The Fractional Excretion of Urea in the Differential Diagnosis of Prerenal Failure and Acute Tubular Necrosis in Neonates

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Background : *Acute renal failure (ARF) in a newborn is a common problem. Fractional excretion of sodium (FENa) has been used to distinguish between the two main causes of ARF, prerenal failure and acute tubular necrosis (ATN). However, the clinical usefulness of FENa could be limited by furosemide diuretic that are commonly prescribed in ARF patients. In contrast, urea is not reabsorbed significantly in the distal nephron, thus the fractional excretion of urea (FE UN) should not be affected by furosemide.*

Objective: *To test the hypothesis that FE UN is not effected by furosemide and useful in differentiating between prerenal failure and ATN.*

Material and Method: *Neonates admitted to the Department of Pediatrics, Thammasat University Hospital from August 2007-May 2009 were studies prospectively for ARF which is defined as urine output < 0.5 ml/kg/hr after the 1st day and serum creatinine > 1.5 mg/dl with normal maternal renal function. FENa and FEUN were performed on the initial time of diagnosis and were repeated on two consecutive days.*

Results: *Neonates with ARF were classified as prerenal failure (n = 38) and ATN (n = 5). The prerenal failure neonates were divided into two groups: those prerenal failure without furosemide (n = 27), those prerenal failure with furosemide (n = 11). The FENa at the initial time of diagnosis and the two consecutive days in prerenal failure neonates (0.33 ± 0.57, 10.1 ± 2.73, 0.8 ± 1.32%, respectively) were lower than ATN neonates (4.74 ± 6.12, 5.05 ± 4.03, 3.98 ± 2.47%, respectively) significantly. Both FENa and FE UN were no statistical difference between the two prerenal failure groups and ATN neonates.*

Conclusion: *A FE Na in prerenal failure is significantly lower than ATN. A FE UN has no benefit in distinguishing between prerenal failure and ATN. Furosemide has no effect on both FENa and FE UN.*

Keywords: *Acute renal failure, Prerenal failure, Acute tubular necrosis, Fractional excretion of sodium, Fractional excretion of urea, Furosemide*

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Acute renal failure (ARF) in the neonate is a common problem. Studies suggest an ARF prevalence rate of 3-8% of neonatal unit admissions[1,2]. Of these, about one-third are preterm[1]. With appropriate management, many cases are reversible but long-term problems are still frequently observed[3]. ARF is typically classified as prerenal failure, intrinsic renal disease and postrenal failure. The prerenal failure results from decreased renal perfusion, which lead to a reduction in glomerular filtration rate (GFR). Postrenal failure is due to obstructive uropathies. The major cause of intrinsic renal disease is acute tubular necrosis (ATN). This disorder is caused by ischemic or nephrotoxic injury to the kidney. Prerenal failure and ATN occur on a continuum of the same pathophysiological process and together account for about 90% of the cases of ARF[4].

Analysis of the composition of the urine allows a degree of differentiation between prerenal failure and ATN. The most discriminating test is measurement of the fractional excretion of sodium (FENa). However the clinical usefulness of FENa could be limited by diuretics which decrease sodium reabsorption and thus increase FENa. In contrast, the

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fractional excretion of urea nitrogen (FEUN) is primary dependent on passive forces and is therefore less influenced by diuretic therapy[5,6]. We conduct the study in an attempt to find a significance of FEUN in differentiating between prerenal failure and ATN in neonates and the effect of furosemide on FENa and FE UN.

Material and Method

This prospective study was undertaken in the neonatal intensive care unit of Thammasat University Hospital from 2007 to 2009. ARF was defined as oliguria (urine output < 0.5 ml/kg/h) beyond the first 24 hours of life associated with serum creatinine > 1.5 mg/dl (133 μmol/ml). Urine output was determined by weighing diapers or was measured directly via a urine catheter. Our standard practice was to insert a urine catheter to monitor urine output more accurately if screening of urine output by weighing diapers suggested oliguria. If the infant's initial serum creatinine value was > 1.5 mg/dl (133 μmol/ml), the maternal serum creatinine at the time of delivery was reviewed. An infant's initial serum creatinine value was not considered indicative of ARF if the maternal serum creatinine value was > 1.5 mg/dl (133 μmol/ml). Infants were excluded if there was obstructive uropathy or if initial urine sample was insufficient for laboratory tests. Initial urine sample was sent for urinalysis, urine urea nitrogen, urine sodium, and urine creatinine and initial blood sample was sent for blood urea nitrogen and serum electrolytes then fluid challenge with 0.9% NSS 20 ml/kg within 2 h was performed. Infants who responded to fluid challenge with an increase in urine output $\geq$ 1 ml/kg/h, decrease blood urea nitrogen and serum creatinine and FENa < 2.5% were defined as prerenal failure without furosemide group. Infants who failed the fluid challenge (urine output < 1 ml/kg/h) were prescribed furosemide 1 mg/kg intravenously to increase urine flow rate. Response to furosemide therapy was used to classified infants as prerenal failure with furosemide group if urine output > 1 ml/kg/d, decrease blood urea nitrogen and serum creatinine and as ATN if urine output still < 1 ml/kg/h, increase blood urea nitrogen and serum creatinine after furosemide therapy. Urine and blood samples were collected after fluid challenge and furosemide therapy and two consecutive days for laboratory tests as same as the intial specimens. The FENa was calculated as [(urine sodium/plasma sodium)/(urine creatinine/plasma creatinine)] x100. The FE UN was calculated as: [(urine urea nitrogen/blood urea nitrogen)/(urine creatinine/plasma creatinine)] x 100.

Statistical analysis

All data were collected and entered into a database for analysis. Parametric results were given as means plus or minus standard error. Continuous variables with normal distribution were analyzed by Student's t-test. Comparison among the groups was tested using the Mann-Whitney test. Significance was defined as $p < 0.05$. In tests presented in nominal form, we determined the sensitivity, the specificity. These tests also were compared by using the Receiver Operator Characteristic (ROC) Curve.

Results

Forty-three neonates with ARF were enrolled to the study. Of these, 29 (67.4%) were males and 14 (67.4%) were females. The male to female ratio was 1.9:1. Mean birth weight were 2,877 $\pm$ 675.75 g (range 780-3,900 g). Mean gestational age were 37.78 $\pm$ 2.91 weeks (range 26-42 weeks). Mean age at onset of ARF were 3.63 $\pm$ 4.15 days (range 2-28 days). The neonates were divided into three groups. The first group was composed of 27 neonates with prerenal failure without furosemide, the second group had 11 neonates with prerenal failure but also given furosemide, and the third group had 5 neonates with established ATN. There were no significant differences in birth weight, gestational age, and age at onset of ARF between these three groups (p-value > 0.05) (Table 1).

The indices evaluated in ARF were shown in Table 2. The initial FENa, FENa 1st day and FENa 2nd day in the first group were lower than the second group but not statistically difference (p-value > 0.05). When examining the combined prerenal group (first and second group) compared with of ATN, it is clear that while initial FENa, FENa 1st day and FENa 2nd day were characteristically low in the prerenal groups, it was significantly higher in the ATN group (p-value 0.003, 0.003, 0.001 respectively). The ROC curve was used to evaluate the positivity of different levels of the initial FE Na in patients with ARF which we found that a FE Na of 0.76% had the best sensitivity and specificity (100 and 93.3%, respectively) in differentiating between prerenal failure and ATN (Fig. 1).

The initial FE UN, FE UN 1st day, and FE UN 2ndday of the three groups were not statistical different (p-value > 0.05).

Discussion

The newborn kidney is vulnerable to injury when faced with endogenous or exogenous stress. For the most parts, that injury is caused by reduced renal

Table 1. Demographic data of studying groups

ARF type	n/N (%)	Male/Female (ratio)	Birth weight (gm) Mean ± SD (range)	Gestational age (weeks) Mean ± SD (range)	Date at onset of ARF (day) Mean ± SD (range)
PreARF without furosemide	27/43 (62.8)	19/8 (2.4:1)	2,836.11 ± 732.64 (780-3,865)	37.44 ± 3.17 (26-42)	3.11 ± 2.06 (2-9)
PreARF with furosemide	11/43 (25.6)	7/4 (1.8:1)	3,130 ± 434.32 (2,600-3,900)	39.09 ± 1.14 (37-41)	4.91 ± 7.67 (2-28)
Total PreARF	38/43 (88.4)	26/12 (2.2:1)	2,921.18 ± 668.14 (780-3,900)	37.92 ± 2.82 (26-42)	3.61 ± 4.42 (2-28)
ATN	5/43 (11.6)	3/2 (1.5:1)	2,300 ± 761 (1,410-3,450)	35.2 ± 4.09 (30-39)	5 ± 2.2 (2-8)

Table 2. Fractional excretion of sodium (FE Na) and urea nitrogen (FE UN) in each ARF group

FE	PreARFwithout furosemide (n = 27)	PreARF with furosemide (n = 11)	p- value	Total Pre ARF (n = 38)	ATN (n = 5)	p-value
Initial FE Na	0.27 ± 0.39	0.56 ± 0.99	0.73	0.33 ± 0.57	4.74 ± 6.12	0.003
FE Na 1st day	0.57 ± 0.57	2.01 ± 4.86	0.83	1.01 ± 2.73	5.05 ± 4.03	0.003
FE Na 2nd day	0.70 ± 1.05	1.05 ± 1.87	0.35	0.80 ± 1.32	3.98 ± 2.47	0.001
Initial FE UN	29.21 ± 13.13	28.39 ± 15.03	0.95	29.02 ± 13.27	48.70 ± 35.39	0.28
FE UN 1st day	45.86 ± 20.01	51.51 ± 57.80	0.22	47.64 ± 35.50	47.40 ± 25.03	0.66
FE UN 2ndday	44.67 ± 17.22	37.01 ± 11.55	0.59	42.42 ± 21.28	37.00 ± 22.28	0.67

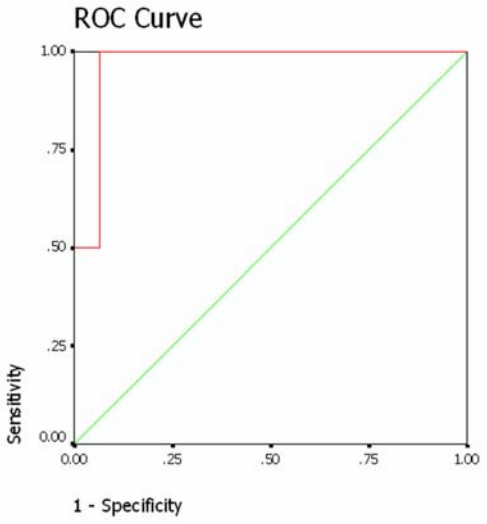

Fig. 1 Receiver Operator Characteristic (ROC) Curve of initial FENa for neonates with prerenal failure and ATN

perfusion. Most of these conditions are transient and disappear after correction of the underlying derailment or disease[7-9]. In 2004, The Acute Dialysis Quality Initiative (ADQI)[10] proposed a multi-dimension system termed the RIFLE criteria (Risk, Injury, Failure, Loss, and End stage renal disease) that classified the degree of renal insult by changes in serum creatinine and/or the duration of oliguria. ADQI also proposed changing the terminology from acute renal failure to acute kidney injury in an effort to focus attention to the early recognition of renal insult and interventions to prevent or mitigate the effects of significant renal failure. However RIFLE criteria has not undergone clinical validation in neonates.

In this study we used the definition of ARF in neonates as described by Gouyon and Guignard[11] which defined ARF in neonates as the plasma creatinine concentration is above 15 mg/l for at least 24-48 h while maternal renal function is normal and oliguria has been defined by a urine output below 0.5-1 ml/kg per hour

after the first day of life.

Our study showed that ARF was male predominate with the male to female ratio of 1.9:1, most patients had age at onset of 2 days and prerenal failure was the main cause of ARF (88.6%) which compares well with observations of Hentschel et al[8] who reported that male gender, age at admission of 1-10 days were the risk factors for neonatal renal insufficiency and type of renal insufficiency consisted of prerenal failure 86%, intrinsic renal failure 11% and postrenal failure 3%.

The FE Na has been proposed to differen tiate ATN from prerenal failure in patients without any previous diuretic treatment. A FE Na greater than 2.5-3.0% was found in term newborn infants with ATN[8,11]. Our study confirmed that neonates with ATN had FE Na higher than prerenal failure significantly. A FE Na of 0.76% had the best discriminatory index (sensitivity and specificity 100 and 93.3%, respectively) in differentiating between prerenal failure and ATN.

A common major limitation in the use of FE Na stems from the fact that diuretic agents are employed frequently in the treatment of prerenal conditions or to enhance urine output in oliguric patients that lead to increase urinary sodium and thus increased FE Na. This study showed that a FE Na was increased in ARF neonate given furosemide but not significantly difference. The reason that may be due to rather small number of neonates with furosemide group.

A FEUN may be a better index to evaluate possible prerenal status in patients who receive diuretic agents that clinically work at distal sites. Urea is not reabsorbed significantly in the distal nephron and is therefore a FEUN should not be affected by their use[5,6]. This is in contrast to FE Na, which is increased by all forms of diuretics. Carvounis CP et al[6] demonstrated that low FEUN ($\leq$ 35%) was found to be a more sensitive and specific index than FE Na in differentiating between prerenal failure and ATN, especially if diuretics have been administered. Our study confirmed the previous studies that a FEUN was not affected by furosemide therapy but failed to discriminate between prerenal failure and ATN. This finding differed from that of a previous report[6] which could be due to rather small number of ATN cases in our study.

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ค่า fractional excretion ของ urea ในการวินิจฉัยแยกโรค prerenal failure และ acute tubular necrosis ในทารกแรกเกิด

จักรชัย จึงธีรพานิช, ภาสกร ศรีทิพย์สุโข, สุขเกษม โฆษิตเศรษฐ, วิไลพร เตชะสาธิต

ภูมิหลัง: *ภาวะไตวายเฉียบพลัน (acute renal failure ; ARF) เป็นปัญหาที่พบบ่อยในทารกแรกเกิด ค่า fractional excretion of sodium (FE Na) สามารถใช้แยกระหว่าง prerenal failure และ acute tubular necrosis (ATN) ได้ แต่มีข้อจำกัดในผู้ป่วยที่ได้รับยาขับปัสสาวะ furosemide ซึ่งมีผลทำให้ค่าFE Na เพิ่มขึ้น แต่ไม่มีผลต่อค่า fractional excretion ของ urea nitrogen (FE UN)*

วัตถุประสงค์: *เพื่อทดสอบสมมติฐานว่าค่า FE UN สามารถใช้ในการวินิจฉัยแยกโรคระหว่าง prerenal failure และ ATN ได้ และยาขับปัสสาวะ furosemide ไม่มีผลต่อค่า FE UN*

วัสดุและวิธีการ: *ศึกษาแบบไปข้างหน้าในทารกแรกเกิดที่ได้รับการวินิจฉัยว่ามีภาวะไตวายเฉียบพลันที่หอผู้ป่วยวิกฤตทารกแรกเกิด โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ระหว่างเดือนสิงหาคม พ.ศ. 2550 ถึงเดือนพฤษภาคม พ.ศ.2552 โดยอาศัยหลักเกณฑ์วินิจฉัยทารกแรกเกิดมีปริมาณปัสสาวะออกน้อยกว่า 0.5 มล./กก./ชม.หลังคลอดเกิน 24 ชม. ค่า serum creatinine > 1.5 มก./ดล. และมารดามีการทำงานของไตปกติ โดยจะส่งตัวอย่างเลือดและปัสสาวะเพื่อตรวจ FE Na และ FE UN ขณะที่วินิจฉัยว่ามีภาวะไตวายเฉียบพลัน และส่งตรวจซ้ำวันละครั้งต่อเนื่องกัน 2 วัน*

ผลการศึกษา: *มีทารกแรกเกิดที่มีภาวะไตวายเฉียบพลันรวม 43 ราย แบ่งเป็นผู้ป่วย prerenal failure จำนวน 38 ราย และผู้ป่วย ATN จำนวน 5 ราย โดยผู้ป่วย prerenal failure แบ่งเป็น 2 กลุ่มได้แก่ผู้ป่วย prerenal failure ที่ไม่ได้รับยาขับปัสสาวะ furosemide จำนวน 27 ราย และผู้ป่วย prerenal failure ที่ได้รับยาขับปัสสาวะ furosemide จำนวน 11 ราย พบว่าผู้ป่วยกลุ่ม prerenal failure มีค่า FE Na ขณะที่วินิจฉัยภาวะไตวายเฉียบพลัน และใน 2 วันต่อเนื่องกัน (ร้อยละ 0.33 $\pm$ 0.57, 1.01 $\pm$ 2.73, 0.8 $\pm$ 1.32 ตามลำดับ) ต่ำกว่าผู้ป่วย ATN (ร้อยละ 4.74 $\pm$ 6.12, 5.05 $\pm$ 4.03, 3.98 $\pm$ 2.4 ตามลำดับ) อย่างมีนัยสำคัญทางสถิติโดยค่า FE Na ขณะที่วินิจฉัยภาวะไตวายเฉียบพลันที่ร้อยละ 0.76 จะมีความไว (sensitivity) ร้อยละ 100 และ ความจำเพาะ (specificity) ร้อยละ 93.3 ในการวินิจฉัยแยกโรคระหว่าง prerenal failure และ ATN แต่ค่า FE Na และ FE UN ในผู้ป่วย prerenal failure ทั้ง 2 กลุ่ม และผู้ป่วย ATN ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ*

สรุป: *ค่า FE Na ใน prerenal failure ต่ำกว่า ATN อย่างมีนัยสำคัญทางสถิติค่า FE UN ไม่สามารถใช้ในการวินิจฉัยแยกโรคระหว่าง prerenal failure และ ATN ได้ และยาขับปัสสาวะ furosemide ไม่มีผลต่อค่า FE Na และ FE UN*