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Comparison of fractional excretion of sodium, uric acid and urea nitrogen in diagnosis of pediatric acute prerenal failure

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ABSTRACT

Background and aim: various factors, in terms of faster diagnosis of acute renal failure have been studied so far, but these studies have been done mostly on adults. Therefore, in this paper we made a comparison of fractional excretion of sodium (FeNa), uric acid (FeUa) and urea nitrogen (FeU) in acute prerenal failure in children to find out which one is more sensitive in diagnosis of acute prerenal failure. Material and Methods: In a cross-sectional study, 5 CC blood was taken from 29 children of 1 month to 15 years old, diagnosed with acute pre-renal failure; the amount of creatinine, sodium, uric acid and urea nitrogen was measured in their plasma. After taking a standard urine specimen, all the mentioned items were measured in patients' urine and put into the formula of FeNa, FeUa and FeU and compared. Results: In this study, 75.8% FeU, 68.9% FeUa and 58.6% FeNa are agreeable to prerenal criteria and the most sensitivity is assigned to FeU. Among the three groups, FeNa is more affected by treatment with diuretic. The difference between FeNa in the receiver group of normal saline and the receiver group of diuretic is more than those groups which did not receive any. Conclusion: Fractional excretion of urea nitrogen in children, especially in the receivers of diuretic is more sensitive in diagnosis of acute prerenal failure. Moreover, this index is more sensitive in diagnosis of acute prerenal failure than the other indexes.

Keywords: Fractional excretion of urea nitrogen, fractional excretion of uric acid, fractional excretion of sodium, acute prerenal failure

INTRODUCTION

Acute renal failure is a prevalent clinical problem. Its prevention and treatment are crucial in patients' outcome. It is very important to distinguish acute prerenal failure from other acute renal failures [1]. Based on some reasons, finding a reliable and quick diagnostic method to distinguish prerenal azotemia from acute tubular necrosis (ATN) in children is very important. Firstly, dehydration is common in children and they are more susceptible to ARF, resulted from dehydration, rather than adults. In case of inappropriate treatment, it will proceed to nonreturnable acute renal failure. Secondly, urinary diagnostic indexes including FeNa and portion of urine osmolality to plasma usually have no acceptable precision because of the consumption of crystalloids and diuretics before coming to hospital[2].

Different factors such as portion of BUN to plasma creatinine, levels of different urinary electrolytes, biomarkers, FENa, FEUa and FeNu have been studied for diagnosis of acute renal failure so far [3, 4, 5]. In most studies, population under the study was adult, while renal bloodstream indexes in children are different from that in adults [2]. FENa less than 1% in prerenalazotemia, and FENa more than 2% support diagnosis of ARF [6].

Urinary indexes of ARF have many limitations; first, they overlap a lot. Second, in conditions like diabetes and prescription of diuresiswe cannot exploit these indexes. Loop diuretics affect sodium adjustment in thick ascending part of the henle loop, and in heavy doses affect function of proximal tubule. Thiazide diuretics prevent terminal reabsorption of sodium. Moreover, reabsorption of proximal tubule can be changed by osmotic diuresis and Finally,

indexes resulted from urinary sodium can be misunderstood during ATN caused by rhabdomyoly sis, contrast agents, ARF caused by uric acid and in many cases oliguric ARFs [4]. Moreover, FeNa in myoglobinuria [3] and sepsis [7] is disrupted, while FeU is not affected by diuretics.

Traditionally, uric acid has been used as a marker of sodium absorption in proximal tubule. By volume decrement, fractional excretion of uric acid decreases and by volume increment, it increases [4]. Fractional excretion of urea is a useful clinical tool. In recent century, most of the studies have focused on the portion of creatinineto urea as a tool for glomerulus failure [8-10].

In some studies, it has been stated that FeU is a more useful index than FeNa in evaluation of patients receiving diuretic and showing azotemia prerenal signs[11, 12]. Pepin et al [13] stated that FeNa is a better index than FeU, either in patients who have received diuretic or not. In another study, sensitivity of FeNa in diagnosis of acute renal failure is more than FeU in patients who have not received diuretics [14].

As mentioned, different studies have shown different results in application of these markers in diagnosis of acute prerenal failure. Therefore, we decided to make a comparison of fractional excretion of sodium, uric acid and urea nitrogen in children acute prerenal failure to find out which one is more sensitive in diagnosis of acute prerenal failure.

MATERIALS AND METHODS

In a cross-sectional study, we entered the study 29 children of 1 month to 15 years old who were suffering from acute prerenal failure (BUN more than 20 and cr more than 1mg/dl) and had been hospitalized in pediatric ward of Kashan ShahidBeheshti hospital in 2014-15. The specimen volume was based on a study done on comparison between fractional excretion of sodium, and uric acid in patients suffering from ARF; the amount of fractional excretion of sodium and fractional excretion of nitrogen was 2+0.4 and 23.6 +4.9 respectively. Regarding reliability of 95% and precision of 0.15 for sodium and 2 for nitrogen, the least needed specimen was calculated 29 persons. In all patients, diagnosis of acute prerenal failure was based on the following criteria:

a. History : Diseases resulting in decrement of renal blood circulation such as bleeding, imperceptible loss of water like burning, diseases that make liquid gather in third space, like sepsis, nephrotic syndrome, congenital heart failure,etc[14];
b. Dehydration criteria based on Nelson book (thirst for water, tachycardia, sunken eyes and fontanelles, reduction of tear, dryness of mucus, decrement of skin turgor, delay in refilling of capillaries, skin coldness and paleness, hypotension, decrement of consciousness) [15];
c. Laboratory criteria including urine osmolality more than 500 mosm/ kg, specific gravity of urine more than 1020[1].

According to above findings, their definite diagnoses were determined and entered the study. Cases having acute renal, postrenal failures, chronic renal failure and also infant group were excluded the study. These children were evaluated in terms of demographic variables (age, sex, height, blood pressure, urine output) and the variables were recorded in a prearranged questionnaire. Then 5cc non-citrated blood was taken from the patients and the amount creatinine, sodium, uric acid, urea nitrogen was measured in their plasma. After taking a standard urine specimen, all the mentioned items was measured in patients' urine. Then, they were put into formula of fractional excretion.

$$Fe = \frac{Urin_{\times} \times Plasma_{creat}}{Plasma_{\times} \times Urin_{creat}}$$

In this study, FeNa less than 1%, FeUa less than 12% and FeU less than 35% were considered as cutoff points for acute prerenal failure. Having collected the information, we made a comparison of the groups by means of chi-square and Fisher tests.

RESULTS

In this research, 29 children afflicted with acute prerenal failure, hospitalized in Shahid Beheshti hospital, were studied. Diagnostic criteria of acute prerenal failure in this study were based on dehydration signs including clinical and laboratory criteria. Out of 29 patients, 9 cases (31%) died of nonreturnable shock resulting from dehydration, brain hemorrhage, sepsis and heart failure. Range of the patients' age was from 2 months to 12 years old. 34.5 % was under the age of 1 and 65.5% comprised other age categories. 55.2 % of the children was female and 44.8 %

was male. In this study, 20.6% of the patients had severe dehydration and GFR less than 25%. 75.8 % had moderate dehydration and 25-75% GFR.

The first common cause of prerenal azotemia was acute gastroenteritis, including 48% of the patients and the second cause was sepsis, including 17% of the patients (Table1). The least amount of patients' blood PH was 6.8 and the most and medium amount was 7.49 and 7.2 respectively. Blood bicarbonate was at least 3, at most, 41 and in average, 13.5. 89.6 % had bicarbonate less than 14 and 75.8% had PH less than 7.35. It means that they were afflicted with metabolic acidosis. There was only one case of metabolic alkalosis caused by bartter's syndrome. In urine analysis of the patients under the study, 7 cases had glucosuria 0f +1 to +3, 2 cases had bacteriuria and 12 cases had proteinuria that 8 cases of them had proteinuria of +1, 3 cases had proteinuria of +2 and 1 case had proteinuria of +3 ; the last case was afflicted with nephrotic syndrome. Microscopic hematuria was reported in 5 cases. There was urine contamination in 2 cases, and there was no positive culture. In the study, out of 29 patients 75.9% were thirsty for water; because of the low level of consciousness or young age in 7 cases (24%) this symptom could not be evaluated. Among the other symptoms, dryness of mucus was observed in 100% of the patients which shows the least moderate dehydration in all the patients. Based on laboratory criteria, urine osmolality more than 500 was recorded in 89.65% that had the most adaptation to prerenal criteria. Urine sodium less than 20 was agreeable to prerenal criteria only in 17.2% of the cases.

In this study, 58.6% FeNa, 68.9% FeUa and 75.8% FeU were agreeable to prerenal criteria and the most sensitivity was assigned to FEU (Table 2). Out of 29 patients under the study, 7 cases received diuretic that 28.6 % FeNa, 71.5% FeUa and 100% Feu were agreeable to prerenal criteria. Among the 3 groups, FeNa was more affected by diuretic than the other fractional excretions. Also, 55% of the patients received normal saline serum in early phases. In these patients 43.7% FeNa, 62% FeUa and 81% FeU were agreeable to prerenal criteria. In comparison to the group which did not receive normal saline, 76.9% FeNa, 69.2% FeUa and 76.9% FeU of the patients were agreeable to prerenal criteria. In this group, index of fractional excretion of sodium has been more affected by normal saline. In the patients who received both normal saline and diuretic for challenge test, 25%FeNa, 75% FeUa, and100% FeU of the patients were agreeable to prerenal criteria. In the group which received none of the mentioned items, 90%FeNa, 70% FeUa, and 60% FeU were agreeable to prerenal conditions.

Table1. Underlying disease caused acute prerenal failure in children under the study

Disease	Frequency	percent
Gastroenteritis	14	48.2
Bartter's syndrome	1	3.4
DKA	2	6.8
Heart disease	1	3.4
Coma	2	6.8
CAH	1	3.4
Nephrotic syndrom	2	6.8
Sepsis	5	17.2
Hemorrhage	1	3.4

Table2. Comparison of FeNa, FeUa and FeU in children with acute prerenal failure

	Frequency	percent
FENa<1%	17	58.6
FEUa<12%	20	68.9
FEU<35%	22	75.8

Table 3. Frequency distribution of factors related to FeNa, FeUa, and FeU in diagnosis of acute prerenal failure

Factors related to Fe		FeNa<1%		P.V	FeUa<12%		P.V	FeU<35%		P.V
		%	Frequency		%	Frequency		%	Frequency	
Diuretic	Received	28.6	2	0. 092	71.5	5	1	100	7	0.289
	Not received	68.2	15		63.6	14		72.7	16	
Normal saline	Received	43.8	7	0. 092	62.5	10	0.357	81.3	13	0.63
	Not received	72.9	10		69.2	9		76.9	10	
Normal saline +diuretic	Received	25	1	0.041	75	3		100	4	0.25
	Not received	90	9		70	7		60	6	
Glucosuria	Having	28.6	2	0. 092	57.1		4 0.66	58.7	6	
	Not having	68.2	15		68.2		15	77.3	17	

In this case, the variance between FeNa in the receiver groups of normal saline and diuretic was more than in other groups which did not received any. This variance was meaningful with P.V 0.041.Due to the fact that obligatory

excretion of sodium is caused by glucosuria, FeNa was evaluated in the patients having glucosuria. In 7 patients, 28.6%FeNa, 57.1% FeUa, and 85.7% FeU were agreeable to prerenal criteria. In the group that had no glucosuria, 68.2% FeNa, 68.2% FeUa and 77.3% FeU were agreeable to prerenal criteria. In this group also, FeNa was more affected by glucosuria than the other groups (Table3).

DISCUSSION

Statistics on acute renal failure are different all around the world, but include about 2-3% of children and 8% of infants hospitalized in ICU [17]. If acute renal failure does not receive appropriate treatment, it can quickly result in renal stabilized failure (ATN); therefore, diagnosis of acute renal failure and prerenal conditions are very important, especially in children as they are more sensitive. Diagnostic indexes of acute renal failure, based on sodium rate and water excretion are often useful. Different studies have stated FeNa as a valuable index for diagnosis of acute prerenal failure [12, 13, 18]. However, this index will not be so valuable if diuretics, glucosuria and bicarbonaturia are used. It could be said that most of FeNa limitations are caused by its reabsorption along the nephron, therefore it can be affected by different factors. Another marker applied in diagnosis of acute prerenal failure is Feu. Although uric acid is not absorbed in parts after the proximal tubule, it is not an ideal marker because of the secretory part in proximal tubule [16]. Another marker which has been recently focused on by most of the studies is fractional excretion of urea [19, 20].

In the present study, in children having acute prerenal failure who received diuretic, normal saline or both of them, FeU was least affected item by the conditions and diagnosed acute prerenal failure with the highest percentage. But FeNa was the most affected item, especially in patients who received diuretic; thus its diagnostic sensitivity has been reduced in these cases.

Also, in the group which had not received diuretic, FeU had more diagnostic sensitivity than FeNa , but that was not palpable in a way thatFeU less than 35% in 72.7% was against FeNa less than 1% in 68.2% , therefore it can be concluded that FeNa and FeU are appropriate indexes for patients who did not receive diuretic. In the group which had not received normal saline and diuretic, FeNa< 1% in 90% of the cases was agreeable to prerenal criteria. It shows that FeNa in absence of influential factors has proper sensitivity for diagnosis of acute prerrenal failure.

Another finding of the study indicates that FeU is the best index for diagnosis of prerenal conditions than FeNa and FeUa because most of the patients were under the treatment with normal saline and lasix in early stage. On the other hand, the present study was done on all the patients afflicted with prerenal failure, hospitalized in pediatric and ICU wards and most of them had modrate dehydration. Therefore it indicates that even in modrate dehydrations FeU is more sensitive in prerenal cases than FeNa.

Kaplan and Kohn in the study of their patients who were under the treatment with diuretic observed that FeNa was high, but FeU was low in all of the patients and it resulted in the fact that FeU is a more useful index in evaluation of the patients receiving diuretic who express prerenal azotemia symptoms [11]. This finding is in tune with the present study. The advantage of the present study over Kaplan's study is that all the receiver patients of diuretic took the medicine at the beginning of the study, but in Kaplan's study the intervals between taking diuretic and urine specimen were so various.

Carvounis et al in their study on 3 groups having prerenalazotomia, prerenalazotomia with consumption of diuretic and acute tubular necrosis based on nephrologist's clinical diagnosis came to the conclusion that FeU is more sensitive and specific in diagnosis of prerenal azotemia, especially in the receiver patients of diuretic. The results are in tune with the present study. Carvounis' study was done only on hospitalized patients in ICU, therefore according to the present study it can be said that FeU is a more efficient index in diagnosis of all patients than FeNa [12].

In Pepin's study it is proved that FeNa is a more efficient index in patients who received and those who did not receive diuretic than FeU. This result is against the theory of Carvounis, Kaplan and the present study [13]. Indeed, in Pepin's study, the interval between receiving diuretic and urine specimen is long and it can be the cause of the better function of FeNa. Also, 30% of the patients had sepsis. As we know, FeU function will be reduced by transition of urea from kidney and colon in existence of infection because of the interference of inflammatory cytokines [13].

Lim did a study similar to Pepin's. In his study it was concluded that FeU like FeNa is a proper factor in diagnosis of prerenal and especially renal failure. In this study, sensitivity of FeNa in diagnosis of patients who had not received diuretic was more than the sensitivity of FeU. But after the prescription of diuretic, FeU index was more

sensitive. In our study, FeU was the better index in patients who received diuretic or not. In case of not receiving diuretic, this difference was not palpable [16].

Diskin et al stated that FeU is more precise than FeNa in patients afflicted with oliguric azotemia. The difference was exclusively because of more FeU in 67 patients who had received diuretic. Both FeU and FeNa had sufficient accuracy in diagnosis of acute tubular necrosis. In the study, the cutoff points of FeU were more similar to the present study than to the other studies; in the present study, it was 35% and in Diskin's study was 40%. It shows that although FeU was supposed different numbers in different studies, its diagnostic value even by increment of its cutoff was more than FeNa [21].

Fahimi et al concluded that FeU< 35% has more sensitivity and specificity than FeNa<1% in distinguishing prerenal from renal azotemia in children. Even FeU<30% was more efficient in comparison to these two. Fahimi's study is the only study done on children [22].

In the study of Steinhduslin et al, 43% of the patients under the study had used diuretic before or during the ARF. In this study, sensitivity of FeNa in acute prerenal failure was 75% and its specificity was78%. Sensitivity of FeU was 68% and its specificity was 12% (4). In the present study, sensitivity of FeU was 68.9% and sensitivity of FeNa was 58.6 %. In Steinhduslin's study, it was stated that in a third of the patients FeU is misleading and cannot be an ideal marker. That is in tune with the present study.

CONCLUSION

In this study, a comparison was made between sensitivity of three diagnostic markers including FeNa, FeUa and FeU. Having compared the results of the present study with the results of the other limited studies which were mostly done on adults we came to this conclusion that Feu is more sensitive in diagnosis of acute prerenal failure in children, especially in those children receiving diuretic. Moreover this index is more sensitive in diagnosis of acute prerenal failure than the other indexes.

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