Rapid Determination of Diuretic Resistant Ascites Using Furosemide Induced Natriuresis Test in Egyptian Cirrhotic Patients

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Abstract: Background: Diagnosis of refractory ascites is a challenging task for physicians. This study aimed to evaluate the value of urinary sodium measurement after a single dose of intravenous furosemide (furosemide natriuresis test) in determination of diuretic resistant ascites. **Methods:** forty five Egyptian cirrhotic patients with massive ascites were included in the present study. All of them were maintained on low sodium diet and were subjected to furosemide natriuresis test then they were given maximum oral diuretic therapy (160 mg furosemide and 400 mg spironolactone) for one week; the response to oral therapy was assessed by the difference in body weight before and after therapy. According to the results of oral therapy the patients were divided into two main groups: Responsive group with decrease in body weight over 4 days >800gms, Resistant group with decrease in body weight over 4 days <800gms. **Results:** No significant difference in liver or renal functions was found between responsive and resistant group. Comparing the results of the furosemide natriuresis test to the results obtained from response to oral diuretic therapy; It was found that all patients resistant to oral therapy (twelve patients) had 8 hours urinary sodium <90mmol/L. In the responsive group (Thirty one patients), twenty eight patients had 8 hours urinary sodium >90mmol/L, three patients had 8 hours urinary sodium <90mmol/L and were found to be responsive to oral therapy. According to these results the sensitivity of the test is 100%, the specificity is 90.3%, the positive predictive value is 80% and the negative predictive value is 100% for detection of diuretic resistant ascites. **Conclusion:** measurement of urinary sodium eight hours after administrating 80 mg of intravenous furosemide is helpful in detection of diuretic resistant ascites patients "[Nature and Science. 2009;7(10):62-67]. (ISSN: 1545-0740).

Key Words: Furosemide natriuresis test; diuretic resistant ascites; single dose of intravenous furosemide.

Introduction:

The diagnosis of refractory ascites carries a poor prognosis with survival rates of 30% to 40% at 1 year. Therefore it is important to identify those patients reliably and rapidly as liver transplantation is urgently needed in this situation ***Spahr et al., 2001.*** For the ascites to be considered as non responsive to diuretic therapy the patient should be on spironolactone 400mg/day and furosemide 160mg/day for at least one week and to be on salt restricted diet of <90mmol/day. Lack of response is defined as a mean weight loss of less than 0.8kg over 4 days and urinary sodium output less than sodium intake. Early recurrence is defined as the reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization. Diuretic induced complications include diuretic induced hepatic encephalopathy, renal impairment (increase is serum creatinine >100% to a value of >2mg/dL) hyponatremia (decrease in serum sodium >10mmol/L to serum sodium <125mmol/L) and hypo or hyperkalemia (a change in serum potassium <3mmol/L or >6mmol/L respectively despite appropriate measures)**.** These complications increase, as the dosage of diuretics is increased ***Arroyo et al., 1996*** & ***Moore et al., 2003***. In addition it is important to ascertain that the lack of response is not related to dietary noncompliance or inadequate dosage of diuretics. Due to these facts, it is very difficult to apply this definition of refractory ascites to patients in outpatient department; identification of refractory ascites according to the proposed definition often requires prolonged observation, preferably in hospital to optimize the diet and the diuretic treatment. In this study, we tried to determine if ascites is truly diuretic resistant rapidly by measuring urine sodium after the administration of intravenous furosemide. The furosemide natriuresis test can be the standard in early differentiation of the response to diuretics treatment.

Patients and Methods

Forty five patients with massive ascites due to liver cirrhosis participated in the study. A written informed consent was obtained from each patient. Diagnosis of liver cirrhosis was based on clinical & laboratory evidences. Patients with malignant ascites, tuberculous, chylous and pancreatic ascites as well as ascites due to constrictive pericarditis, hepatic venous congestion, ovarian tumors spontaneous bacterial peritonitis and ascites due to bowel perforation were excluded from the study.

All patients were subjected to the following: Liver enzymes (AST and ALT), serum albumin, serum bilirubin (direct and indirect), prothrombin time and Child- pugh scoring was obtained after full clinical evaluation. Urea, creatinine, creatinine clearance, abdominal ultrasound, viral markers, diagnostic abdominal paracentesis, follow up of serum sodium and potassium, urea and creatinine all through the study time.

Patients were subjected to the furosemide test as follows: All diuretics were withdrawn for 3 days. On the fourth day the patient was asked to void his bladder and a bolous of furosemide, 80mg I.V. was injected. The urine was collected for 8 hours for detection of urinary sodium and urinary volume. The blood pressure was measured immediately and after 12 and 24 hours respectively and patients were asked about symptoms of hypotension ***(Spahr et al., 2001).***

Then after two days, All patients were given intensive diuretic therapy in hospital (160mg furosemide and 400mg spironolactone) for one week while being under sodium restriction. <90mmol/day (= less than 5.2gm/day) ***(Moore et al., 2003).*** The body weight was measured over the last 4 days and the average weight was taken. Two patients did not complete the study because of diuretic induced hepatic encephalopathy and were not included in further data analysis.

According to the obtained results from the oral therapy the forty three patients who completed the study were classified into 2 groups without knowing the results of the furosemide test: Diuretic responsive group: in which the loss in body weight was >800gms over the last 4 days (the loss is >200gms/day). b- Diuretic resistant group: in which the loss in body weight was <800gms over the last 4 days (the loss is <200gms/day). Patients of resistant group were subjected to 24 hours urine collection and 24 hours urinary sodium excretion was measured to confirm dietary sodium restriction (Patients who excrete greater than 90 mmol of sodium per day, and who fail to lose ascites are not compliant with their diet) ***Moore et al., 2003***

Statistical methodology

Analysis of data was done by IBM computer using SPSS (statistical program for social science package 16) as follows Description of quantitative variables as mean, SD and range description of qualitative variables as no and %, Chi-square test was used to compare qualitative variables, Unpaired t-test was used to compared two independent groups as regard a quantitative variable, paired t-test was used to compare variables in the same group before and after, correlation co-efficient rank test was used to rank different variables against each other in linear correlation. sensitivity = true +ve /true +ve + false -ve = ability of the test to detect +ve cases, specificity = true -ve/ true -ve + false +ve = ability of the test to exclude negative cases, positive predictive value (PPV) = true +ve/ true +ve + false +ve = % of true +ve cases to all positive cases, NPV = true-/true-ve + false -ve = % of the true -ve to all negative cases. Level of significance; P value >0.05 insignificant, P<0.05 significant, P<0.01 highly significant. ***Altman, 1994.***

Results:

43 Egyptian patients with liver cirrhosis secondary to hepatitis C infection and massive ascites were included in this study. They were 33 males and 10 females, their age range from 42 to 63. 15 patients were Child-pugh class B and the remaining 28 patients were of Child- pugh class C. According to the results of oral diuretic therapy while being on sodium restricted diet; the patients were divided into two groups:

Responsive group: Those with decrease in body weight over 4 days >800gms. Included 31 patients, 24 males and 7 females, mean age was 47.3±8.4. 12 patients were of Child B class and 19 of Child C.

Resistant group: Those with decrease in body weight over 4 days <800gms. Included 12 patients, 9 males and 3 females, mean age was 50.3±7. 3 patients were of Child B class and 9 of Child C.

No significant difference was found between responsive and resistant groups as regard age, sex or Child-pugh class. No statistically significant difference was found between the two groups regarding biochemical variables before the test as shown in Table 1.

Table (1): Comparison between both groups as regard different laboratory data before the test

Variables	Resistant		Responsive		t	P
	Mean	±SD	Mean	±SD		
Serum Na (mEq/L)	136.75	4.883	136.35	5.161	0.22	>0.05
Serum K (mEq/L)	4.267	0.624	4.071	0.445	1.15	>0.05
AST (mg/dl)	65.083	24.942	52.871	13.031	1.72	>0.05
ALT (mg/dl)	35.833	14.345	27.839	10.733	1.999	>0.05
Total bilirubin (mg/dl)	3.067	1.425	2.845	1.456	0.450	>0.05
Direct bilirubin (mg/dl)	1.158	0.793	1.106	0.681	0.213	>0.05
Total protein (g/dl)	7.142	0.699	7.071	0.773	0.275	>0.05
Albumin (g/dl)	2.467	0.481	2.545	0.492	0.471	>0.05
PT (minutes)	16.667	1.702	16.781	1.995	0.174	>0.05
INR	1.446	0.173	1.506	0.331	0.593	>0.05
Urea (mg/dl)	25.0	7.311	30.0	11.855	1.359	>0.05
Creatinine clearance (ml/min)	91.083	13.601	96.355	12.643	1.201	>0.05
Serum creatinine (mg/dl)	1.375	0.480	1.190	0.322	1.461	>0.05

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Following furosemide natriuresis test, it was found that 8 hours urine volume and 8 hours urinary sodium showed highly significant decrease in resistant than responsive group (table 2)

Table (2): Comparison of Results of furosemide natriuresis test between both groups

Variables	Resistant		Responsive		t	P
	Mean	±SD	Mean	±SD		
Urine volume (ml)	612.92	254.85	1062.7	313.21	4.43	**<0.0001****
Urine Na (mEq)	76.583	7.317	115.39	18.422	7.042	**<0.0001****
Serum Na (mEq)	136.42	4.379	134.81	3.719	1.212	>0.05
Serum K (mEq)	4.117	0.525	3.939	0.479	1.064	>0.05

In the responsive group, following furosemide natriuresis test there was highly significant decrease in body weight, significant decrease in serum sodium and non significant decrease in serum potassium (Table 3). While there was no significant change in any of these parameters in the resistant group (Table 4)

Table 3 : Changes in body weight and serum electrolytes before and after the test among responsive group

Variables	Before		After		t	P
	Mean	±SD	Mean	±SD		
Weight (kg)	70.62	9.91	68.33	9.64	3.342	<0.01
Serum Na (mEq/L)	136.35	5.16	134.81	3.71	2.179	<0.05
Serum K (mEq/L)	4.07	0.44	3.93	0.47	3.017	<0.05

Table (4): Changes in body weight and serum electrolytes before and after the test among resistant group

Variables	Before		After		t	P
	Mean	±SD	Mean	±SD		
Weight (kg)	74.20	13.08	74.12	13.15	0.518	>0.05
Serum Na (mEq/L)	136.75	4.88	136.42	4.37	0.741	>0.05
Serum K (mEq/L)	4.26	0.62	4.11	0.52	1.964	>0.05

No significant change in blood pressure was detected in both groups in serial blood pressure follow up after furosemide natriuresis test except for significant decrease in systolic blood pressure 12 hours after the test in the responsive group (110.97±6.38 twelve hours after the test versus 116.13± 7.154 before the test, t= 2.998, p<0.05).

In the responsive group 8 hours urinary sodium after the test were statistically correlated versus all studied variables before the test and no significant correlation could be detected with any one of them. The results were presented in table (5). The same correlation was studied in diuretic resistant group and no significant correlation was found.

Table (5): Correlation between urinary Na 8 hours after the test versus other variables among responsive group

Variables	r	P
Age	-0.288	>0.05
Weight	-0.001	>0.05
Serum Na	0.056	>0.05
Serum K	0.331	>0.05
AST	-0.022	>0.05
ALT	-0.098	>0.05
Total bilirubin	0.020	>0.05
Direct bilirubin	0.101	>0.05
Total protein	0.057	>0.05

Albumin	-0.069	>0.05
PT	0.300	>0.05
INR	0.224	>0.05
Urea	-0.306	>0.05
Creatinine clearance	-0.034	>0.05
Serum creatinine	-0.028	>0.05

The results of the furosemide natriuresis test were compared with the results obtained from response to oral diuretic therapy. According to these results, the sensitivity and specificity of the test as well as its positive and negative predictive value were calculated. The sensitivity was 100% which means that all cases with urinary sodium <90mmol/L were found to be resistant to oral therapy (12 cases) (true +ve cases). The specificity was 90.3% which means that among 31 patients responsive to diuretic therapy, 28 patients only had urinary sodium >90mmol/L (true -ve) and 3 patients had urinary sodium <90mmol/L (false +ve). The PPV of the test was 80% which means that among the fifteen patients with urinary sodium <90mmol/L 12 patients only were truly resistant to oral therapy (true +ve). The NPV was 100%, which means that all patients with urinary sodium >90mmol/L (28 patients) were responsive to oral therapy (true –ve).

Discussion:

The development of ascites in patients with cirrhosis indicates a poor prognosis. The probability of death in cirrhotic patients hospitalized with ascites is nearly 40% at 2 years. The prognosis is worse for those with refractory ascites, ***Moore et al., 2003.*** This study was designed to evaluate the furosemide induced natriuresis test as simple, cheap and rapid method for early determination of the resistant type of refractory ascites**.**

Result of the present study revealed that the number of resistant cases was 28% of total cases while responsive cases represented the remaining 72%. This is in accordance with ***Zervos and Rosemurgy, 2001 and Moreau et al., 2004***; both authors reported that percentage of refractory ascites was less than that of responsive one, and less than 30% of total cases. It was proved that medical treatment based on sodium-restricted diets, anti-mineralocorticoids, and loop diuretics achieves a response rate in up to 90% of patients without renal failure in controlled clinical trials ***Moore et al., 2003***. However the selection of patients for the present study could account for higher percentage of diuretic resistance as we selected patients with massive ascites which reflects more disturbances in salt and water homeostasis. We found non significant difference in almost all studied biochemical parameters between diuretic resistant and responsive patients; it was reported that the course of underlying chronic liver disease and the prognostic factors in relation to the outcome of ascites have not been determined and refractory ascites may occur in the absence of poor liver function ***Moreau et al., 2004***.

The pathophysiological basis of ascites development in cirrhotic patients could explain the highly significant increase in urine sodium 8 hours after the test in the responsive group in comparison with resistant group. The later patients have significant abnormalities in their fluid and electrolyte balance which is manifested mainly by development of ascites and edema ***Cardenas and Arroyo, 2005.*** The response of ascites is usually better in patients with moderate sodium retention than in those with marked sodium retention ***Bernardi et al., 1993.*** With the progression of the disease, patients with severe urinary sodium retention develop refractory ascites ***Cardenas and Arroyo, 2005.*** Accordingly urinary sodium excretion in some cases of severe resistant ascites may approximate to zero ***Cárdenas and Arroyo, 2003.***

Impaired water handling is common in cirrhotic patients as indicated by an impaired ability to eliminate water load ***Cardenas and Arroyo, 2005.*** This explains the highly significant decrease in urine volume in the resistant group in comparison with the responsive group. In addition, ***Arroyo et al., 1996*** reported that when the renal ability to excrete free water is markedly reduced, patients become unable to eliminate excess ingested water and dilutional hyponatraemia develops.

The significant decrease in serum Na after the test among patients of responsive group is most probably the result of the increase in urinary sodium excretion

in this group as a response to the test and the significant decrease in serum K after the test in this group is most probably the side effect to IV furosemide ***Arroyo et al., 1996.***

The furosemide natriuresis test was statistically evaluated as regard its value in diagnosing resistant ascites and its safety for the patient. Firstly, eight hours urinary sodium was statistically correlated with all studied biochemical variables as well as the child classification in both groups. The results revealed non significant correlation of 8 hours urinary sodium with any of the studied variables. This result indicates stability of the test which means that is not changeable in response to any other variable except the degree of response of ascites. Data of the present study supports the findings of other authors who proposed furosemide natriuresis test as a simple test to identify patients with refractory ascites ***Spahr et al., 2001*** .

Conclusion: From this study we can conclude that when urinary sodium excretion following 80mg IV furosemide injection is >90mmol/L (under dietary sodium restriction) the patient can be diagnosed as responsive to diuretics. Meanwhile when it is <90mmol/L (under the same restriction) the patient is 80% resistant to diuretics. Accordingly, the test is highly sensitive but not highly specific.

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