Fractional Excretion of Urea in Pediatric Patients with Acute Kidney Injury

Pediatrik Akut Böbrek Hasarında Fraksiyone Üre Ekskresyonu

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ABSTRACT

Objective: Fractional excretion of sodium (FeNa) and fractional excretion of urea (FeU) are used to differentiate prerenal and renal injuries in acute kidney injury (AKI). In this study, we aimed to compare the discriminative power of FeU with FeNa between prerenal and renal azotemia groups as well as among AKI stages according to pRIFLE criteria.

Material and Methods: Laboratory and medical records of 55 pediatric AKI patients who had the measurements of random urine excretions of urea, creatinine and sodium as well as serum urea, creatinine and sodium levels in order to calculate FeU and FeNa values at the time of AKI diagnosis were evaluated retrospectively. Patients were divided into prerenal and renal injury groups according to the clinical findings and laboratory data. Sensitivities and specifities of FeNa and FeU in differentiating prerenal versus renal injury were determined. FeNa and FeU values were compared in patients with different RIFLE stages.

Results: Among 55 pediatric AKI patients 31 were boys, 24 were girls. The mean age at the time of diagnosis was 71.1 ± 83.5 months (min-max: 1-216). When we grouped the patients as having FeU<35% and FeU≥35%, the difference between the numbers of the patients in prerenal and renal groups was significant (p=0.039). The sensitivity and specificity of FeU to determine prerenal vs renal injury were calculated as 50% and 77.1% respectively. When FeNa and FeU were used together (FeNa>1% and FeU>35%) in order to distinguish prerenal and renal injuries the specificity increased to 81% (p=0.020). Mean FeU was significantly different between AKI stages (p=0.022), and was higher in Injury and Failure stages when compared with the Risk stage.

Conclusion: Fractional urea excretion is as important as FeNa in evaluating children with AKI. We recommend to obtain FeU in pediatric AKI in order to differentiate prerenal and renal etiology and to differentiate the severity of the injury according to the AKI stages in order to arrange the treatment.

Key Words: Acute kidney injury, Children, Fractional urea excretion, pRIFLE

ÖZ

Amaç: Fraksiyone sodyum ekskresyonu (FeNa) ile fraksiyone üre ekskresyonu (FeU) akut böbrek hasarında prerenal ve renal hasarı ayırt etmek için kullanılmaktadır. Bu çalışmada, FeNa ve FeU değerlerinin prerenal ve renal azotemi grupları ile pRIFLE kriterlerine göre akut böbek hasarı evrelerini ayırdetmedeki gücünü kıyaslamayı amaçladık.

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Gereç ve Yöntemler: Akut böbrek hasarı tanısı sırasındaki FeU ve FeNa değerlerini hesaplamak amacıyla spot idrar üre, kreatinin ve sodyum ekskresyonları ile serum üre, kreatinin ve sodyum değerleri elde olunan 55 pediatrik akut böbrek hasarı hastasının laboratuvar ve klinik verileri retrospektif olarak değerlendirildi. Hastalar klinik ve laboratuvar bilgiler ışığında prerenal ve renal hasar grupları olarak ikiye ayrıldı. Prerenal ve renal hasarı ayırt etmede FeNa ve FeU testlerinin sensitivite ve spesifisiteleri hesaplandı. Farklı RIFLE evreleri olan hastalar arasında FeNa ve FeU yüzdeleri kıyaslandı.

Bulgular: Elli beş pediatrik akut böbrek hasarı hastasının 31'i erkek, 24'ü kızdı. Tanı anında ortalama yaş 71.1±83.5 ay (min-max: 1-216)'di. Hastaları FeU değerlerine göre FeU<%35 ve FeU ≥35% olarak iki gruba ayırdığımızda prerenal ve renal gruplardaki hasta sayıları arasındaki fark anlamlıydı (p=0.039). Prerenal ve renal hasar ayırımını belirlemede FeU testinin sensitivitesi %50, spesifisitesi %77.1 olarak hesaplandı. FeNa ve FeU birlikte kullanıldığında (FeNa >%1 ve FeU >%35) spesifisite %81'e yükseldi (p=0.020). FeU ortalaması akut böbrek hasarı evreleri arasında anlamlı olarak farklıydı (p=0.022) ve Risk evresiyle kıyaslandığında Injury ve Failure evrelerinde daha yüksekti.

Sonuç: Fraksiyone üre ekskresyonu, pediatrik akut böbrek hasarı olan çocukların değerlendirilmesinde FeNa kadar önemlidir. Prerenal ve renal hasarı ayırt etmede ve akut böbrek hasarı evrelerine göre böbrek hasarının şiddetinin belirlenmesinde FeU değerinin elde edilmesini öneriyoruz.

Anahtar Sözcükler: Akut böbrek hasarı, Fraksiyone üre ekskresyonu, pRIFLE

INTRODUCTION

Acute kidney injury (AKI), is characterized by an abrupt increase in serum urea and creatinine concentrations, a decrease in glomerular filtration rate (GFR) and the disability of the kidneys to regulate acid-base, water, and electrolyte balance (1-3). AKI is an important problem to assess. Mortality in patients with AKI increases along with the increase in serum creatinine (4). The Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) classification determines the grade of AKI based on serum creatinine level or glomerular filtration rate (GFR) and urine output (5). Pediatric RIFLE (pRIFLE) is a modified version for the setting of AKI in children (6).

AKI is usually multifactorial, and it is a diagnostic challenge to differentiate prerenal insult from acute tubular necrosis (ATN) (5,7). Distinguishing these two entities is important in order to manage the patient properly and to assess the outcome (5). Prompt diagnosis of intrinsic renal injury and exclusion of other causes might enhance better outcome (1,8). There is a lack of a clinical gold standard used for that purpose. The blood urea nitrogen-to-creatinine ratio (BUN/Cre), urinary/plasma creatinine and urinary/plasma osmolarity ratios, urinary sodium concentration, and fractional excretion of sodium (FeNa) are used to differentiate prerenal AKI from intrinsic injury (5,9,10).

Fractional excretion of sodium, is the most reliable and available test that is widely used to differentiate prerenal and intrinsic renal failure, particularly ATN (1). A value less than 1% suggests transient or prerenal AKI, whereas FeNa greater than 1% supports acute tubular necrosis or persistent AKI. However FeNa has some limitations in various conditions such as diuretic administration, contrast nephropathy, sepsis, bilateral renal artery stenosis, acute glomerulonephritis, acute interstitial nephritis, acute rejection, glucosuric states, metabolic alkalosis, and ATN superimposed upon chronic effective volume depletion (heart failure, nephrotic syndrome) (1,2,5,11-14). Fractional excretions of other substances such as chloride, urea, uric acid, and lithium were studied to differentiate these conditions (1,15-17). Together with FeNa, fractional excretion of urea (FeU) has been studied by many investigators (18,19).

Proximal segment of the nephron is the major site for the reabsorption of urea and the reabsorption is not directly affected by diuretics, therefore FeU is thought to be a better diagnostic measure than FeNa (5).

In this study we evaluated the utilization of FeU in the setting of pediatric AKI. We aimed to show the advantages of using FeU together with FeNa in differentiating prerenal vs renal injury, and in addition to that, we wanted to show if FeU and FeNa are different among AKI stages.

MATERIAL and METHODS

From the database of our hospital, we retrospectively analyzed the medical records of the pediatric patients with the diagnosis of acute kidney injury. We included 55 patients who had random plasma and urine urea, creatinine, sodium results (at the time of diagnosis of acute kidney injury) in order to calculate fractional excretions of urea and sodium, respectively. Newborns were excluded due to the immaturity of their renal tubular functions.

Demographic data, age, serum urea, creatinine, sodium, potassium levels, FeNa, FeU and AKI stages determined according to pediatric RIFLE criteria were recorded. Patients at the Loss stage and the End-stage renal disease stages were not included in the study since most of these patients were anuric. Patients were divided into prerenal and renal injury groups according to the history of the disease, BUN/Cre ratio (>20 is supportive of prerenal causes), and presence or absence of rapid amelioration of renal function with volume repletion. Patients were further divided into four subgroups according to their fractional excretion results as FeNa<1%, FeNa≥1% and FeU<35%, FeU≥35%, and the patient numbers were compared (in order to calculate sensitivities and specificities of the tests) between prerenal/renal injury groups and among RIFLE stages.

The study was approved by the Local Ethics Committee (Ankara City Hospital, Clinical Studies E2-21-330) and the study was conducted by the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS for Windows (SPSS version 17.0). Student t test was performed for normally distributed data, and Mann-Whitney U test for non-normally distributed data. To evaluate the difference between FeU and FeNa among different AKI stages (Risk-Injury-Failure), one-way analysis of variance and Tukey's post hoc tests were used. Pearson Chi-Square test was used to evaluate the difference between FeU and FeNa in between prerenal and renal injury groups.

Frequencies and percentages were used as descriptive values in the categorical data. Arithmetical mean±standard deviation was used for the normally distributed data, and median and interquartile range (IQR) were used for the non-normally distributed data.

Statistical significance was accepted as 0.05.

RESULTS

The study included 55 (female/male:24/31) pediatric AKI patients. Mean age at diagnosis was 71.1±83.5 months (min-max:1-216). Twenty patients were classified as having prerenal AKI and 35 patients as having renal injury. In the prerenal azotemia group, the etiology of prerenal AKI was acute gastroenteritis and dehydration in most of the cases, whereas in renal injury group acute glomerulonephritis and acute tubulointersitial nephritis were common. According to pediatric RIFLE criteria 24 patients were classified as the Risk stage, 16 patients as the Injury stage and 15 patients as the Failure stage.

Mean serum urea, creatinine, sodium, potassium levels were similar in prerenal and renal groups (Table I). Mean serum urea is 58.5±31.5 mg/dL at the Risk stage, 55.7±27.8 mg/dL at the Injury stage, 90.2±51.1 mg/dL at the Failure stage. Mean serum urea was significantly different between AKI stages (p=0.018). Mean serum creatinine is 0.99±0.31 mg/dL at the Risk stage, 0.95±0.17 mg/dL at the Injury stage, 1.88±0.55 mg/dL at the Failure stage. Mean serum creatinine was significantly different between AKI stages (p<0.001).

Table I: The clinical and the laboratory data of prerenal and renal injury groups.

	Prerenal	Renal	p
Number of the patients	20	35	
Age (months)	97±86	55±78	0.072
BUN (mg/dL)	35±14	28±20	0.198
Serum Urea (mg/dL)	75±30	61±42	0.198
Serum creatinine (mg/dL)	1.12±0.39	1.28±0.61	0.291
Serum sodium (mmol/L)	136±12	137±8	0.721
Serum potassium (mmol/L)	4.4±0.8	4.0±0.8	0.153
FeNa (%)	1.5±2.9	4.4±3.6	0.004
FeU (%)	8.2±18	56±21	0.003
FeNa<1% (n)	15/20	3/35	<0.001
FeU<35% (n)	10/20	8/35	0.039

Table II: FeNa and FeU values between different stages of pRIFLE.

RIFLE	n	Mean±Std. Dev.	Median (Min-Max)	p*
FeNa (%)				
Risk Stage	24	1.90±1.78	1.45 (0.06- 6.98)	0.004
Injury Stage	16	2.25±3.48	1.38 (0.19-13.09)	
Failure Stage	15	6.35±4.5	6.11 (0.82-13.39)	
FeU (%)				
Risk Stage	24	40.31±17.31	35.12 (15.88-80.06)	0.022
Injury Stage	16	55.5±22.8	56.16 (18.75-96.44)	
Failure Stage	15	58.5±23.16	62.8 (17.17-91.78)	

**Kruskal Wallis test*

Among 18 patients with FeNa<1%, 15 (83.4%) of them had prerenal causes, and among patients with FeNa≥1%, 32 (86.4%) of them had renal causes. When we compared FeNa<1% group with FeNa≥%1 group, prerenal etiology was significantly predominant in FeNa<1% group (p<0.001). This is consistent with the fact that FeNa less than 1% supports prerenal etiology. The sensitivity and specificity of FeNa to determine prerenal vs renal injury were calculated as 75% and 91.4 % respectively.

The fractional excretion of urea less than 35% is supportive of prerenal etiology. When we grouped the patients according to their FeU levels as FeU<35% and FeU≥35, the difference in patients' numbers in prerenal and renal groups was significant (p=0.039). The sensitivity and specificity of FeU to determine prerenal vs renal injury were calculated as 50% and 77.1% respectively. When FeNa and FeU were used together, the difference in patients' numbers between prerenal and renal groups was significant (p=0.02), and the specificity of the tests to differentiate prerenal vs renal injury was calculated as 81%.

Mean FeNa was 1.9% at the Risk stage, 2.25% at the Injury stage, and 6.35% at the Failure stage. Mean FeNa was significantly different between AKI stages (p=0.004). Mean FeU was 40.31% at the Risk stage, 55.5% at the Injury stage, and 58.5% at the Failure stage. Mean FeU is significantly different between AKI stages (p=0.022) (Table II).

The possibility of FeU being less than 35% at the Risk stage was 2.901 times higher than that of Injury and Failure stages (Odds ratio 2.901 CI: 95%, 0.906-9.286). The possibility of FeU being more than 35% at the Failure stage was 4.333 times higher than the Risk stage (Odds ratio 4.333 CI: 95%, 0.86-21.843).

DISCUSSIONS

The present study supports that the utilization of FeU, as well as FeNa, is useful to differentiate prerenal azotemia from renal injury. Prerenal azotemia is a more common condition than

intrinsic renal failure (18,20). Contrary to the literature, the number of our subjects in the prerenal injury group seems to be less when compared with the renal injury group, this is due to the retrospective nature of our study, and to the fact that prerenal azotemia is usually corrected quickly with adequate hydration, and further evaluation is usually preserved for the suspicion of renal injury.

Differentiating prerenal and intrinsic renal injury is extremely important, since correcting the volume status of the patient will ameliorate the ongoing problem. The FeNa and FeU are both useful tests used to discriminate these two entities. The primary use of FeNa which mainly reflects the function of distal nephron is that low levels of it (<1%) suggests prerenal failure whereas a high level (2%) favors intrinsic renal failure (1,13,21). However active transport of sodium chloride can be affected by diuretic usage leading to an alteration in FeNa, and this affects the utilization of FeNa in patients who were administered diuretics (9).

Urea is a lipid-soluble molecule that can cross the membranes of the cell easily by passive diffusion (1,21). In the glomerulus urea is freely filtered, and then reabsorbed mainly in the proximal tubule, finally 50-60% of the filtered urea is excreted (1,21). Urea is also actively transported in the renal tubules. When there is a decrease in perfusion, urea reabsorption increases, and as a result of this, the excretion of urea decreases (usually <35%). If the patient has an intrinsic renal failure due to the tubular insult, urea reabsorption decreases and FeU exceeds 50% (1,13). However, many conditions such as sepsis, gender, aging, protein infusion, liver disease, certain drugs interfere with the active transport of urea affecting the result of FeU (18,22).

It is shown that endotoxemia causes cytokines to downregulate urea transporters (18,23). In other words, among cases with endotoxemia or sepsis FeU results may erroneously suggest a prerenal etiology in the presence of an intrinsic renal injury. When compared with the literature, in our study we found slightly lower sensitivity and specificity of FeU to differentiate prerenal azotemia from intrinsic renal injury (50% and 77.1% respectively). The most common possible etiology of prerenal AKI was acute gastroenteritis in children enrolled in this study. We can speculate that, the possible infectious etiology in our patients might have affected the excretion of urea therefore leading to the lower sensitivity and specificity of FeU found in our study. Infectious diarrhea might have also caused an increase in intestinal urea loss, and as a consequence of that, even in prerenal azotemia cases elevated FeU results might have been found contrary to expectations (4).

Fractional excretions of certain substances such as uric acid and urea are difficult to quantify in newborns especially in premature babies due to the immaturity of tubular function (24). Fractional excretion of uric acid is shown to be very high at birth and declines over the first month of life (25). Therefore, we excluded the newborns from our study.

Fahimi et al. (1) showed that FeU was a better index than FeNa to differentiate prerenal from intrinsic renal failure. Although both indices were higher in patients with intrinsic renal failure, FeU <35% better discriminated prerenal patients than did FeNa<1%. They also found that FeU <30% had a higher sensitivity than previously reported FeU<35% in the adult population to discriminate prerenal failure patients. In our study FeNa<1% had higher sensitivity and specificity to discriminate prerenal from renal injury when compared with FeU. Since our study is retrospectively designed, we cannot detect the patients with diuretic administration.

Carvounis et al. (13) in their cohort, analyzed the data of 50 subjects with prerenal azotemia, 27 subjects with prerenal azotemia treated with diuretic administration, and 25 subjects with acute tubular necrosis. They reported the sensitivity and specificity of Feu<35% to differentiate prerenal azotemia were 90% and 96%, respectively.

Pepin et al.(5) concluded that, in patients not receiving diuretics, FeNa is more able to distinguish transient from persistent AKI, whereas in patients treated with diuretics, neither FeNa nor FeU can be used. Diskin et al.(18) evaluated FeNa and FeU in 100 azotemic oliguria patients and concluded that both tests accurately differentiate prerenal from intrinsic renal injury and FeU appears to be more accurate in patients receiving diuretics.

Our results support that FeU together with FeNa is a useful marker to differentiate prerenal azotemia from renal injury. We showed the utilization of FeNa and FeU together differentiates prerenal from renal injury with a specificity of 81%.

We also found that both FeU and FeNa are both significantly lower at the Risk stage when compared with the Injury and Failure stages. Tubular function is much better in especially early stages of AKI, in other words, renal capacity to reabsorb certain molecules is better at the beginning of the insult (1). The low FeU and FeNa results at the Risk stage could be explained by this fact. When the damage advances, kidney's ability of reabsorption diminishes, and FeNa and FeU increase (1). To the best of our knowledge, this is the first study evaluating both FeNa and FeU in different stages of AKI.

The restrictions of our study are its small size and retrospective nature. Furthermore we were not able define the patients with diarrhea or sepsis, and/or receiving diuretics.

Acute kidney injury is associated with a high mortality rate, therefore early interventions are important to avoid the renal damage. In a patient with suspected acute kidney injury, FeU together with FeNa should be obtained in order to differentiate prerenal injury from renal insult, and also to distinguish an early stage of AKI from advanced stages.

CONCLUSION

The fractional excretion of urea is an important tool similar to FeNa in evaluating children with AKI. We recommend to obtain FeU together with FeNa in children with AKI to differentiate

prerenal azotemia from intrinsic renal failure excluding the patients with sepsis or diuretic administration. FeU and FeNa are both found to be significantly lower at the early stages of AKI than advanced stages, and might be helpful for the arrangement of treatment strategies.

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