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Frequency of low levels of fractional excretion of lithium and sodium in patients with prerenal azotemia on diuretics

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ABSTRACT

Background: Fractional excretion of sodium is widely used for evaluation of prerenal azotemia. Diuretic treatment in these patients can lead to false elevation in fractional excretion of sodium but has less influence on fractional excretion of lithium. Our study will estimate frequency of low levels of fractional excretion of lithium in prerenal azotemia as compared to fractional excretion of sodium so that appropriate strategies can be developed for the diagnosis of these patients and prompt management can be ensured to halt further complications. The objective of this study is to determine the frequency of low levels of fractional excretion of lithium and sodium in patients with prerenal azotemia on diuretics.

Materials and Methods: This cross sectional study was conducted at Bahawal Victoria Hospital from September 2018 to March 2019 and tests were carried out in Pathology department, Quaid-e-Azam Medical College, Bahawalpur. A total of 120 patients between the ages of 20-60 years admitted in Bahawal Victoria Hospital with prerenal azotemia and on diuretics for ≥ 48 hours were included in the study. The evaluation included blood and spot urine samples for sodium, lithium and creatinine.

Results: Low levels of fractional excretion of lithium (<7%) was obtained in 111 (92.5%) of patients with prerenal azotemia on diuretics while only 28 (23.3%) of these patients had low fractional excretion of sodium.

Conclusion: Low levels of fractional excretion of lithium were found in more patients with prerenal azotemia taking diuretics as compared to low levels of fractional excretion of sodium hence making it a more reliable index for diagnosis of these patients.

Keywords: kidney, prerenal azotemia, fractional excretion, sodium, lithium, diuretics

INTRODUCTION:

Acute kidney injury is a major clinical problem with rising incidence and high mortality [1]. It is classified into three categories: prerenal azotemia, intrarenal causes and postrenal obstruction [2]. Out of them prerenal azotemia is the most common form of acute kidney injury [3] . It is important to diagnose it at an early stage because if it is not promptly corrected it will lead to irreversible kidney damage [4]. For this purpose various urinary indices have been proposed [1,4]. Among them fractional excretion of sodium is commonly used in assessing prerenal azotemia [4]. Fractional excretion of sodium is less than 1% in prerenal azotemia because in this condition most of the filtered sodium is reabsorbed along the renal tubules leadingo decreased excretion [3]. However, many patients with prerenal azotemia receive

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diuretics, which decrease sodium reabsorption and thus increase its fractional excretion [1,5]. As lithium ions are reabsorbed only in proximal tubules parallel to sodium and no lithium is reabsorbed in distal tubules [3]. So diuretics acting on distal tubules, such as thiazide and loop diuretics do not directly affect the fractional excretion of lithium. The fractional excretion of lithium is less than 7% in prerenal azotemia [1] and as it remains unaffected by the diuretics it may be considered a more accurate marker of prerenal azotemia. But another study shows that only 60% of lithium is reabsorbed in proximal tubules and 20% is reabsorbed in the distal tubules so the diuretics have a similar effect on both sodium and lithium reabsorption [5]. As there are conflicting results available regarding the effect of diuretics on fractional excretion of sodium and lithium hence their role in diagnosing prerenal azotemia is somewhat controversial [3]. According to a study only 48% of patients with prerenal azotemia on diuretic therapy had low fractional excretion of sodium while another shows 93% of these patients had low fractional excretion of lithium [3,5]. Our study will estimate the possible association between low levels of fractional excretion of lithium and prerenal azotemia, and its diagnostic value, compared with the traditionally used index, fractional excretion of sodium so that appropriate strategies could be developed for the diagnosis of all patients with prerenal azotemia especially those on diuretics can be reviewed and prompt management can be ensured to halt further complications.

MATERIALS AND METHODS:

STUDY DESIGN: Cross sectional study.

SETTING: The study was conducted at various wards (i.e. samples obtained from patients admitted in medical, surgical, gynecology, nephrology, cardiology and intensive care unit) of Bahawal Victoria Hospital and tests were carried out in Pathology department, Quaid-e-Azam Medical College, Bahawalpur.

DURATION OF STUDY: The study started on 20th September 2018 and was finished on 27th March 2019.

SAMPLE SIZE: 120 patients were included in the study.

SAMPLING TECHNIQUE: Nonprobability purposive sampling.

SAMPLE SELECTION:

Inclusion criteria: Patients aged 20-60 years, of both sexes admitted in Bahawal Victoria Hospital with prerenal azotemia (urine output less than 500 ml/24 hours, plasma level of creatinine more than 1.6 mg/dl in males and 1.3 mg/dl in females, glomerular filtration rate up to 50 ml/mim, urine and plasma creatinine ratio more than 30, developed within hours to weeks) and on diuretics for ≥ 48 hours at the time of admission.

Exclusion criteria: Patients with acute intrinsic renal failure, postrenal obstruction, chronic renal failure, diabetes mellitus and hypertension will be excluded.

DATA COLLECTION PROCEDURE: After approval of the study by the local ethics committee, patients with prerenal azotemia admitted in Bahawal Victoria Hospital were identified. After explaining the purpose of study a written informed consent was taken and patients were enrolled in the study. Data from the willing patients was collected by a predesigned proforma. The evaluation included blood and spot urine samples for sodium, lithium and creatinine. Plasma sodium, lithium and urinary sodium, lithium were measured by EASYLYTE ISE while plasma and urinary creatinine were measured by fully automated chemistry analyzer (Beckman Coulter AU 680). Urine volume was taken from the input output chart maintained in wards. The fractional excretion of lithium and sodium was calculated in each patient using formula. The cost of all investigations was borne by the researcher.

SAMPLECOLLECTION PROCEDURE: After noting the name, age and sex 5 ml of venous blood was drawn into a sterile syringe with aseptic precautions. The sample was immediately transferred in a cool box to the clinical chemistry Laboratory of QAMC.

CHEMICAL ASSAYS: In the pathology laboratory, the collected samples were centrifuged at 3000 rpm for 10min and the serum obtained was separated. Plasma and urinary creatinine were run on AU 680, which is a fully automated analyzer while plasma sodium, lithium and urinary sodium, lithium will be measured by EASYLYTE ISE. Measurement bias was controlled by calibration of instruments and repeating each test two times and taking their mean. All tests were performed by pathologist with at least five years' experience.

DATA ANALYSIS: Statistical package for social sciences (SPSS version 24.0) was used to analyze the data on computer. Mean and standard deviation values for fractional excretion of lithium and sodium, age of patients and duration of diuretics intake was calculated. T-test was used for comparison of mean values. Frequency for low levels of fractional excretion of lithium and sodium was also calculated. Effect modifiers like age, gender and duration of diuretics intake were analyzed after stratification and chi-square test was used to see the difference. Differences were considered to be significant at p-value ≤0.05 level.

RESULTS

A total of 120 patients with prerenal azotemia on diuretics between the ages of 20 to 60 years participated in the study. There were 78 males and 42 females.

Patients were divided in to various categories according to the underlying cause of PRA. Majority of the patients (45%) were diagnosed cases of liver cirrhosis while other causes were CCF, septic shock, nephrotic syndrome, burns, PPH, gastroenteritis, peritonitis, pulmonary edema and hemorrhage in order of their frequency as mentioned in table 1.

Table 1: Diagnosis of patients with prerenal azotemia

Diagnosis	Number of patients N (%)
Liver cirrhosis	54 (45)
Congestive cardiac failure (CCF)	26 (21.7)
Septic shock	12 (10)
Nephrotic syndrome	07 (5.8)
Burns	05 (4.2)
Postpartum hemorrhage (PPH)	05 (4.2)
Gastroenteritis	04 (3.3)
Peritonitis	03 (2.5)
Pulmonary edema	02 (1.7)
Hemorrhage	02 (1.7)

Table 2 shows that PRA episodes were observed in all hospitalization areas. 46.7% occurred in medical department, 10% in surgical units, 23.3% in ICUs, but only 6.7% of ARF patients were admitted in nephrology department. Only 9.2% of patients were admitted in CCU and 4.2% in gynecology departments.

Table 2: Prerenal azotemia and hospital related aspects

Name of Ward	Number of patients N (%)
Medical unit	56 (46.7)
Surgical unit	12 (10)
Intensive care unit (ICU)	25 (23.3)
Coronary care unit (CCU)	14 (9.2)

Obstetrics & Gynecology	05 (4.2)
Nephrology	08 (6.7)

The clinical characteristics and the urinary indices of all the patients included in the study are summarized in table 3. Urinary sodium excretion was increased (>20 mmol/L) in PRA patients receiving diuretics while the urine/plasma creatinine ratio in these patients was <30. The mean duration of diuretics intake was 76.08±3.52 hours. The fractional excretion of sodium and lithium were calculated as 1.32±0.33 and 6.24±0.47 respectively by using the formula. T-test was used for the comparison of mean values leading to a significant difference (p-value 0.0001).

Table 3: Characteristics and urinary indices of patients with prerenal azotemia

Variable	Mean±SD	p-value
Age (years)	38.14±10.37	0.0001
Duration of diuretics intake (hours)	76.08±34.95	0.0001
Urine volume (ml/24 hours)	317.3±104.13	0.0001
Plasma sodium (mmol/L)	136.8±2.57	0.0001
Plasma lithium (µmol/L)	0.65±0.11	0.0001
Plasma creatinine (mg/dl)	3.67±1.35	0.0001
Urine sodium (mmol/L)	63.41±10.61	0.0001
Urine lithium (µmol/L)	1.42±0.16	0.0001
Urine creatinine (mg/dl)	126.47±34.93	0.0001
Urine/plasma creatinine ratio	36.06±6.12	0.0001
Fractional excretion of sodium (%)	1.32±0.33	0.0001
Fractional excretion of lithium (%)	6.24±0.47	0.0001

It is clear from table 4 that FE_{Na} was characteristically high (>1%) in patients with PRA when diuretics were administered, only 23.3% had low FE_{Na}. By contrast, FE_{Li} was found to be characteristically low in about 92.5% of patients showing a statistically significant (p-value 0.0001) difference obtained by using chi square test but there was no significant association observed between age, gender and duration of diuretics intake of our study population with changes in fractional excretion of these solutes.

Table 4: Comparison of fractional excretion of sodium and lithium

	Yes N (%)	**No N (%)**
Low FE_{Na} (<1%)	28 (23.3)	92 (76.7)
Low FE_{Li} (<7%)	111 (92.5)	09 (7.5)

*FE_{Na} = Fractional excretion of sodium, FE_{Li} = Fractional excretion of lithium

DISCUSSION:

The current study revealed that decompensated liver cirrhosis, CCF, septic shock and nephrotic

syndrome were the major causes of prerenal azotemia accounting for approximately 82.5% of the study population while other causes included burns, PPH, gastroenteritis, peritonitis and hemorrhage. Similar results were depicted by Ackay et al [6] and Albright [7] in their studies on causes of acute renal failure.

Our work illustrates the fact that PRA is a universal problem in medical practice as it develops in all areas within the hospital, that is, medical, surgical or ICUs. As a result, any physician may face a patient with an ARF episode independently of his/her speciality or working place. PRA episodes were observed in all hospitalization areas. 46.7% occurred in medical department, 10% in surgical units, 23.3% in ICUs, but only 6.7% of ARF patients were admitted in nephrology department. These results are comparable with Liano et al [7] with a slight difference in percentage of patient distribution. Several factors may explain these discordant results, which may be probably due to comparatively small sample size and less duration of our study.

Males present with PRA more frequently than females (78 vs. 42). These data are in agreement with the percentage of males recorded from the large, multicenter, community based study [8].

Prerenal azotemia was observed to be relatively more common in older age group. 45% of patients were above the age of 40, where the major cause of this condition was CCF, liver cirrhosis and septic shock while other causes mentioned above were found in younger age group i.e. less than 40 years. But the change in renal indices such as fractional excretion was not significantly associated with age and gender of these patients [7].

Similarly the changes in fractional excretion of solutes were also found to be independent of the duration of diuretics. Similar results were reported by Steinhauslin et al [9] who compared the efficacy of fractional excretion of three major solutes i.e. sodium, lithium and urea in their study. None was found to be affected by the duration of diuretics intake.

As cited earlier, several urinary indices have been proposed to improve the early diagnosis of PRA. FE_{Na} has emerged as a dominant tool and is conventionally used for this purpose. On the other hand, coexistence of diuretics intake negate the effectiveness of this index because diuretics decrease sodium reabsorption and thus increase FE_{Na} [7,10]. Out of 120 patients with PRA on diuretics only 28 (23.3%) had low FE_{Na} (<1%). These results are in accordance with several other studies which showed that in patients without diuretic use, FE_{Na} is a better marker of PRA but in patients administered with diuretics, FE_{Na} cannot be used accurately as it lacks both sensitivity and specificity [11,12].

The ability of a solute to provide a reliable index of renal function would be one that has the following properties:
(1) Complete excretion of filtered load under volume replete conditions (euvolemia or hypervolemia)
(2) Avid reabsorption under volume deplete conditions (hypovolemia)
(3) Tubular fluid to plasma concentration at the end of proximal tubule is very near to zero.
(4) No reabsorption beyond proximal tubule
(5) Reabsorption unaffected by drugs or aberrant medical conditions [9]
In this study we have evaluated the ability of FELi as a more specific marker to circumvent the recognized limitations of FENa. Lithium may be more accurate because it is reabsorbed in parallel to sodium in proximal tubule. Its postproximal reabsorption is probably limited so diuretics do not appear to influence the FE_{Li} [10]. During PRA the proximal tubular reabsorption of sodium and lithium is markedly enhanced, so that FENa and FELi are expected to be low. Commonly used diuretics such as thiazides and loop diuretics which act mainly beyond the proximal tubule should not primarily affect FELi, whereas they should increase FENa [9].

But there is little scientific evidence to support the clinical use of FE_{Li}. Only few studies have evaluated the accuracy of FE_{Li} in prerenal azotemia when diuretics have been administered, however, this one to our knowledge is the first in Pakistan to elaborate

this issue. The results of the previous studies are somewhat conflicting. Our study showed a low FE_{Li} (<7%) in 111 (92.5%) of patients which is in agreement with the study by Steinhauslin et al [9]. In this study, FE_{Li} was 93% sensitive and 72% specific in PRA. Conversely, another study found poor diagnostic accuracy of FE_{Li}. The selection bias and differences between the institutions and study populations may explain the discrepancies.

According to another study loop diuretics have been shown to acutely increase FE_{Li} [13, 14]. On this basis; several authors have suggested that lithium may be transported in the loop of Henle. Theoretically, the lithium ion can be reabsorbed in the loop of Henle because of its permeability characteristics. But in our study, all of the patients treated with loop or thiazide diuretics had low FE_{Li}. This suggests that these diuretics have no measureable effects and argues against a significant reabsorption of lithium postproximal sites in the conditions reported in this study.

Furthermore, because the indiscriminate use of diuretics may be particularly detrimental in prerenal failure by further compromising renal perfusion and thus facilitating progression towards ATN. FE_{Li} may be clinical benefit by allowing recognition of those patients who are at the highest risk of developing ATN.

Finally, during the study predictable limitations in the use of FE_{Li} were identified. Theoretically, any substance acting on sodium reabsorption in the proximal tubule may increase FE_{Li} [13]. But still this approach has several advantages as it does not interfere with renal function and does not require specific study conditions.

CONCLUSION:

Low levels of fractional excretion of lithium were found in more patients with prerenal azotemia taking diuretics, as compared to low levels of fractional excretion of sodium. This finding demonstrates that the false elevation in fractional excretion of sodium due to diuretics, limits its utility in the diagnosis of this condition. But fractional excretion of lithium appears to have an advantage over fractional excretion of sodium as it remains unaffected by diuretics, thus making it a more reliable and sensitive indicator of prerenal azotemia.
The test is reasonably easy and quick to do, and presents no risk to the patient so we suggest using fractional excretion of lithium in the evaluation of these patients so that all of them especially those on diuretics can be assessed and prompt management can be ensured to halt further complications. Larger studies are however, needed to confirm its validity and cost/benefit ratio in the diagnosis of prerenal azotemia and to delineate its usefulness in other causes of acute renal failure.

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