiac decomposition and use of angiotensin converting enzyme inhibitors (ACEI) are the important risk factors.[21-24] Although spironolactone is the most widely used diuretic in cirrhotic patients having ascites but it can lead to hyperkalemia by its anti-aldosterone mechanism, which in turn leads to high morbidity and mortality in these patients.[25,26]

Present study was also conducted to see the impact of different risk factors on hyperkalemia in cirrhotic patients. These findings may help in early detection of hyperkalemia development.

MATERIAL & METHODS

This cross sectional descriptive study was carried out in the medicine department Shalamar Hospital, Lahore. Sampling was done by non-probability consecutive sampling method. Sample size 150 was distributed in hyperkalemic (group I with raised potassium level) and normokalemic groups (group II with normal serum potassium) with 95% confidence interval and 90% power of test with an expected odds ratio for ascites, 3.5% for hyperkalemic group and 62% exposure to ascites in normokalemic group.

A total of 150 patients with age range of 30-70 years, having sonographically documented liver cirrhosis (regardless of etiology) and at least from two weeks on spironolactone were included in the present study. Patients were excluded from the study if they had chronic renal failure or taking angiotensin converting enzyme inhibitors.

After ensuring the confidentiality of their personal information and taking care of ethical aspects, various parameters such as child Pugh score, total bilirubin and blood pressure were measured. After informal consent, 5mLof venous blood sample was drawn in two different vials from cubital vein applying proper antiseptic measures. Two mL blood was taken in EDTA vial to check the prothrombin time (PT) and 3 mL in clotted vial to measure serum potassium, sodium, creatinine, urea, albumin, and bilirubin in serum after centrifugation. To see the variation in blood potassium level before and after using the spironolactone, two different dosages of spironolactone (>100 mg/day and <100 mg/day) were used in present study to find its affect in hyperkalemia development.

Using SPSS v23.0 for data analysis, qualitative variables like gender, ascites etc. were expressed in percentages and frequencies, while Quantitative variables i.e. albumin, creatinine etc. were expressed as Mean ± SD. Chi-square test was applied for comparison of nominal variables. Confidence interval was taken as 95 %/ and dependent sample t-test was applied to the two potassium values.

RESULTS

A total of 150 patients suffering from decompensated liver disease were entitled to be part of the present study. Patients were placed in group-1 and group-2. Mean age of group-1and group-2 patients was 53.29±10.09 and 51.69±10.14 years respectively. In group-1, 52(69.30%) patients were male and 23(30.70%) were female and in group-2 the participation of male and female patients was 52(69.30%) and 23(30.70%) respectively.

In group-1 and group-2, the ratio of cirrhotic patients with ascites (clinically and sonographically) was 55(73.30%) and 16(21.30%) respectively. In group-1; child- class category A, B and C of liver disease was examined in 12(16%), 29(38.67%) and 34(45.33%) patients respectively. In group-2, the ratio of child-class category A, B and C was 56(74.67%), 10(13.33%) and 9(12%) as revealed in table-I. In group-1, 59(78.66%) patients were receiving spironolactone more than 100 mg/day and 16(21.33%) less than 100 mg/day while, in group-2, 21(28%) and 54(72%) patients received high and low dosage of spironolactone respectively (Table-II).

The serum creatinine level of most of the

hyperkalemic patients (Group-1) was higher 63(84%) in the present study as compared to normokalemic patients 7(9.33%) (Group-2) as depicted in Table-III. As shown in Table-IV, the bilirubin level was also found higher in most of the group-1 patients 54(72%) as compared to normokalemic patients 39(52%) of this study.

When we compared baseline (Day-0) mean values of serum potassium with 2 weeks post spironolactone therapy mean values of the patients, there was statistically significant difference (Table-V). Patients with raised bilirubin and creatinine levels in the serum were noted to have significantly raised serum potassium level (p=0.020 and 0.001 respectively). They also had significantly low albumin (p value=0.018) (Table-VI) and had decompensated liver disease as evident from child class c (p= 0.000).

Child-Pugh Class	Hyperkalemia (Group-1) (n=75)	Normokalemia (Group-2) (n=75)	P-Value
A	12(16%)	56(74.66%)	0.000
B	29(38.67%)	10(13.33%)	
C	34(45.33%)	9(12.00%)	

Table-I. Comparison of child-pugh class.

Dosage	Hyperkalemia (Group-1) n=75)	Normokalemia (Group-2) (n=75)	P-Value
>100 mg/day	59(78.66%)	21(28.00%)	0.000
<100 mg/day	16(21.33%)	54(72.00%)	

Table-II. Impact of spironolactone dosage on serum potassium.

Serum Creatinine	Hyperkalemia (Group-1) (n=75)	Normokalemia (Group-2) (n=75)	P-Value
>1.3 mg/dL	63(84.00%)	7(9.33%)	0.000
<1.3 mg/dL	12(16.00%)	68(90.66%)	

Table-III. Impact of raised serum creatinine on serum potassium.

Serum Creatinine	Hyperkalemia (Group-1) (n=75)	Normokalemia (Group-2) (n=75)	P-Value
>2.8 mg/dL	54(72%)	39(52%)	0.000
<2.8 mg/dL	21(28%)	36(48%)	

Table-IV. Impact of serum bilirubin levels on serum potassium.

Serum Potassium Levels	n	Mean value	Std. Deviation	Std. Error Mean	P-Value
Baseline (Day-0)	150.00	5.03	1.76	0.14	0.000007
After 2 weeks of therapy	150.00	3.10	1.70	0.14	

Table-V. Comparison of means of serum potassium.

Serum Albumin	Hyperkalemia (Group-1) (n=75)	Normokalemia (Group-2) (n=75)	P-Value
<2.5mg/dl	52(69.33%)	23(30.67%)	0.018
>2.5mg/dl	38(50.67%)	37(49.33%)	

Table-VI. Impact of serum albumin levels.

DISCUSSION

Hyperkalemia in patientswith liver cirrhosis is not the commoncomplication unless the patient isconcurrently using drugs such as potassium-sparing diuretics e.g. spironolactoneor ACEI.[30,31] This is further potentiated by excessive dietary potassiumintake and renal dysfunction with falling glomerular filtration rate.[30] Severe and life threatening hyperkalemia may occurin the setting of metabolic acidosis secondary to end-stage liver disease.[28] Therefore, it was extremely vital to identify the risk factors leading to hyperkalemia in these patients**.**

In our findings Child-Pugh class B and C were the most prominent risk factors for hyperkalemia development. Mainly the hyperkalemia was observed in Child-Pugh class C liver cirrhotic patients followed by Child-Pugh class B. In Child-Pugh class C, 45.33% patients developed hyperkalemia, while in Child-Pugh class B the percentage of hyperkalemic patients was 38.67%. The same situation was also observed in liver cirrhotic patients in previous study.[29] It was evident from that study that the incidence of hyperkalemia was more in cirrhotic patients. Raised baseline serum potassium level and higher Child-Pugh class (child class C) were independent risk factors for the development of hyperkalemia in those patients.

Cirrhotic patients with high serum potassium level, raised BUN and creatinine levels, hyperbilirubinemia, hypoalbuminemia, hyponatremia, decompensate liver status and receiving spironolactone dosage >100mg/ dayalways remain at high risk to develop hyperkalemia.[3,6] In present study, we also found that hyperkalemia developed in most of the patients with decompensated liver disease (as evident from Child-Pugh class C) and raised creatinine and bilirubin levels. These patients also had hypoalbuminemia and were receiving spironolactone >100mg/day. Previously, hyperkalemic episodes were also noted in hospitalized patients with advanced liver cirrhosis.[8] Common co-morbiditiesin those patients were chronic kidney disease, diabetes mellitus, hypertension, heart failure and ischemic heart disease. Acute renal dysfunction and metabolic acidosis were the common metabolic abnormalities found in those patients. Out of those patients, 88.01% were receiving at least one drug which can alter serum potassium level. It indicates that to avoid hyperkalemia with raised creatinine and bilirubin levels and had Child-Pugh class B or C special care is needed before starting potassium-sparing diuretics e.g. spironolactone or ACEI.

In conclusion, the findings of present study revealed that the chances of hyperkalemia development in ascites patients with liver cirrhosis increases if they are with raised creatinine and bilirubin levels and also belong to Child-Pugh class B or C. Before starting potassium-sparing diuretics in these patients special care is needed. High dosage of potassium-sparing diuretics e.g. Spironolactone or ACEI may also increase the chances of hyperkalemia and it may cause end stage liver complication in these patients.

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2	Sajjad Iqbal	Statistical analysis, Tables and figures preparation, manuscript design, references style.	
3	Muhammad Haroon Yousuf	Final review and approval.	
4	Naseer Nazeer Memon	Data collection.	
5	Sajid Iqbal	Proof reading.	