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Study of Serum Cystatin C, Urinary β 2 Microglobulin and Renal Doppler Ultrasound Among Newborn Infants Suffering from Perinatal Asphyxia

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ABSTRACT

Perinatal asphyxia has been identified as an important cause of vasomotor nephropathy (VMPN) in the newborn infants. The aim of the study was to evaluate the rule of serum cystatin C, urinary β2 microglobulin and renal Doppler ultrasound in prediction of kidney injury and vasomotor nephropathy in asphyxiated newborn infants. Case control study was carried out on 27 newborn infants with perinatal asphyxia and 14 control normal newborn infants admitted to the Neonatal Intensive Care Units (NICU) of Al-Zahraa University Hospital, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. There was significant difference between the control group and VMNP group as well as without VMNP group regarding mean values of Blood Urea (BU), serum Cystatin C, Urinary β 2M on the first day and third day of life. The sensitivity and specificity of Cystatin C was 100% on the first and third day at cut off point of >323 and >317 mg dL^{-1}. The sensitivity and specificity of β 2M was 100% on first and third day at cut off point of >0.3 and >0.32 mg dL^{-1}. Renal Doppler Ultrasound (US) showed decrease in Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV) and increased R1 mean values in the first day of life. It was concluded that Cystatin C is more sensitive biomarker for glomerular filtration rate than serum creatinine. B2 microglobulin is a highly sensitive marker for detection of early subtle tubular dysfunction and vasomotor nephropathy. Doppler US measurement of renal blood flow velocity is early non-invasive screening techniques for assessment of renal blood flow to detect early acute kidney injury, it has diagnostic and prognostic importance.

Key words: Vasomotor nephropathy, NICU, perinatal asphyxia, newborn infant, renal injury

INTRODUCTION

Perinatal asphyxia is the third leading cause of neonatal death and the main cause of long-term neurodevelopment handicap throughout the world. The kidney is one of the most common affected organs in perinatal asphyxia. Perinatal asphyxia affects both the glomerular and the tubular function. The asphyxiated infant is at risk of Acute Tubular Necrosis (ATN) and for syndrome of inappropriate secretion of antidiuretic hormone.

Perinatal asphyxia has been identified as an important cause of vasomotor nephropathy (VMNP) in the newborn infants[1].

The term VMNP was often used as an imprecise alternative for prerenal acute kidney injury. It indicates renal dysfunction, with or without parenchymal damage due to reduced renal perfusion. VMNP may cause irreversible renal injury. The second most

frequent condition leading to neonatal VMNP was perinatal hypoxemia or asphyxia, generally during severe Respiratory Distress Syndrome (RDS).

The diagnosis of Acute Kidney Injury (AKI) is problematic, as current diagnoses rely on two functional abnormalities; functional changes in serum creatinine and oliguria. Both are late consequences of injury and not markers of the injury itself. Serum creatinine is the most common method to monitor renal function and to diagnose AKI, but it has significant shortcoming[2].

Cystatin C is intensified protein catabolism, or dietetic factors. It does not change with age or muscle mass like creatinine dose. It can be used as marker for GFR due to its unique structure[3].

Measurement of urinary level of β 2 microglobulin, a low molecular weight protein freely filtered through the glomerulus and reabsorbed almost completely in the proximal tubule of even immature kidneys, may provide a sensitive indicator of subtle proximal renal tubular dysfunction[1].

Ultrasonography Doppler ultrasound (US) is a noninvasive, easy and relatively inexpensive imaging technique, it can aid in early detection of renal disease in the newborn. Neonatal renal hyper-echogenicity has been described after hypoxemic insults[4].

The research question is: Could serum cystatin C, urinary β2 microglobulin and renal Doppler ultrasound predict kidney injury and vasomotor nephropathy in asphyxiated newborn infants?

Hypothesis is: Serum cystatin C, urinary β2 microglobulin and renal Doppler ultrasound are effective in prediction of mildor subtle kidney injury and vasomotor nephropathy in asphyxiated newborn infants.

The aim of study was the early detection of acute subtle kidney injury and vasomotor nephropathy by evaluating serum cystatin C, urinary β2 microglobulin and test the efficacy of renal Doppler ultrasound for rapid assessment of renal function. Timely diagnosis permits earlier intervention and prevents progression of renal insufficiency to renal failure and allows accurate treatment and adjustment of drug dosages.

MATERIALS AND METHODS

This was analytic, case control study that was carried out on 41 neonates admitted to the neonatal intensive care units of Al-Zahraa University Hospital, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.

Patients: This study population included 27 newborn infants diagnosed as perinatal asphyxia and 14 healthy control normal newborn infants. Patients were classified into two groups:

- VMNP group (Asphyxiated newborn infant with vasomotor nephropathy, 8 patients)
- Without VMNP(Asphyxiated newborn infant without vasomotor nephropathy, 19 patients)

Inclusion criteria: One-Newborn infants diagnosed as perinatal asphyxia whose postnatal age for initial enrollment was not to exceed to 24 h.

Essential criteria of perinatal asphyxia[5]

- Profound metabolic or mixed academia pH <7.00 on an umbilical cord arterial blood sample
- Persistence of an Apgar score of 0 to 3 >5 min
- Clinical neurologic sequelae in the immediate neonatal period (e.g., seizures, hypotonia, coma or HIE)
- Evidence of multiorgan system dysfunction in the immediate neonatal period

Criteria for vasomotor nephropathy[6]:

- Urine output <0.5 mL^{-1} kg^{-1} h
- Blood urea >40 mg dL^{-1}
- Serum creatinine >1 mg dL^{-1}
- Presence of significant hematuria or proteinuria

These criteria were applied on 3rd day of life and any three of four criteria when fulfilled were considered as indication of renal failure.

- Normal control (not asphyxiated baby with unknown confounding factor believed to alter renal functions such as septicemia, NEC, RDS, etc.) whose postnatal age for initial enrollment is not to exceed 24 h

Exclusion criteria include other cases of neonatal encephalopathy, preterm infants and congenital anomalies mainly involving the kidneys and\or urinary tract.

Methods: All studied cases were subjected to thorough history taking, clinical evaluation, routine laboratory tests (CBC, liver enzymes and serum electrolytes) and estimation of Cystatin C and B2 microlobulin as well as renal ultrasonography and renal Doppler sonography.

Estimation of β 2-microglobulin: B2M was determined in fresh urine samples in the first and third day of life using β 2M ORG 5BM immunometric enzyme linked immunoassay (ELISA) for the quantitative determination of B2M in urine.

Estimation of cystatin C: Estimation of cystatine C was done by using Bio Vendor human cystatin C ELISA. Cystatin C was measured in serum (from centrifugation of 2 cm blood) in the first and third day of life, the sample were stored frozen at -20°C for 6 months.

Imaging procedures: Renal ultrasonography was done for all studied cases and control on the first and third days of life utilizing a Siemens Sondine Elegra 4.2 ultrasound system, with 3.5 PL 28 transducer or a 7.5 MHz linear array transducer.

The longitudinal and transverse diameters of both kidneys and parenchymal thickness were measured. The renal echogenicity was noted.

This was followed by Doppler ultrasonography for evaluation of renal blood flow. The color mode was added for vascular imaging using color sensitivity of 100%. The 35-40 db and a velocity range in the intrarenal arteries of 6-10 cm sec. The intrarenal arteries were visualized in real-time/color coded Doppler mode images. The peak systolic velocity, the end diastolic velocity and Resistivity Index (RI) were measured.

Statistical analysis: All the data were analyzed by using PC, SPSS version 11. The data were tested for its distribution and degree of Skewness then C1 was done for each variable at 95 and 5%, the unpaired T test was used for the comparison between two independent groups when normally distributed. Paired T test for the comparison of cases in the same group, Chi square test was used for comparison between raw non-quantitative variables and column variable.

ROC-curve, receiver Operating Characteristic curve analysis was used for detection of sensitivity and specificity for each marker.

RESULTS

Results of this study showed that there was no difference between the control and the study groups regarding GA, gender as well as body measurements. There was difference regarding Apgar score that proof asphyxia in the study groups. The studied parameters as Urea and creatinine showed variable statistical differences weather between VMNP group, nonVMNP and control groups. Valuable results were observed from study of B 2 microglobulin, cystatin C as sensitive markers for prediction of vasomotor nephropathy on the first and third day. Renal echogenicity in asphyxiated newborn infants with vasomotor nephropathy when compared to control group in the 1st and 3rd days of life while differ only on the first day of the nonVMNP group. Doppler data are diagnostic and can help in clinical management of the asphyxiated group too. These are explained in detail in Table 1 to 7 and Fig. 1.

There was no significant differences related to GA, birth weight and gender between asphyxiated and control groups, only significant difference related to Apgar score was noted at 1, 5 and 10 min (Table 1).

Table 1: Neonatal demographic data of asphyxiated newborn infants and control group

	Groups				
	Asphyxiated newborn infants (n=27)		Controls (n=14)		T-test
Day	Range	Mean±SD	Range	Mean±SD	p-value
GA (Weeks)	38-41	39.62±0.94	37.41	39.45±0.10	0.506
BW (kg)	25-4.30	3.29±0.60	25-5.25	3.32±0.56	0.877
Length (cm)	44-54	49.92±2.46	45-51	49.30±1.53	0.396
Skull (Circumference (cm))	31-38	35.4±1.45	34-37	35.00±0.92	0.335
Gender	No.	%	No.	%	
Males	19	70	10	71	
Females	8	30	4	28.5	
Chi-square p-value	0.944				
	Groups				
	Asphyxiated newborn infants (n=27)		Controls (n=14)		T-test
Apgar (min)	Range	Mean±SD	Range	Mean±SD	p-value
1	0-3	1.54±0.76	6-9	6.7±0.86	<0.001*
5	3-6	4.85±0.97	8-10	9.0±0.73	<0.001*
10	5-10	8.00±1.23	10-10	10.0±0.00	<0.001*

GA: Gestational Age, BW: Birth Weight, *95%

Table 2: Comparison of urea, creatinine, cystatin C, urinary B2M, renal echogenicity and Doppler findings among VMNP and control group in the 1st and 3rd day of life

	VMNP	Control	T	P
1st day of life				
Urea (mg dL^{-1})	30.75±12.9	19.92±13.91	2.95	0.008
Creatinine (mg dL^{-1})	0.8±0.29	0.7±0.15	0.886	0.38
CystatinC (ng dL^{-1})	1815.5±7	265.42±4.26	7.63	0.000
Urinary B2M (mg L^{-1})	5.88±2.6	0.225±0.073	8.29	0.000
PSV (cm sec^{-1})	27.91±16.29	41.64±7.3	-3.22	0.005
EDV (cm sec^{-1})	5.4±1.5	9.48±1.6	-5.16	0.000
R1	0.86±0.6	0.73±0.03	6.01	0.000
Renal size	N:100%	N:100%		
Cortico-medullary	N: 99.03%	N: 100%		
differentiation	Loss: 0.07%	Loss: 0%		
Renal echogenicity	N: 37.5%	N: 100%		0.003*
	H: 62.5%	H: 0%		
3rd day of life				
Urea (mg dL^{-1})	46±15.75	19.07±3.31	6.26	0.000
Creatinine (mg dL^{-1})	1±0.27	0.7±0.16	2.86	0.01
CystatinC (ng dL^{-1})	1794.9±941	244.8±49.8	6.26	0.000
Urinary B2M (mg L^{-1})	6.47±2.9	0.229±0.04	8.29	0.000
PSV (cm sec^{-1})	22.55±8.8	42.7±5.1	-6.44	0.000
EDV (cm sec^{-1})	8.5±3.1	9.9±1.53	-1.40	0.17
RI	0.78±0.07	0.071±0.03	2.80	0.01
Renal echogenicity	N: 50%	N: 100%		0.01*
	H: 50%	H: 0%		

Unpaired T test, *5%, Mean±SD, PSV: Peak Systolic Velocity, EDV: End Diastolic Velocity, RI: Resistivity Index

Table 3: Comparison of urea, creatinine, cystatin C, urinary B2M, renal echogenicity and Doppler findings among asphyxiated newborn infants without VMNP and control group in the 1st and 3rd day of life

	Without VMNP	Control	T	P
1st day of life				
Urea (mg dL^{-1})	28.21±11.9	19.9±3.9	2.49	0.18
Creatinine (mg dL^{-1})	0.71±0.18	0.70±0.15	0.101	0.92
Cystatin C (ng dL^{-1})	1887.85±964.9	265.42±42.6	6.26	0.000
Urinary B2M (mg L^{-1})	5.65±3.5	0.25±0.73	5.75	0.000
PSV (cm sec^{-1})	28.74±14.7	41.64±7.3	-2.90	0.007
EDV (cm sec^{-1})	5.9±2.83	9.4±1.06	-4.08	0.000
RI	0.80±0.11	0.73±0.03	2.25	0.033
Renal size	N:100%	N:100%		
Cortico-medullary differentiation	N: 100%	N: 100%		
Renal echogenicity	N: 73.7%	N: 100%		0.037
	H: 26.3%	H: 0%		
3rd day of life				
Urea (mg dL^{-1})	1887.85±964.9	19.07±3.3	3.23	0.003
Creatinine (mg dL^{-1})	0.77±0.139	0.70±0.163	1.29	0.2
Cystatin C (ng dL^{-1})	1601.15±964	265.42±42.6	5.20	0.000
Urinary B2M (mg L^{-1})	3.826±2.6	0.229±0.4	5.022	0.000
PSV (cm sec^{-1})	35.17±13.4	42.71±5.1	-1.96	0.0
EDV (cm sec^{-1})	10.16±2.7	9.9±1.5	0.225	0.82
RI	0.707±0.52	0.712±0.03	-.339	0.73
Renal echogenicity	N: 78.9%	N: 100%		0.067
	H: 21.1%	H: 0%		

Unpaired T test, Mean±SD, Chi-square test, N: Normal echogenicity, H: Hyperechogenicity

Table 4: Comparison of urea, creatinine, cystatin C, urinary B2M, renal echogenicity and Doppler findings among asphyxiated newborn infants with VMNP and without VMNP in the 1st and 3rd day of life

	VMNP	Without VMNP	T	P
1st day				
Urea (mg dL^{-1})	30.75±12.9	28.21±11.9	0.49	0.62
Creatinine (mg dL^{-1})	0.8±0.29	0.71±0.18	0.90	0.37
Cystatin C (ng dL^{-1})	1815.5±7	1887.85±964.9	-0.188	0.85
Urinary B2M (mg L^{-1})	5.88±2.6	5.65±3.5	0.158	0.87
PSV (cm sec^{-1})	24.91±16.29	28.74±14.73	-0.522	0.6
EDV (cm sec^{-1})	5.4±1.57	5.9±2.83	-0.436	0.6
RI	0.86±0.06	0.803±0.11	1.26	0.2
Renal echogenicity	N: 37.5%	N: 73.7%	Chi square	0.02
	H: 62.5%	H: 26.3%	test	
3rd day				
Urea (mg dL^{-1})	46±15.75	27.66±9.4	3.75	0.001
Creatinine (mg dL^{-1})	1±0.27	0.77±0.139	2.71	0.01
Cystatin C (ng dL^{-1})	1794.9±941	1601.15±964	0.47	0.63
urinary B2M (mg L^{-1})	6.47±2.9	3.826±2.6	2.27	0.032
PSV (cm sec^{-1})	22.55±8.8	35.17±13.44	-2.10	004
EDV (cm sec^{-1})	8.500±3.19	10.16±2.76	-1.19	0.24
RI	0.78±0.077	0.70±0.05	2.53	0.02
Renal echogenicity	N: 50%	N: 78.9%	Chi square	0.14
	H: 50%	H: 21.1%	test	

Unpaired T test, Chi square test, N: Normal echogenicity, H: Hyper echogenicity, Mean±SD

Table 5: Sensitivity, specificity, +PV, –PV and the best cut off point of urea and creatinine in detection of vasomotor nephropathy in asphyxiated new born infants in the first and third day of life

Criterion 1 day	Sensitivity	Specificity	+PV	-PV
Urea >23* mg dL^{-1}	59.26	92.86	94.1	54.2
Creatinine 1 mg dL^{-1}	11.1	0.1	17.06	0.0
Criterion 3 day	Sensitivity	Specificity	+PV	-PV
Urea >24* mg dL^{-1}	62.96	100.00	100.0	58.3
Creatinine >1 mg dL^{-1}	22.2	100	100.0	40.0

The differences in biochemical and Doppler profiles between the Vasomotor nephropathy and control newborn infants are presented in Table 2. There was no significant changes related to serum creatinine on the first day of life.

The differences in biochemical and Doppler profiles between the newborn infant without Vasomotor nephropathy and control are presented in Table 3. Neither Urea nor creatinine was significant on the first day, this can mask the diagnosis of kidney injury.

The differences in biochemical and Doppler profiles between the newborn infant with Vasomotor nephropathy and without VMN are presented in Table 4. There were no significant differences in all biochemical and Doppler data except in the Renal echogenicity.

The ability to detect renal injury using urea and creatinine were low on the first and third day of life as detected by low sensitivity as shown in Table 5.

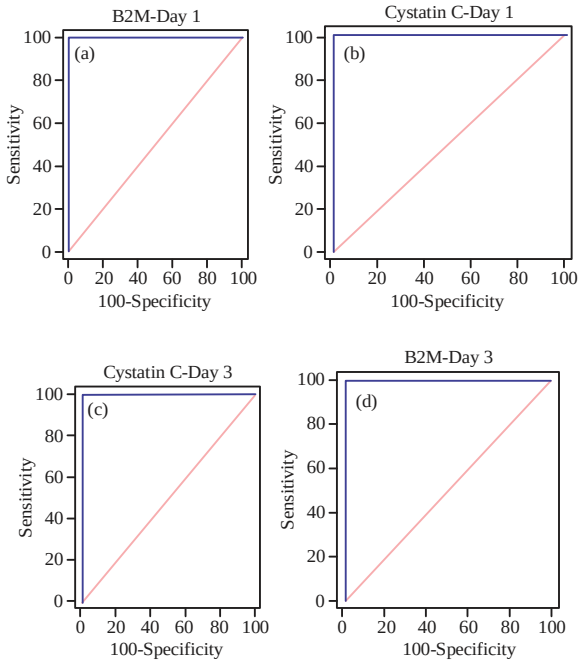
The ability to detect renal injury using Cystatin C and B2M were superior to creatinine and urea as shown in Table 6 and 7.

Table 6: The sensitivity of the studied parameters in asphyxiated newborn infants without VMNP in the first and third day of life

	AUC	SE	95% CI	p-value
Cystatin c day one	100.0	0.000	0.894 to 1.000	0.004
Urea day one	75.4	0.0849	0.573 to 0.886	
Cystatin c day three	100.0	0.000	0.894 to 1.000	0.024
Urea day three	85.9	0.0623	0.694 to 0.955	
B2M day one	100.0	0.000	0.894 to 1.000	0.001
Creatinine day one	61.3	0.103	0.428 to 0.777	
B2M day three	100.0	0.000	0.894 to 1.000	0.001
Creatinine day three	50.8	0.110	0.328 to 0.685	
B2M day one	100.0	0.000	0.894 to 1.000	0.004
Urea day one	75.4	0.0849	0.573 to 0.886	
B2M day 3	100.0	0.000	0.894 to 1.000	0.024
Urea day 3	85.9	0.0623	0.694 to 0.955	

Table 7: The sensitivity of the studied parameters in asphyxiated newborn infants with VMNP in the first and third day of life

	AUC	SE a	95% CI b	p-value
B2M day 1	100.0	0.000	0.846 to 1.000	0.001
Creatinine day 1	55.4	0.133	0.329 to 0.763	
B2M day 3	100.0	0.000	0.846 to 1.000	0.001
Creatinine day 3	58.5	0.125	0.358 to 0.788	
Creatinine day one	55.4	0.133	0.329 to 0.763	0.001
Cystatin C day one	100.0	0.000	0.846 to 1.000	
Creatinine day 3	58.5	0.125	0.358 to 0.788	0.001
Cystatin C day 3	100.0	0.000	0.846 to 1.000	



Criterion 1 day	Sensitivity	Specificity	+PV	-PV
a) B2 M >0.3*	100.00	100.00	100.0	100.0
b) Cystatin C >323*	100.00	100.00	100.0	100.0
Criterion 3 day	Sensitivity	Specificity	+PV	-PV
c) Cystatin C >317*	100.00	100.00	100.0	100.0
d) B2M >0.32*	100.00	100.00	100.0	100.0

Fig. 1: Assessing the sensitivity and specificity in the first and third day

DISCUSSION

Perinatal asphyxia lead to multiorgan dysfunction and a redistribution of cardiac output to maintain cerebral cardiac and adrenal perfusion while potentially compromising renal, GIT and other organs perfusion. It was therefore not surprising that vasomotor nephropathy is common in the asphyxiated neonate[7]. Continued VMNP can lead to irreversible renal damage.

The diagnosis of renal dysfunction in neonates was difficult because the routine clinical and biochemical parameters were affected by maternal parameters and many non-renal factors as medications (e.g., cimetidine) or steroid use, or protein loading[8,9].

In this study there were statistically significant difference in Apgar score between the studied asphyxiated newborn infants and the control group at 1, 5 and 10 min. This agrees with Hassan[10] and EL Meneza[11] and Yanhong *et al.*[12] who found that low Apgar score was identified as independent risk factors for impaired renal function in neonates. The resulted hypoxia can lead to inappropriate antidiuretic hormone secretion syndrome and acute kidney injury[13,14]. The incidence of renal affection in this study cases were 29%. Kaur *et al.*[15] and Ashraf *et al.*[16] reported a higher percentage of AKI.

Significant increase of serum Blood Urea Nitrogen (BUN) was found in asphyxiated newborn infant with vasomotor nephropathy when compared to the control group in the first and third day of life. There was significant elevation of BUN among asphyxiated newborn infant without VMNP when compared to the control group on the third day, however its values were within normal ranges so, renal injury could be missed. This result agreed with those of other researchers[17,18].

There was significant increase of serum BUN in asphyxiated newborn infant with VMNP in the 3rd day of life. This agrees with Gupta *et al.*[6]. Despite of these results, serum BUN was of little value in the newborn infants as it was influenced by numerous non-renal factors as catabolism, dehydration, high protein load (e.g., oral, intravenous, gastrointestinal bleeding and all these conditions are common to occur in newborn infants). This was documented by assessing the sensitivity of BUN in the first and third day of life. The sensitivity of BUN in detecting vasomotor nephropathy was 59.26% and the specificity was 92.86% at the first day of life at cut off point >23. In the third day of life, sensitivity of serum BUN was 62.96% and the specificity was 100% at cut off point >24.

The glomerular function was assessed by measurement of serum creatinine concentration. In the first day of life there was no significant difference of serum creatinine in all asphyxiated newborn infants with and without vasomotor nephropathy when compared to serum creatinine level in the

healthy control group. This can be explained by the fact that in the first 48 h of life, serum creatinine level reflects maternal renal function[19]. In the third day of life there was significant increase of serum creatinine in asphyxiated newborn infants with vasomotor nephropathy when compared to healthy control group.

Serum creatinine was significantly different between asphyxiated newborn infants with vasomotor nephropathy and asphyxiated newborn infants without vasomotor nephropathy in the third day of life. Sarafidis *et al.*[20] found similar results.

When in this study assessed the sensitivity and the specificity of serum creatinine in detecting vasomotor nephropathy in all asphyxiated newborn infants, found that its sensitivity was 11.1% and its specificity was 0.1% at cut off point = 1 in the first day of life. In the third day of life, the sensitivity of serum creatinine was 22.2% and the specificity was 100 at cut off point >1. It was obvious that serum creatinine had low sensitivity in detecting vasomotor nephropathy in newborn infants. Data from several researches revealed low sensitivity of serum creatinine too[17,19,21].

Serum creatinine is not a good marker of renal dysfunction in neonate, due to; first, the creatinine concentration reflects the maternal level for up to 72 h after birth, rendering it unhelpful in the assessment of the neonate in the immediate postnatal period[22]. Second large changes in the Glomerular Filtration Rate (GFR) occur in the absence of a change in serum creatinine, moreover, there was significant variability in neonatal GFR/creatinine values, which change rapidly in the immediate postnatal period as the infant adapts to extra uterine life. In addition, the potential to under estimate creatinine level because of interference with a commonly used assay by hyper bilirubinemia, which is particularly problematic in the first week of life. Also, serum creatinine takes days to rise after injury. There is an urgent need for better biomarkers to permit more timely diagnosis of AKI[23] in the first 48 h that would aid in the diagnosis[7].

Serum Cystatin C is freely filtered by the glomerulus and reabsorbed and catabolized by the proximal tubular cells. Its serum concentration was less dependent on extra renal factors than serum creatinine. Therefore, it could be a better marker of glomerular function (GFR) than serum creatinine[21].

In this study serum cystatine C was elevated in all asphyxiated neonates either with or without vasomotor nephropathy when compared to control group, in the 1st and 3rd days of life. The sensitivity and specificity of serum cystatin C showed that serum cystatin C had 100% sensitivity and 100% specificity in the first and third days of life. On comparing the sensitivity between serum cystatin C and creatinine in the first and third day of life, found that serum cystatin C had higher sensitivity than serum creatinine in all asphyxiated newborn infants with and without vasomotor nephropathy in the first and third day.

On comparing the sensitivity between serum cystatin C and serum BUN in all asphyxiated newborn infants with and without vasomotor nephropathyin the first and third day of life found that serum cystatin C was more sensitive than serum BUN in all asphyxiated newborn infants. This means that serum BUN was not early marker for neonatal vasomotor nephropathy.

Serum cystatin C was more sensitive than serum BUN and creatinine in detecting acute kidney injury; all asphyxiated newborn infant with or without vasomotor nephropathy had acute kidney injury from the first day of life as detected by cystatin C, while only 29% of cases was detected by serum urea and creatinine. Several researchers[17,24,25] found similar results to this study.

In this study found significant elevation of urinary beta-2-microglobulin (B2M) in all asphyxiated newborn infants with and without vasomotor nephropathy in the first and third days of life when compared to the healthy control group. B2M was specific urinary marker of renal tubular damage, it can detect renal damage from asphyxia within 48 h of the insult[7]. Also in the third day of life asphyxiated newborn infants with vasomotor nephropathy showed significant increase of urinary B2M.

The sensitivity and the specificity of urinary B2M in detection of vasomotor nephropathy were 100% in the first and third days of life in all asphyxiated newborn infant. On comparing creatinine and urinary B2M, found urinary B2M was a more sensitive marker in detection of early tubular injury than creatinine in all asphyxiated newborn infant with and without vasomotor nephropathy in the first and third day of life. So, urinary B2M was more sensitive marker in detecting early tubular injury than BUN in asphyxiated newborn infants.

There was loss of cortico-medullary differentiation in 0.07% of VMNP group. There was statistically significant increase in renal echogenicity in all asphyxiated newborn infants with and without vasomotor nephropathy when compared to control group in the first day of life. The 62.5% of the asphyxiated newborn infants with vasomotor nephropathy had diffuse hyper echogenicity in the first day of life, this percentage declined to 50% in the third day of life. From these results concluded that renal injury was reversible as evidenced by gradual improvement in echogenicity. Cortical hyper echogenicity can be explained by the changes in the vascular perfusion of the cortex. Also, rapid physiological redistribution of blood flow to the outer cortical area of the kidney in the

newborn was accompanied by subcellular and molecular processes that may be responsible for the transient nature of ultrasound findings.

In the present study, compared renal blood flow velocities between asphyxiated newborn infants with vasomotor nephropathy and control group and found significant decrease of PSV and EDV and increase in RI in the first day of life. Perinatal asphyxia may lead to significant regional hemodynamic disturbances.

Also, comparing asphyxiated newborn infants without vasomotor nephropathy with control group on the 1st day of life, there were significant decrease in PSV, EDV and increase in RI.

In the 3rd day of life, there were no statistically significant differences and the abnormal Doppler parameters returned to normal values. This reinforces the suggestion that asphyxiated newborn infants without vasomotor nephropathy had acute kidney injury but milder than newborn infants with vasomotor nephropathy

On day three, PSV were significantly reduced and RI were significantly increased in VMNP group. So, perinatal asphyxia induces acute kidney injury in all asphyxiated newborn infants despite the absence of clinical and laboratory indices.

PA affects the renal hemodynamics, as renal vessels become involved, the arterial resistance increases and ultimately this rise in resistance manifests as a decrease in diastolic blood flow which in turn, would cause an increase in the RI.

Doppler ultrasound may be better than serum creatinine as blood flow changes appeared from the first day of life, while serum creatinine needs three days to rise and need marked affection in GFR, so not detect early injury. The changes in PSV, EDV and RI in studied asphyxiated newborn infant without vasomotor nephropathy proceeds the changes in biochemical parameter and it predicts renal improvement earlier.

CONCLUSION

All studied asphyxiated newborn infants had renal affection from the first 24 h of life even without significant rise of renal indices or vasomotor nephropathy. Cystatin C was more sensitive biomarker for glomerular filtration rate than serum creatinine. B2 microglobulin was a highly sensitive marker for detection of early subtle tubular dysfunction and vasomotor nephropathy.

Doppler US measurement of renal blood flow velocity is one the early easy non-invasive screening techniques for assessment of renal blood flow velocity to detect early acute kidney injury, it has diagnostic and prognostic importance as it showed reversibility of renal hypoperfusion even before improvement of biochemical indices and progressive decrease of RI which was correlated to the progressive recovery of renal function.

RECOMMENDATION

We propose that all neonates with birth asphyxia admitted in neonatal intensive care units should be screened for acute kidney injury. We recommend use of cystatin C to assess glomerular functional impairment and urinary B2M in early assessment of tubular dysfunction and Doppler US for assessment of renal blood flow.

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