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Original Article

The fractional excretion of sodium in patients with cystic fibrosis treated with oral sodium chloride

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Abstract: *Background:* Cystic Fibrosis (CF) is a chronic disease associated with low sodium status. The patients are usually treated with oral sodium chloride to control the side effects of low sodium status. Therefore, the fractional excretion of sodium (FE_{Na}) was assessed in patients with cystic fibrosis (CF) treated with oral sodium chloride (NaCl). *Methods:* This was a prospective cross-sectional study that was conducted on forty children with cystic fibrosis who were under treatment with oral NaCl and were referred to Imam Hossein Hospital-Isfahan-Iran between 2017 to 2019. The patients were under treated with 2-4 mEq/kg per day oral NaCl and urinary and plasma sodium and creatinine, as well as FE_{Na}, were assessed after three months of taking NaCl. Also the patients were compared in terms of efficacy of treatment based on sodium level (between 135 and 145 mmol/L) and acceptable FE_{Na} level (between 0.5% and 1.5%). The sensitivity and specificity of FeNa and plasma sodium were assessed with ROC curve test. *Results:* Plasma sodium was normal in 65% of treated patients, and FE_{Na} was also normal range in 47.5% of treated patients. The treatment also was desirable for 35% of the patients. The sensitivity and specificity of FeNa were 42.9% and 57.7%, respectively, and the sensitivity and specificity of plasma sodium were 85.7% and 26.9%, respectively. *Conclusion:* Using of plasma sodium had higher sensitivity than FeNa and FeNa had higher specificity than plasma sodium to follow up of patients with CF.

Keywords: Sodium, creatinine, cystic fibrosis, children

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder common to all races [1, 2]. The disease is caused by a genetic mutation in the CFTR gene that leads to the reduced amount of CFTR protein and increases sodium channels in airway epithelial cells [3-5], which gradually leads to pulmonary dehydration and cilia dysfunction. Primary problems in CF patients are a chronic obstruction and recurrent infections in the respiratory system, as well as digestive system disorders [6-8]. The incidence of CF is reported as 0.7 per 10000 people in Europe [9], which indicates a relatively high prevalence of this disease [1, 9]. Electrolyte imbalance is one of the most important risk factors in CF patients. Hyponatremia is the most important and common type of electrolyte imbalance in CF patients [10-12]. Studies have also shown that sweat gland ducts are relatively impermeable to chloride in CF patients and consequently, the concentration of chloride increases in sweats at the skin surface [13, 14]. Therefore, sodium ions are less reabsorbed by sweat glands in order to maintain sodium balance in blood cells. Consequently, sodium concentration increases in sweat. Therefore, measurement of blood sodium levels and even urinary sodium are not desirable indicators of sodium level in the human body [15, 16].

CF patients with sodium loss are characterized by chronic fatigue, low blood pressure, and loss of appetite. It is essential to maintain accurate electrolyte balance (e.g., sodium) in CF patients because severe electrolyte has irreversible complications in CF patients. The balance may even be affected by temperature and climatic conditions. The FE_{Na} is used to measure sodium levels and detect electrolyte imbalances. The FE_{Na} formula involves the measurement of urinary and plasma sodium and creati-

nine [17]. This is a more desirable indicator of sodium level in the human body. Electrolyte balance and diet should be closely monitored in CF patients, especially the intake of oral NaCl. Otherwise, electrolyte imbalance causes severe problems in CF patients [10]. Given the importance of electrolyte balance (especially sodium) in CF patients and informal assessment of sodium level in the human body via FE_{Na}, the present study aimed to assess FE_{Na} in CF patients treated with oral NaCl.

Materials and methods

Subjects

This was a prospective cross-sectional study that was conducted on forty children with cystic fibrosis who were under treatment with oral NaCl and were referred to Imam Hossein Hospital-Isfahan-Iran between 2017 to 2019. The protocol of present study was approved in the ethical committee of Isfahan University of Medical Sciences-Isfahan-Iran and the patients had informed consent for statement for enrollment to study.

Inclusion criteria were included children with CF who were under treatment with oral NaCl, without any problems such as acute infections, inflammatory diseases, renal failure, diabetes mellitus, Syndrome of inappropriate antidiuretic hormone secretion (SIADH), cardiac failure or liver failure. In addition, the patients were not under treatment with diuretics. Those participants who failed to take oral sodium, required to hospitalization, and reluctance to cooperate were excluded from the study. The patients were under treated 2-4 mEq/kg per day oral NaCl required for CF [5].

Assessments

After enrolling the patients to study based on inclusion and exclusion criteria, the patients were visited to lung clinic every three months for periodic examinations. A questionnaire was designed based on studied factors that was included age, gender, urine Na, urine Cr, plasma Na, and Urine Cr. Serum and urinary sodium and creatinine levels were measured in patients after three months of taking NaCl. The FE_{Na} was calculated based formula $FENa = \frac{UNa \times PCr}{UCr \times PNa} \times 100$ and also desirable treatment was defined sodium level (between 135 and 145 mmol/L) and acceptable FE_{Na} level (between 0.5% and 1.5%). In addition, serum sodium was sorted in < 135, between 135 and 145 and > 145, and FE_{Na} was sorted < 0.5%, between 0.5% and 1.5% and > 1.5%, respectively.

Statistical analysis

All information was entered into SPSS version 24 (IBM, USA) after recorded in the data collection form. Desired analyses were performed in SPSS. Numerical data were reported as mean (median) and standard deviation (minimum and maximum) and non-numerical data as number and percentage. Independent t-test was used to compare quantitative data between the two genders. Chi-Square test was used to compare qualitative data between the two genders. Fisher's exact test and Pearson correlation were also used. Also the ROC Curve was used to determine sensitivity and specificity of plasma sodium and FE_{Na}. $P < 0.05$ was considered significant level.

Results

Demographical

Forty patients participated in this study consisting of 28 males and 12 females. Mean age of the patients was 6.25 ± 3.60 years.

Experimental results

Urinary and plasma sodium and creatinine, as well as FE_{Na}, were measured. The mean of FeNa in patients was 0.97 ± 0.79. Other data are summarized in **Table 1**.

Plasma and FE_{Na} levels are also shown as qualitative data. Plasma sodium < 135 in 35% of patients and normal range (135-145 mmol/L) in 65% of patients. FE_{Na} < 0.5% in 27.5% of patients, normal range (0.5-1.5) in 47.5% of patients, and FE_{Na} > 1.5% in 25% of patients. The treatment was desirable for 35% of patients (plasma sodium concentration and FE_{Na} were normal) (**Table 2**).

The mean of FeNa in boys (1.11 ± 0.89) was significantly higher than girls (0.65 ± 0.35) ($P = 0.004$). Also, in patients with serum sodium levels higher than 135 (1.10 ± 1.9), the

Table 1. Variables of study between two groups

Variables	Mean	SD	Minimum	Maximum
Age (Years)	6.25	3.60	1	14
Urine Na (mmol/L)	140.30	56.69	18	228
Urine Cr	77.25	36.06	12	155
Plasma Na (mmol/L)	136.90	3.69	127	144
Plasma Cr (mmol/L)	0.54	0.14	0.25	0.9
FeNa (%)	0.97	0.79	0.07	3.51
Urine Na/Cr	2.48	1.95	0.15	7.9

Table 2. Qualitative variables studied

Variables		Frequency	Percent
Gender	Boy	28	70
	Girl	12	30
Plasma Na	< 135	14	35
	135-145	26	65
FeNa	< 0.5	11	27.5
	0.5-1.5	19	47.5
	> 1.5	10	25
Treatment	desirable	14	35

mean FeNa was significantly higher than normal sodium (0.52 ± 0.80) (P = 0.001). On the other hand, in patients whose treatment was desirable (0.71 ± 0.24), FeNa levels were significantly lower than those who did not have a desirable treatment (1.11 ± 0.95) (P < 0.001).

There was no significant correlation between FeNa with age, urinary and plasma sodium and plasma creatinine (P > 0.05). However, there was a significant reverse correlation between FeNa and urine creatinine (P < 0.001, r = -0.70) (**Figure 1**).

Sensitivity, and specificity of FeNa and plasma sodium

Based on the ROC Curve, considering 0.646 as cutoff and 0.484 as the area under diagram, the sensitivity, and specificity of FeNa were 42.9% and 57.7%, respectively (**Figure 2**).

Also, if the Cutoff value was 137 and area under diagram was 0.849 to estimate the sensitivity and specificity of plasma sodium, its sensitivity and specificity are obtained at 85.7% and 26.9% respectively (**Figure 3**).

Discussion

The results of this study showed that FE_{Na} was desirable in 47.5% of cases and plasma sodium levels were acceptable in 65% of cases, and 35% of patients underwent a desirable treatment (plasma sodium and FE_{Na} were normal) in CF children treated with oral NaCl.

Also, the use of plasma sodium or FeNa to follow up these patients was different because the sensitivity of plasma sodium was higher than FeNa and the specificity of FeNa was higher than plasma sodium to estimate the desirability of the treatment.

Regarding normonatremic hyponatremia that serum sodium is normal but the total sodium decreased and also the patients with CF undergoing treatment with oral or injection sodium, this normonatremic hyponatremia not be detectable. In this study, we evaluated the FeNa in these patients than in the patients with desirable treatment (normal plasma sodium and FeNa) the sensitivity of plasma sodium was more than FeNa.

Knepper *et al.* showed that FE_{Na} < 0.5 in 71.4% of CF patients and FE_{Na} was normal in ten CF children (n = 35) [17]. In the former study, the CF children were not treated with NaCl and FE_{Na} was normal in 28.5% of them. However, FE_{Na} was normal in 47.5% of children treated with NaCl and FE_{Na} < 0.5 in 27.5% of them in our study. Therefore, prescription of NaCl can return FE_{Na} to normal level in CF patients.

Coates *et al.* treated CF patients with oral sodium. They showed that CF is a chronic disease associated with sodium loss that impedes optimal growth. They also showed that sodium loss is due to normonatremic Na^+ depletion, which impairs the growth of CF children. However, other causes are also involved in growth impairment. The sodium-to-creatinine ratio had a strong correlation with FE_{Na} in the former study [18].

Various studies have reported that the FE_{Na} < 0.5% is associated with low sodium levels [18, 19]. FE_{Na} < 0.5% in 27.5% of the patients was also associated with sodium level < 135 in th-

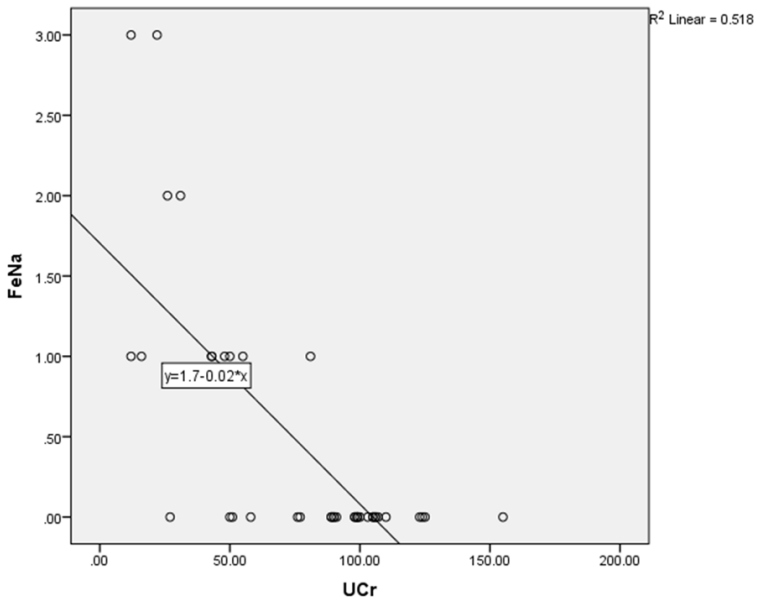

Figure 1. Reverse correlation between Urine Cr and FeNa.

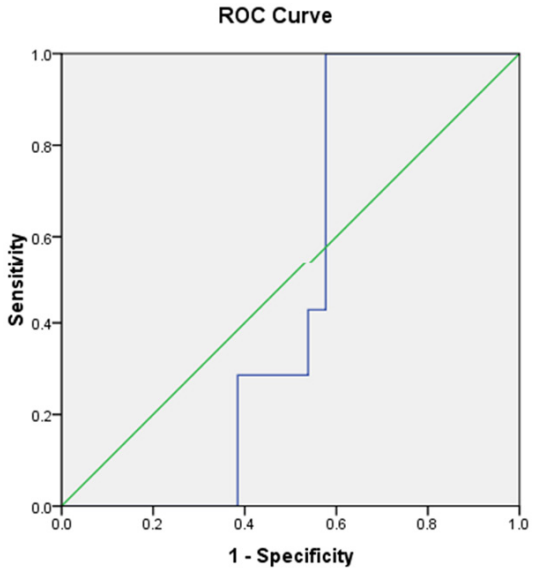

Figure 2. ROC diagram to determine the FeNa sensitivity and specificity.

is study. There was also a significant and inverse relationship between FE_{Na} and urinary creatinine in CF patients treated with NaCl. However, the relationship between FE_{Na} and plasma and urinary sodium in CF patients treated with NaCl was investigated for the first time in this study. The results showed that the prescription of NaCl improves plasma sodium levels and FE_{Na} in CF patients. The treatment was desirable and acceptable for 35% of cases. It can prevent sodium depletion and hyponatremia in these patients.

Based on study by Aladjem, concluded that the urine Na volume extraction in the CF patients was significantly higher than healthy control and also the glomerular filtration rate (GFR) in the CF patients was significantly lower than healthy control, so the volume expansion in the patents with CF causes of lower tubular reabsorptive capacity of sodium and the reduced the GFR [20].

Based on ESPEN-ESPGHAN-ECFS guidelines, sodium supplemtation is critical nutrition supporting for children with CF that urinary sodium: creatinine ratio must be recommending for evaluating of this patient [21].

Limitations of the study were relatively low sample size, absence of control, and limited studies in this field. Other effective factors in sodium loss were not also investigated in this study.

On the other hand, plasma sodium had a higher sensitivity to FeNa and was an effective factor in determining the desirable treatment in CF patients.

Also, due to the dry weather conditions of Iran, and because oral therapeutic protocols are defined according to European and American guidelines, the likelihood of normonatermic hyponatremia is higher in Iran.

Also, given that normonatermic hyponatremia affects growth parameters, it is important to diagnose and prevent it.

Nevertheless, further studies should be conducted in this field since there is no similar study in this study for comparison and limitations of this study should be eliminated in future studies.

Disclosure of conflict of interest

None.

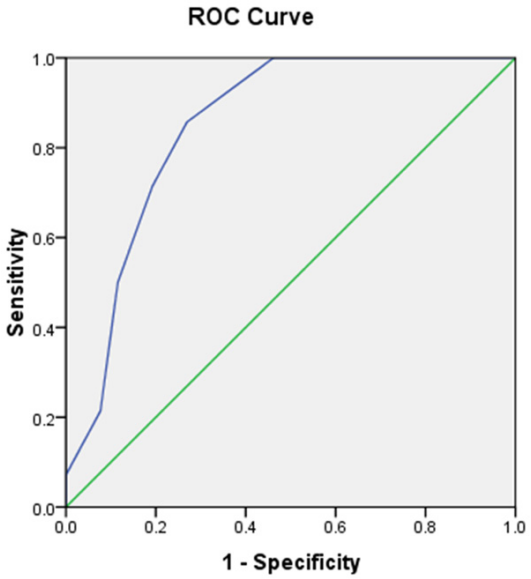

Figure 3. ROC diagram to determine the sensitivity and specificity of plasma sodium.

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