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DIAGNOSTIC USEFULNESS OF THE RANDOM URINE NA/K RATIO IN PREDICTING THERAPEUTIC RESPONSE FOR DIURETICS IN CIRRHOTIC PATIENTS WITH ASCITES

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Abstract

Ascites is a major complication of liver cirrhosis which carries a poor prognosis. Diuretics are used in treatment of ascites in addition to salt restriction. Monitoring of diuretic response can be achieved by measurement of 24 hours urinary sodium.

This study evaluated the accuracy of using spot urinary sodium/potassium ratio as a reliable alternative to 24 hours urinary sodium in assessment of dietary sodium compliance in patients with liver cirrhosis receiving diuretics.

Fifty patients presented with liver cirrhosis and ascites were divided into 2 groups: GI 14 (28%) patients diuretic resistant with 24 hours urinary sodium < 78 mEq) and GII 36 (72%) patients diuretic sensitive with 24 hours urinary sodium > 78 mEq.

The results showed highly significant correlation between 24 hours urinary sodium and spot urine sodium/potassium ratio with sensitivity 87.5% specificity 56% and accuracy 70% at cutoff point of 1.8.

Key words: Cirrhotic patients, Ascites, Therapeutic response, Urine Na/K Ratio

Introduction

Liver cirrhosis is a common problem in Egypt (Strickland**,** 2006) due to prevalence of hepatitis C virus (Wahib *et al*, 2006). Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), portal hypertension, variceal bleeding and hepatorenal syndrome (HRS) (Heidelbaugh and Sherbondy, 2006). Ascites is a condition of pathologic fluid collected within the abdominal cavity (Ginès and Cárdenas, 2008). It is estimated that about 50% of patients with compensated cirrhosis will develop ascites within 10 years of observation (Ginés *et al*, 1987). The development of ascites in patients with liver cirrhosis is associated with poor prognosis and an increased risk of mortality, as approximately 50% of patients with ascites are expected to die within 2 years (D'Amico *et al*, 1986).

The development of ascites is secondary to renal retention of sodium and water because of underlying activation of neurohormonal mechanisms (Yu and Hu, 2001). Thus, patients who accumulate ascites have urinary excretion of

sodium that is significantly lower than their dietary salt intake. This means that, in order to achieve successful ascites mobilization, patients should have a negative sodium balance. This can be achieved through education regarding dietary sodium restriction, in addition to oral diuretic therapy (Ginès *et al,* 2004).

Limiting sodium intake to 2 grams per day (including all foods and medications) is the most important step. Thus is to counteract the central problem of sodium retention (Runyon *et al,* 1989).

Diet alone is useful only in a small number of patients; hence diuretics are very important for urinary sodium loss of more than 78 meq/day. Most patients with cirrhosis and fluid overload are treated with a combination of dietary sodium restriction and diuretics. This approach is effective in approximately 90% of patients and 10% are considered diuretic-resistant and second-line therapy is indicated for ascites mobilization (Cárdenas and Ginès, 2005).

However, patients who are not compliant with diet may also show inadequate response to maximum diuretic doses. Assessment of dietary compliance is important in order to avoid mislabeling patients with refractory ascites, while their problem is inadequate dietary salt restriction (Ginès and Cárdenas, 2008).

Monitoring of cirrhotic patients with ascites usually requires 24h urine collection to evaluate urinary sodium secretion. However, the main problem here is that it may be difficult for the patient to accurately collect 24 h urine. Spot urine Na+/K+ ratio has been proposed as an accurate alternative measurement to detect diuretic-sensitive (DS) patients (excretion > 78 mmol of sodium per day), when the ratio more than a given cut value (one in some studies) is equivalent to 24 h sodium more than 78 mmol Na/day (Metaxaki *et al*, 2003).

The aim of this work was to evaluate the accuracy of using spot urinary sodium/ potassium ratio as a reliable alternative to 24 hours urinary sodium in assessment of dietary sodium compliance in patients with liver cirrhosis receiving diuretics.

Patients, Materials and Methods

Fifty in-patients with liver cirrhosis and ascites, who received diuretic therapy, were selected from December 2012 and May 2013.

Exclusion criteria: Evidence of renal disease or hepatic encephalopathy, Hypo-natraemia (<120 meq/l), ascites due to causes other than liver cirrhosis or SBP

Patients were subjected to the following: 1- Full medical history taking and thorough clinical examination with special stress on: Symptoms of liver disease, history of ascites and its complications, assessment of compliance to dietary sodium restriction, history of diuretics use, type, dosage and duration and history of complications related to use of diuretics.

2- Laboratory investigations: Complete blood picture, Liver profile: Aspartate aminotranseferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, albumin and prothrombin

time (PT), renal function tests and electrolytes: serum creatinine, blood urea, serum sodium, serum potassium, 24 hours urine sample for calculation of sodium. Samples were collected in labeled sterile plastic containers with recording volume in 24 hours. Verbal instructions were given to assure completeness of collection. Samples were centrifuged to avoid the effect of any pus cells or RBSs if present; Sodium concentration was measured in meq/L. Spot urine sample for measurement of sodium, potassium. Samples were handled as previously described for 24 hours samples except that volume was not recorded as it has no significance in this setting, with Na/K ratio, Ascitic fluid analysis (ascitic fluid albumin, total protein, cytology). 3-Abdominal ultrasound (Nazeer *et al*, 2005)

Statistical analysis: Data was collected, coded and entered to a personal computer (P.C.) IBM compatible 2.6 GHZ, and analyzed with the program (SPSS) statistical package for social science under windows version 11.0.1.

Results

Patients were divided into two groups: GI: 36 patients (72%), diuretic sensitive (DS) with 24 hours urinary sodium more than 78 meq/day with mean age of 52.972±52.972years, GII: 8 patients (28%), diuretic resistant (DR) with 24 hours urinary sodium less than 78 meq/day) with mean age of 50.357±13.431years.

Table 1: Diuretic resistant and sensitive cases as regard mean age.

	Age						T-test	
	Range			Mean	±	SD	t	P-value
GI	35.000	-	68.000	52.972	±	9.229	0.788	0.434
GII	30.000	-	84.000	50.357	±	13.431		

p> 0.05 not significant.

Table 2: Type of used diuretics and Child Pugh class in groups:

Treatment	No.	Percentage
F1S1	17	34.00
F1S2	2	4.00
F2S2	25	50.00
F2S1	2	4.00
Toresemide10 mg	1	2.00
Toresemide20mg	2	4.00
Lasilactone 50 mg	1	2.00

Patients were 26 males (52%) and 24 females (48%), with mean age of 52.24±10.493, 17 patients (34%) were on Frusemide 40mg (F1) and spironlactone 100mg (S1), 25 (50%) on Frusemide 80mg. (F2) and spironlactone 200 mg. (S2), 2 (4%) on Frusemide 40mg. and aldactone 200 mg., 2 (4%) on Frusemide 80 mg. and aldactone 100 mg., 2 (4%) on Toresemide 20 mg., one (2%) on Toresemide 10 mg. and last one (2%) on lasilactone 50 mg.

Table 3: Distribution of Child Pugh class in all patients:

		N	%
Child	B	22	44.00
	C	28	56.00

Table 4: Diuretic resistant and sensitive cases as regards mean Na/K ratio in spot urinary sample

	Na/k ratio						T-test	
	Range			Mean	±	SD	t	P-value
GI	0.700	-	26.900	6.663	±	6.894	1.748	0.087
GII	1.000	-	12.857	3.243	±	3.699		

P>0.05 not significant

Table 5: Diuretic resistant and sensitive cases as regards mean 24 hours urinary sodium

	24 h urinary Na						T-test	
	Range			Mean	±	SD	t	P-value
GI	82.000	-	877.000	209.613	±	190.577	3.322	0.002*
GII	3.300	-	77.000	38.750	±	25.796		

P<0.01 Highly Significant

Table 6: Correlation between 24h urinary Na and Na/K ratio

R	P-value
-0.083	0.573

P>0.05 not significant

Table 7: Comparison between groups as regard blood pictures.

		Range			Mean	±	SD	t	P-value
WBCs	GI	2.700	-	10.900	4.717	±	1.892	0.806	0.424
	GII	1.300	-	7.900	4.236	±	1.898		
Hb	GI	4.100	-	11.000	9.094	±	1.460	1.144	0.259
	GII	6.900	-	10.500	8.586	±	1.193		
PLT	GI	22.000	-	158.000	80.265	±	40.054	- 0.723	0.473
	GII	28.000	-	172.000	89.571	±	41.641		

p>0.05 not significant

Table 8: Coefficient between Na/K ratio and RBCs, WBCs and platelets levels.

Na/k ratio	R	P-value
WBCs	0.138	0.350
RBCs	-0.202	0.206
Hb	0.297	0.047*
PLT	-0.339	0.021*

P>0.05 non-significant, r: correlation coefficient

Mean levels of AST, ALT, INR, total bilirubin, PT were higher in GII than those in GI. None variables reached significant difference between groups except prothrompin time (15.771±2.353 in GI vs. 18.821±3.786 in GI. Mean serum albumin level was lower in GII (2.464mg/dL) than in GI (2.357mg/dL) but difference not significant (P > 0.05).

Table 9: Diuretic resistant and sensitive cases as regard liver profile tests:

		Range			Mean	±	SD	t	P-value
S.Alb	GI	1.600	-	2.800	2.464	±	0.376	-0.782	0.438
	GII	1.600	-	3.500	2.357	±	0.556		
S.bil	GI	0.500	-	5.600	2.231	±	1.198	-0.943	0.350
	GII	0.500	-	5.800	2.643	±	1.801		
PT	GI	10.000	-	25.000	15.771	±	2.353	-3.416	0.001*
	GII	15.000	-	30.000	18.821	±	3.786		
ALT	GI	40.000	-	115.000	82.424	±	22.315	-0.462	0.646
	GII	60.000	-	181.000	86.214	±	32.631		
AST	GI	40.000	-	100.000	69.500	±	16.719	-1.649	0.106
	GII	40.000	-	101.000	78.071	±	15.911		

P>0.05 not significant *P<0.05 Significant

Table 10: Coefficient between Na/K ratio and the liver functions test.

Na/k ratio	R	P-value
S.Alb	0.157	0.293
S.bil	-0.084	0.571
INR	-0.022	0.883
ALT	0.037	0.808
AST	-0.014	0.924

P>0.05 not significant

Table 11: Diuretic resistant and sensitive cases as regards mean kidney function tests and serum electrolytes:

		Range			Mean	±	SD	t -test	P-value
Na	GI	120.000	-	142.000	129.257	±	7.229	2.168	0.035
	GII	120.000	-	140.000	124.231	±	6.870		
K	GI	2.500	-	4.500	3.615	±	0.487	-3.425	0.001
	GII	3.500	-	4.900	4.131	±	0.395		
Creatinine	GI	0.300	-	14.000	1.094	±	2.301	0.370	0.713
	GII	0.500	-	1.500	0.835	±	0.279		
Urea	GI	12.000	-	72.000	33.743	±	15.474	1.490	0.143
	GII	7.700	-	54.000	26.550	±	14.714		

P>0.05 not significant

Table 12: Coefficient between Na/K ratio and kidney function tests, sera of both

Na/k ratio	R	P-value
Na	0.199	0.184
K	-0.066	0.661
Creatinine	-0.120	0.436
Urea	-0.009	0.954

P>0.05 not significant

Table 13: Diuretic resistant and sensitive case as regards Child classification

Child	GI		GII		Total	
	No.	%	No.	%	No.	%
B	20	55.56	2	14.29	22	44.00
C	16	44.44	12	85.71	28	56.00
Total	36	100.00	14	100.00	50	100.00
X^2	7.648					
P-value	0.006*					

P<0.01 highly significant

Figure 1: ROC curve for best cutoff point to differentiate between diuretic sensitivity and resistance using spot urine Na/K ratio

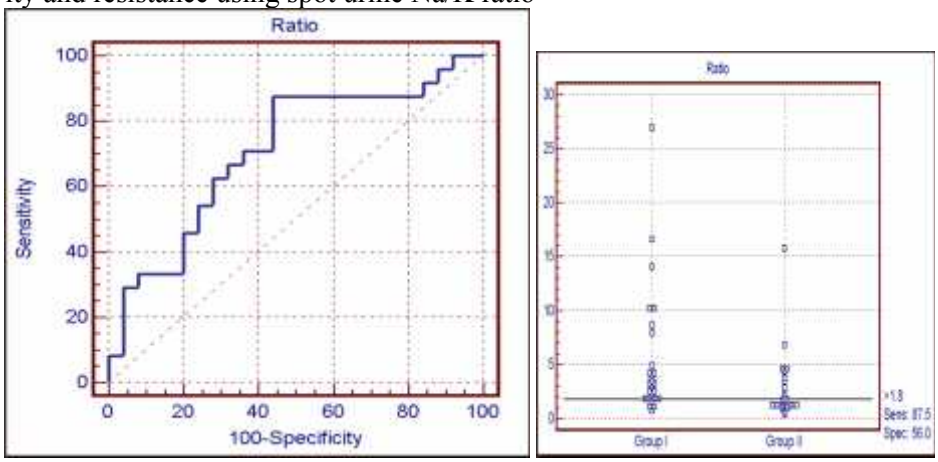

Table 14: Sensitivity, specificity, positive and negative predictive values and accuracy of best Na/K ratio cutoff point to determine diuretic resistance or sensitivity

ROC curve between GI and GII as regard Na/K Ratio					
Cutoff	Sensitivity	Specificity	+ve predictive value	-ve predictive value	Accuracy
> 1.787	87.5	56.0	65.6	82.4	0.708

Discussion

Ascites is a major complication of cirrhosis, occurring in 50% of patients over 10 years of follow up. The development of ascites is associated with 50% mortality over two years, and signifies the need to consider liver transplantation (Moore *et al,* 2003). The usual treatment for ascites in patients with cirrhosis is dietary sodium restriction and diuretics (Moore and Aithal, 2006).

The most accepted diet compliance one is collection of 24 hours urinary sodium. Patients with 24 hours urinary sodium excretion exceeding 78 mEq should be losing weight and if they are not responding then dietary sodium restriction should be the next step not increasing the diuretic dose or labeling as refractory ascites (Runyon, 2004).

This study evaluated the accuracy of using spot urinary sodium/potassium ratio as an alternative to 24 hours urinary sodium in assessment diuretic response in cirrhotic patients and ascites.

In this study, patients were divided into two groups according to 24 hours urinary sodium excretion, those with sodium less than 78mEq/24 hours were labeled as diuretic resistant and those with more than 78mEq as diuretic sensitive group.

In the present study, patients in diuretic resistant group were 14 patients (28%) and those in diuretic sensitive one were 36 patients (72%). In study of Stiehm *et al*. (2002) 7% of samples were from diuretic resistant patients and 93% of samples were from diuretic sensitive patients. While in the study by Karatapanis ***et al.*** (2003) 9.8% of

the samples were from diuretic resistant patients and the remaining 90.2% from diuretic sensitive patients. In the study done by El-Bokl *et al*. (2009) 60% of samples were diuretic resistant, while 40% of samples were diuretic sensitive.

In the present study, there was no significant difference regarding age between the two groups. This agreed with Cho *et al*. (2003); Spahr *et al*. (2001); El-Bokl *et al*. (2009).

Also, there was no significant difference between both groups as regards white blood cells, hemoglobin, or platelets. The results agreed with Cho *et al*. (2003). But, El-Bokl *et al*. (2009) found significantly lower platelet count and white blood cell count in diuretic resistant group when compared to diuretic sensitive group, that difference might arise from that the number of diuretic resistant patients in the present study.

Patients with more advanced liver disease had more deterioration in liver function and marked degrees of circulatory dysfunction and neurohumoral activation including antidiuretic hormone (ADH), which results in enhanced sodium renal tubular reabsorption, and therefore, more diuretic resistance (Cárdenas *et al*, 2000; Cárdenas and Ginès, 2005). This was noted in the present study, as patients in the diuretic resistant group had more advanced liver disease in the form of lower serum albumin, higher serum bilirubin and INR when compared to those in the diuretic sensitive group, but only the difference as regard INR was statistically significant ($P<0.05$). This agreed with El-bokl *et al*. (2009), but only differed in serum albumin, which was significant ($P<0.05$). Also, results agreed with Spahr *et al*. (2001) and Cho *et al*. (2003) but none of those parameters showed significantly different between GI and GII.

Serum albumin, bilirubin and INR are included in the Child-Pugh classification which reflects the liver function status. In the current study, 12 patients in the diuretic resistant group were Child class C (85.71%) while only 44.44% of patients in diuretic sensitive group were Child class C with highly statistically significant difference between both groups. The results agreed with Spahr *et al*. (2001); Stiem *et al*. (2002) and El-Bokl *et al*. (2009). However, in study by Cho et al. (2003) the difference between both groups as regard Child-Pugh class was not significant.

In the present study, ALT and AST levels was not significant in both groups. This agreed with Cho *et al*. (2003) and El-Bokl *et al*. (2009) who neither found significant different neither in serum AST, ALT or ALP nor between both groups.

Serum Na was significantly higher in diuretic sensitive group (129.257± 7.229) than that in diuretic resistant group (124.231±6.870), but the serum K was significantly higher in diuretic resistant group (4.131±0.395) than that in diuretic sensitive group (3.615±-0.487). Spahr *et al*. (2001) reported the same data as resistant group had lower serum sodium (131±6) than that in the sensitive one (135±2). El-Bokl *et al*. (2009) found that serum sodium in the

resistant group was significantly lower (128±5.4) than in the sensitive group (136±5.5).

In the present study, there was no significant difference between both groups as regards serum creatinine or urea, which agreed with El-Bokl *et al*. (2009) who reported a significantly higher BUN in the resistant group (24±8) than in the sensitive one (18±4), and with Stiem *et al*. (2002) who reported that BUN was highly significantly (mean 24) in the diuretic resistant group than in the sensitive one (mean 18). The reason of this difference could not be reached. None showed a difference between both groups as regards serum creatinine.

In the present study, there was a significant negative correlation between Na/K ratio and platelet count among patients (r= -0.339, p=0.021), also a significant positive correlation between Na/K ratio and hemoglobin level among patients (r=0.297, p=0.047). El-Bokl *et al*. (2009) reported positive significant correlation between 24-h urinary sodium and Na/K ratio (r= 0.76, P= 0.001), Na/Cr ratio (r = 0.56, P = 0.001), serum sodium (r= 0.59, P= 0.001), and negative significant correlation was noted between 24-h urinary sodium and serum BUN (r = -0.31, P= 0.046) and Child class (r= -0.31, P= 0.05).

There was highly significant difference between 24 hours urinary sodium in both groups, being lower in the diuretic resistant group (38.750±25.796) than in diuretic sensitive one (209.613 ±190.577). Cho *et al*. (2003) found that 24 hours urinary sodium in the resistant group (63±11) was lower than in the sensitive one (125±18). But, El-Bokl *et al*. (2009) found that 24 hours urinary sodium in the resistant group was (33±19.7), compared to (126±46) with a highly significant statistical difference. This may be explained by lose weight; patients should have negative sodium balance. Patients compliant to dietary sodium restriction receive 2 gm sodium per day which is equivalent to 88mEq. Non urinary sodium losses are 10mEq /day. So, in order to lose sodium, urinary loss should exceed 78mEq/ day; 88 minus 10 (Yu and Hu, 2001).

The present study revealed that spot urine Na/K ratio was lower in patients in the diuretic resistant group (3.243± 3.699) than in the sensitive one (6.663±6.894) but the difference was not significant. Karatapanis *et al*. (2003) reported that patients in the resistant group had significantly lower Na/K ratio (mean=0.52) than in the sensitive one (mean=3.81). Also, Stiehm *et al*. (2002) found resistant patients had significantly lower Na/K ratio (mean 0.55 and range 0.1-3.5) than in the sensitive one (mean 4.01 and range 0.12-17). El-Bokl *et al*. (2009) reported that spot urine Na/K ratio was significantly lower in the diuretic resistant patients (1.31±1.34) than in sensitive one (3.7±1.62) ($P<0.01$).

In the present study, the correlation between spot urine Na/K and 24 hours urinary sodium using ROC curve showed a significant correlation with sensitivity 87.5% and specificity 56% with accuracy 70%. Stiehm *et al*. (2002) reported sensitivity 63.8%, specificity 91% and accuracy 89.1%.

Karatapanis *et al*. (2003) found highly significant correlation with accuracy 86%. El-Bokl *et al.* (2009) reported a highly significant correlation with sensitivity 87.5%, specificity 87.5%, and accuracy 87%. A single difference was that in the present study, the cutoff point of Na/K ratio that showed highest accuracy 70% was 1.8, while with Stiem *et al.* (2002), and Karatapanis *et al*. (2003), was one. Also, with El-Bokl *et al.* (2009) the highest accuracy 87% was at a cutoff point 2.5.

Also, spot urine Na/K greater than 1.25 was sensitive and specific for prediction of 24 hours urinary sodium greater than 78 mmol (Park *et al*, 2010). These authors evaluated the diagnostic value of morning and afternoon random urine Na/K with 24 hours urinary sodium and found that anytime random urine Na/K greater than 1.25 is an accurate, cost-effective, and convenient method for replacing 24 hours urinary sodium. Saint-Remy *et al*. (2012) stated that sodium is a modifiable risk factor, accounted for a decrease of BP with a sodium restricted diet. Increased potassium intake has been also recommended in hypertension management. They added that restoring well-balanced sodium/potassium ratio intakes could be a non-pharmacological opportunity to improve blood pressure control.

Conclusion

The outcome results showed that random urine Na/K >1.8 was an accurate cost effective, convenient method for replacing 24 hours urinary Na for evaluating diuretic response. For monitoring diuretic response; spot urine sodium: potassium ratio, using a cut value of 1.8, may be an easier and more rapid alternative for the ordinary 24 hours urinary collection for urinary sodium, with adequate sensitivity, specificity and accuracy.

Patients who exhibited diuretic resistance were having more advanced liver disease and thus worse prognosis.

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