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Predictors of Induction and Sustainability of Response to Diuretic Therapy in Patients with Decompensated Chronic Liver Disease

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Abstract

Background: **Factors involved in individual's response to loop diuretics in cirrhotic patients with ascites are many, which renders it difficult to austerely predict response to diuretic therapy in those patients. The aim of this study was to evaluate factors which determine initial response to loop diuretic therapy in those patients and to determine whether such factors can predict a sustained diuresis response.** ***Patients and Methods:*** **One hundred and ten patients with non-malignant chronic liver disease and ascites were treated with IV furosemide in doses according to serum creatinine together with oral spironolactone 50mg twice daily. Before and during the diuretic therapy a set of clinical and laboratory variables were investigated as possible predictive factors influencing the therapeutic response to diuretics. The renal arterial resistive index (RI) (reflecting renal vascular resistance) was estimated with duplex Doppler ultrasonography.** ***Results:*** **Our study revealed statistically significant relation between high ascites grade(p=0.013), higher Child-Pugh class (p< 0.001), higher baseline serum creatinine & lower eGFR (p< 0.001), and high renal resistive index (p=0.002) with poor diuretic response.** ***Conclusion:*** **combining both clinical and laboratory findings together with elevated baseline renal resistive index would be helpful in early identification of the subgroup of patients who are at higher risk of diuretic resistance.**

Keywords: cirrhosis, urinary sodium, sodium retention, loop diuretics

Introduction

Sodium restriction and diuretic therapy constitute the standard medical management for ascites and are effective in approximately 95% of patients. Multiple diuretic classes are used to treat patients with liver disease[(1)]. aldosterone antagonists, such as spironolactone, represent first-line diuretics in the treatment of ascites in patients with cirrhosis. The initial dose is 100–200 mg/dl[(2)]. The addition of loop diuretics, which act by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle, potentiates the natriuretic effects of aldosterone antagonists.

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Furosemide is the most widely used loop-type diuretic and is erratically absorbed with an absolute bioavailability of 49±17%[3]. There are three major types of adverse events associated with furosemide: hypovolemia and electrolyte imbalance due to diuresis, hypersensitivity, and ototoxicity, This side effect occurs more commonly in the elderly, CKD patients, and patients taking non-steroidal anti-inflammatory drugs (NSAIDs)[4]. Ascites that does not respond or recurs after high-dose diuretics and sodium restriction should be considered refractory ascites[1]. This should not be confused with diuretic tolerance which is a predictable decline of response to diuretic therapy that can be observed in majority of patients. Frequently, there is a gradual deterioration in renal function as cirrhosis advances. Patients with diuretic-resistant ascites have been designated to have pre-hepatorenal syndrome and a poor prognosis. The effect of this deterioration is basically an inability to maintain the extracellular fluid volume within normal limits. Factors involved in individual's response to loop diuretics include dose, bioavailability, kidney function, hemodynamic stability, renin–aldosterone system and serum albumin. The multiplicity of these factors renders it difficult to austerely predict response to diuretic therapy and may explain in part the variability from study to another in evaluating the importance of individual factors[5]. Changes in renal perfusion can play a key role in determining differences in the dose–response curve of diuretics. In fact, the increased renal arterial resistance can cause water and sodium retention due to the reduction in glomerular filtration pressure[6].

Patients and Methods

This study included patients of both sex with decompensated chronic liver disease of any etiology who presented for follow up at Suez Canal university hospitals. Patients who met the following criteria were included: a) age between 25-75 years, b) no evidence of hepatocellular carcinoma or any other malignancy, c) no evidence of systemic infection or spontaneous bacterial peritonitis, d) a mean arterial pressure equal to or more than 75 mmHg, e) no evidence of active GIT bleeding f) no evidence of hepatic encephalopathy g) serum sodium more than 115 mEq/L and serum potassium more than 3.4 mEq/L, h) serum creatinine less than 3.5 mg/dl, i) can stop diuretics for a diuretic wash-out period of 4 days. The study was carried out as before after experiment on a single cohort of patients and included 110 patients who were admitted for 3 days to assess initial and response to furosemide therapy, and the following data were collected 24 hours before starting diuretics: sex, age, body weight, mean arterial blood pressure, 24 hour urine output, ascites grade, prothrombin time, serum albumin, serum bilirubin, serum creatinine, eGFR, blood ph., and renal resistive index. Also, patients received salt restricted diet (Na 100 mmol/day). Then IV furosemide was started in the following doses (according to serum creatinine): S. CR. <1mg/dl (60 mg), S. CR. >1 to <1.4 mg/dl: (80 mg), S. CR. >1.4 to <1.8 mg/dl: (120 mg), S. CR. >1.8 to < 2.5 mg/dl: (160 mg) and S.CR. >2.5 to 3.5 mg/dl: (200 mg). Together with spironolactone in the fixed dose of 50 mg twice daily orally, with daily monitoring of urine output and body weight. At the end of this period initial response is assessed. At day 4,5, and 6 patients were maintained on 150% of initial furosemide dose but received orally, with the same dose of spironolactone.at day 7 the same IV doses received, and sustained response is assessed. Response to diuretic therapy was determined at a cut-off point of an increase in urine output of $\geq$ 50 ml/Kg/ day, and/or weight reduction of $\geq$ 0.3 kg/50 kg BW per day.

Table 1: Diuretic responders and non-responders regarding demographic characteristics, medical and clinical data

Parameters	Responders No. (%)	Non-responders No. (%)	*p*- value
Socio-demographics			0.097[1]
Age in years			
<45	6 (12.8%)	7 (11.1%)	
45-	32 (68.1%)	32 (50.8%)	
>60	9 (19.1%)	24 (38.1%)	
Mean ± SD	54.7 ± 7.4	56.5 ± 9.2	0.281[2]
Gender			
Male	24 (51.1%)	37 (58.7%)	0.424[1]
Female	23 (49.9%)	26 (41.3%)	
Body weigh in kg			0.858[3]
< 75	28 (59.6%)	35 (55.6%)	
75 – 90	17 (36.2%)	24 (38.1%)	
> 90	2 (4.3%)	4 (6.3%)	
Mean ± SD	74.2 ± 9.3	74.8 ± 9.4	0.913[4]
Clinical data			
Mean blood pressure			0.975
< 90 mmHg	27 (57.4%)	36 (57.1%)	
90 – 120 mmHg	20 (42.6%)	27 (42.9)	
Mean ± SD	88.2 ± 8.9	87.5 ± 10.7	0.647[4]
Ascites grade			0.013[1]*
Grade 2	26 (55.3%)	20 (31.7%)	
Grade 3	21 (44.7%)	43 (68.3%)	
Child paugh classification			< 0.001[1]*
B	41 (87.2%)	28 (44.4%	
C	6 (12.8%)	35 (55.6%)	

*1. Chi square test; 2. Student's t test; 3. Fisher's exact test; 4. Mann Whitney U test; *Statistically significant at p < 0.05.*

Statistical analysis

Continuous variables were described as mean ± standard deviation and discrete variables as frequencies. Bivariate comparison of the two groups of patients for the explanatory factors that may predict diuresis response (i.e. age, sex, body weight, mean blood pressure, basal resistive index, ascites grade, child-Pugh score, GFR, arterial blood Ph, basal $FeNa^+$, Basal urine chloride). Bivariate comparisons were made using the Chi-square test for qualitative data and the paired T test for quantitative data. Similar bivariate comparisons of laboratory measurements were made for "changes" induced by furosemide diuresis in each of the laboratory variables in the two phases (i.e. differences induced by intervention at days 3 and 7). Odds ratios was estimated for the potential predictors in a logistic regression model, using the composite binary variable (response/no response) as the dependent outcome variable. The independent potential predictors included the basal clinical and sonographic characteristics, Logistic regression was modeled to evaluate predictors of response at days 3 and 7, separately.

Results

One hundred and ten patients with chronic liver disease were enrolled in the study. There was a significant relationship between both grade 3 ascites and Child -Pugh class C and diuretic resistance (p-value

0.013 &<0.001 respectively). While no significant difference was found regarding age, gender, mean BP, or chronic illnesses (Table 1). There was significant relation between good response and lower renal resistive index, lower S. creatinine and albumin, higher eGFR, higher basal pH. Also, it shows that average urine output in responders was (1645.2 ± 408.5) and average daily weight loss (0.45 ± 0.13) (Table 2). Table (3) shows binary logistic regression analysis to find the best predictor of response to furosemide-induced dieresis at day 3. Only resistive index (P-value0.002) and Child Pugh classification (P <0.001) were significant predictors of response to furosemide-induced diuresis. Logistic regression analysis of predictors of response to furosemide diuresis therapy on day 7 is demonstrated in table (4). Only resistive index (P-value 0.023) and Child Pugh classification (P-value <0.001) were significant predictors of response to furosemide-induced diuresis.

Table 2: Baseline laboratory and radiological data among diuretic responders and non-responders

	Responders Mean ± SD	Non-responders Mean ± SD	*p*- value
Resistive index	0.66 ± 0.04	0.69 ± 0.05	< 0.001[1]*
Blood PH	7.40 ± 0.04	7.38 ± 0.05	0.005[1]*
Urinary creatinine (mg/dl)	83.6 ± 29.7	96.1 ± 27.5	0.020[1]*
S. creatinine (mg/dl)	0.94 ± 0.36	1.28 ± 0.56	< 0.001[1]*
S. Na (mmol/l)	133.4 ± 2.66	133.4 ± 2.7	0.747
S. K (mmol/l)	3.7 ± 0.49	3.7 ± 0.58	0.771
eGFR (MDRD)	88.3 ± 32.4	72.9 ± 56	< 0.001[1]*
Albumin (gm/dl	1.8 ± 0.97	2.5 ± 0.50	< 0.001[1]*
INR	1.4 ± 0.21	1.6 ± 0.31	< 0.001[1]*
Total bilirubin (mg/dl)	1.8 ± 0.97	2.6 ± 1.54	0.001[1]*
Direct bilirubin (mg/dl)	0.81 ± 0.72	1.4 ± 0.86	< 0.001[1]*
Average daily urine output (ml)	1645.2 ± 408.5	953.8 ± 292	< 0.001[1]*
Average daily weight loss (kg)	0.45 ± 0.13	0.02 ± 0.09	< 0.001[1]*

1. Mann Whitney U test; *Statistically significant at $p < 0.05$.

Discussion

An understanding of what determines patients' response to a diuretic is a prerequisite to the correct use of these drugs. Unfortunately, studies that evaluates predictors of response to diuretics in patients with cirrhosis are few. Univariate analysis of clinical data of study participants revealed that high ascites grade can predict poor response to diuretics. This comes in agree with the Tunisian study by Ennaifer and his colleagues (2016) which revealed that ascites grade 3 was predictive factor of diuretic resistant ascites development in univariate analysis (OR=4.17; p= 0.004)[7]. Furthermore, in a prospective study by Ljubicić et al (1998) large amounts of ascites at the time of diuretic therapy are significant predisposing factors that probably influence drug-induced diuresis (p<0.05)[8]. Moreover, both univariate and multivariate analysis in this study revealed that high Child-Pugh class is risk factor for the development of diuretic resistant ascites. This seems reasonable and agree with other studies as in the prospective Spanish study of Planas et al (2006), in which Child-Pugh >8 at inclusion was an independent predictor of diuretic resistant ascites with an OR of 1.47[9]. Moreover, the Egyptian study by El-Bokl and his colleagues (2009) showed that diuretic resistant group had higher child paugh score[10]. In the present data high RRI is an independent predictor of poor response to diuretic therapy in our

patients (p<0.001 and 0.002 in univariate and multivariate analysis respectively). Supporting to our results, the results of Ljubicić and his colleagues (1998) showed that the renal arterial RI was significant predictive factor influencing the therapeutic response during diuretic treatment of ascites in non-azotemic cirrhotic patients[8]. Similarly, study by Gornik, and his colleagues (2013) showed that the RRI could be used to guide diuretic treatment in non-hypovolemic, non-hypotensive septic patients[11]. Another study by Iacoviello and his colleagues in (2015) showed that RRI is independently associated with high dose loop diuretics[12]. Univariate analysis of this study revealed that poor diuretic response was associated with higher baseline serum creatinine, lower eGFR (P<0.001), This comes in agreement with analysis from RELAX-AHF study by Voors and his colleagues in (2014) where poor responders were more likely to have lower baseline e GFR and high baseline serum creatinine (p <0.0001)[13].

Conclusion

This study revealed that high renal resistive index and higher Child-Pugh class are independent risk factors for poor diuretic response and this agree with most studies, also our study revealed that there is no significant correlation between age, gender, and mean arterial blood pressure and diuretic response, and this disagreed with other studies.

Table 3: logistic regression analysis of predictors of response to furosemide therapy at day 3

Covariates	B	*p*-value	OR (95% CI)
Age	0.026	0.408	1.002 (0.965 – 1.093)
Gender	0.306	0.581	1.359(0.458 – 4.028)
Weight	-0.027	0.397	0.973 (0.914 – 1.036)
Resistive index	-24.774	0.002[1*]	0.00 (0.00 – 0.00)
Child paugh classification	-2.751	< 0.001[1*]	0.064 (0.017 – 0.239)
Mean blood pressure	-0.003	0.922	0.922 (0.946 – 1.051)
GFR	0.007	0.246	1.007 (0.995 – 1.019)
Baseline Ph	-4.920	0.487	0.007 (0.00 – 7706.925)
Constant	56.822	0.300	4.527
χ^2 = 50.710		< 0.001[1*]	

*Statistically significant at $p < 0.05$.

Table 4: logistic regression analysis of predictors of response to furosemide diuresis therapy at day 3.

Covariates	β	*p*-value	OR (95% CI)
Age	0.055	0.081	1.057 (0.993 – 1.025)
Gender	-0.115	0.831	0.891 (0.309 – 2.570)
Weight	0.000	0.994	1.00 (0.941 – 1.063)
Resistive index	-15.669	0.023*	0.000 (0.00 – 0.117)
Child paugh classification	-2.677	< 0.001*	0.069 (0.020 – 0.240)
Mean blood pressure	0.008	0.777	1.008 (0.956 – 1.061)
GFR	0.004	0.458	1.004 (0.993 – 1.016)
Baseline PH	4.256	0.545	70.498 (0.00 – 67216861)
Constant	-20.476	0.702	0.000
χ^2 = 47.524		< 0.001*	

**Statistically significant at $p < 0.05$.

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